Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	July 27, 2017
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Product Names:	Namenda (memantine hydrochloride) Namenda XR (memantine hydrochloride) extended-release
Pediatric Labeling Approval Date:	July 3, 2014
Application Type/Number:	NDAs: 021487 (tablet), 021627 (oral solution), 022525 (extended-release capsule)
Applicant/Sponsor:	Forest Labs, LLC
OSE RCM #:	RCM 2017-346

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for memantine and memantine extended-release (XR) in pediatric patients.

Memantine was first approved in 2003, followed by the approval of memantine XR in 2010, for the treatment of moderate to severe dementia of the Alzheimer's type. Memantine and memantine XR are not currently approved for use in the pediatric population. This BPCA review was initiated by a pediatric labeling change on July 3, 2014 for memantine XR. Memantine XR failed to demonstrate efficacy in two 12-week controlled clinical studies of 578 pediatric patients aged 6-12 years with autism spectrum disorders.

The Division of Pharmacovigilance (DPV) identified 12 pediatric cases of memantine or memantine XR reporting a serious outcome, received by the FDA from September 23, 2011 to January 31, 2017 in the FDA Adverse Event Reporting System (FAERS) database. Off-label usage was reported in 6 of the 12 cases. The remaining 6 cases included 2 cases of accidental exposure to memantine and 4 cases from the clinical trials for the safety and tolerability of memantine XR in pediatric patients with autism spectrum disorder. There were no new pediatric safety signals identified, no apparent increase in the severity or frequency of any labeled adverse events, and there were no pediatric deaths reported with memantine or memantine XR.

From July 1, 2014 through January 31, 2017, pediatric patients aged 0-16 years accounted for less than 1% (approximately 5,500 pediatric patients) of total patients who received prescriptions dispensed for memantine and memantine XR in the U.S. outpatient retail pharmacy setting. Of note, although our analyses show prescriptions dispensed to pediatric patients, patient utilization could not be validated due to lack of access to patient medical records.

Overall, we found limited use of memantine or memantine XR among pediatric patients, and no new patterns of FAERS cases or trends suggestive of new or unexpected adverse events attributable to the use of the memantine or memantine XR were identified. DPV recommends no labeling changes at this time, and will continue to monitor adverse events associated with the use of memantine and memantine XR.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Namenda (memantine) is an N-methyl-D-aspartate (NMDA) receptor antagonist indicated for the treatment of moderate to severe dementia of the Alzheimer's type. Memantine is available in the dosage forms and strengths as shown in **Table 1.1**.

Table 1.1. Approval Date, Dosage Form, and Dosage Strength of Memantine

Product Name	NDA	Approval Date	Dosage Form	Dosage Strength
Namenda	021487 021627	October 16, 2003 April 18, 2005	Tablet Oral solution	5 mg, 10 mg 2 mg/mL
Namenda XR	022525	April 21, 2010	Extended-release capsule	7 mg, 14 mg, 21 mg, 28 mg

Memantine and memantine extended-release (XR) are not currently approved for use in the pediatric population. This Best Pharmaceuticals for Children Act (BPCA) review was initiated by the pediatric labeling change on July 3, 2014 for memantine XR (no labeling change was made for memantine tablet or oral solution). The following is an excerpt from the pediatric labeling change for memantine XR in Section 8.4 Pediatric Use:[1]

> *Safety and effectiveness in pediatric patients have not been established.*
>
> *Memantine failed to demonstrate efficacy in two 12-week controlled clinical studies of 578 pediatric patients aged 6-12 years with autism spectrum disorders (ASD), including autism Asperger's disorder and Pervasive Development Disorder - Not Otherwise Specified (PDD-NOS). Memantine has not been studied in pediatric patients under 6 years of age or over 12 years of age. Memantine treatment was initiated at 3 mg/day and the dose was escalated to the target dose (weight-based) by week 6. Oral doses of memantine 3, 6, 9, or 15 mg extended-release capsules were administered once daily to patients with weights < 20 kg, 20-39 kg, 40-59 kg and ≥ 60 kg, respectively.*
>
> *In a randomized, 12-week double-blind, placebo-controlled parallel study (Study A) in patients with autism, there was no statistically significant difference in the Social Responsiveness Scale (SRS) total raw score between patients randomized to memantine (n=54) and those randomized to placebo (n=53). In a 12-week responder-enriched randomized withdrawal study (Study B) in 471 patients with ASD, there was no statistically significant difference in the loss of therapeutic response rates between patients randomized to remain on full-dose memantine (n=153) and those randomized to switch to placebo (n=158).*
>
> *The overall safety profile of memantine in pediatric patients was generally consistent with the known safety profile in adults [see Adverse Reactions (6.1)].*

Additional information from the memantine XR labeling regarding the adverse reactions from these two studies are summarized here. In Study A, the adverse reactions in the memantine XR group (n=56) that were reported in at least 5% of the patients and twice that in the placebo group (n=58) were: cough, influenza, rhinorrhea, and agitation. The reported adverse reactions leading to discontinuation in more than one patient in either treatment group included: aggression and irritability. In Study B, the adverse reaction in patients randomized to placebo (n=160) and reported in at least 5% of patients and twice that of the full-dose memantine XR treatment group (n=157) was irritability (5.0% vs 2.5%).

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The FDA-approved labeling for memantine XR includes the following safety information:[1]

> **----------CONTRAINDICATIONS ----------**
> NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation (4)
> **----------WARNINGS AND PRECAUTIONS ----------**
> Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine (5.1, 7.1)
> **----------ADVERSE REACTIONS ----------**
> The most commonly observed adverse reactions occurring at a frequency of at least 5% and greater than placebo with administration of NAMENDA XR 28 mg/day were headache, diarrhea and dizziness (6.1)

See **Section 1.1** of this review for the pediatric safety information from Section 8.4 Pediatric Use of the memantine XR labeling.

The FDA-approved labeling for memantine includes the following safety information:[2,3]

> **----------CONTRAINDICATIONS----------**
> • NAMENDA is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation. (4)
> **----------WARNINGS AND PRECAUTIONS----------**
> • Conditions that raise urine pH may decrease the urinary elimination of memantine, resulting in increased plasma levels of memantine. (5.1, 7.1)
> **----------ADVERSE REACTIONS----------**
> Most common adverse reactions (≥ 5 % and greater than placebo) are dizziness, headache, confusion and constipation. (6.1)

Additionally, the pediatric safety information from Section 8.4 Pediatric Use of the memantine labeling states, “Safety and effectiveness in pediatric patients have not been established.”

1.3 PREVIOUS OSE POST-MARKETING SAFETY REVIEWS

On October 5, 2011, the Division of Pharmacovigilance (DPV) completed a review of postmarketing reports, received by the FDA from October 16, 2003 (US approval date for the

first memantine product) to September 22, 2011, for all adverse events associated with the use of memantine in pediatric patients (0-17 years old).[4] The Division of Psychiatry Products requested this review as part of their review of a Proposed Pediatric Study Request for the use of memantine for autism (IND 73075). From a search of the Adverse Event Reporting System (AERS) database[a], DPV identified 11 cases in patients aged 3 to 17 years. Eight cases reported indications for treatment, which included Autism Spectrum Disorders (4), and 1 case each of the following Attention Deficit Hyperactivity Disorder (ADHD), Tourette's syndrome, epilepsy, and improvement of hypoxic brain damage. Of the remaining 3 cases, 2 reported accidental drug exposure in a 3- and 4-year-old, and the third case reported an overdose/suicide attempt. Among the reported adverse events in the 11 cases, we did not identify any new safety concerns in the pediatric population.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to FDA to conduct this analysis. Detailed database descriptions are provided in **Appendix A**.

2.1.1 Data Sources Used

The QuintilesIMS, National Sales Perspectives™ was used to determine the settings of care where all memantine products in bottles or packages were distributed from the manufacturers to various U.S. distribution channels in 2016.

The QuintilesIMS, Total Patient Tracker™ database was used to obtain the nationally estimated number of patients who received a dispensed prescription for all memantine from U.S. outpatient retail pharmacies, stratified by patient age (0-4 years, 5-11, 12-16, 17 years and older) from July 1, 2014 through January 31, 2017, aggregated.

[a] Adverse Event Reporting System (AERS) is the previous adverse event and medication error reporting system before the implementation of the FDA Adverse Event Reporting System (FAERS) on September 10, 2012.

2.2 RESULTS

2.2.1 Settings of Care

According to QuintilesIMS' sales distribution data for 2016, approximately 64% of memantine and memantine XR bottles or packages were sold to U.S. retail outpatient pharmacies, 30% to non-retail settings and 6% to mail-order/specialty pharmacy settings. Based on these results we focused our analysis on the U.S. outpatient retail pharmacy setting; data from mail-order/specialty and non-retail pharmacy settings were not included in this review.

2.2.2 Outpatient Pharmacy Patient Level Data

Table 2.2.2. Nationally Estimated Number of Patients with a Dispensed Prescription for memantine and memantine XR* Stratified by Patient Age, from U.S. Outpatient Retail Pharmacies, July 1, 2014 - January 31, 2017

	July 1, 2014 - January 31, 2017	
	Patients (N)	***Share %***
Total Patients	**1,374,429**	***100.0%***
Age 0 - 16 years	**5,462**	***0.4%***
0 - 4 yrs	**421**	***7.7%***
5 - 11 yrs	**2,569**	***47.0%***
12 - 16 yrs	**2,919**	***53.4%***
Age 17 years and older	**1,358,117**	***98.8%***
Age Unknown	**25,525**	***1.9%***

Source: QuintilesIMS, Total Patient Tracker™. July 2014 - January 2017. Extracted May 2017.File: TPT 2017-2894 memantine BPCA May 2017.xls

****Pediatric patients aged 0-16 years accounted for 0.2% of total patients who received a prescription for Namenda (memantine) XR.***

Note: subtotals may not sum exactly because of patients aging during the study period and may be counted more than once in the individual age categories. Therefore, summing across patient age bands is not advisable and will result in overestimates of patient counts.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in **Table 3.1.1**. See **Appendix B** for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of Search	February 24, 2017
Time Period of Search	September 23, 2011* - January 31, 2017
Search Type	FBIS Quick Query
Product Terms	Product Active Ingredient: Memantine, memantine hydrochloride
Search Parameters	All ages, all outcomes, worldwide

Abbreviation: FBIS = FAERS Business Intelligence Solution
* Start date was determined by the end date of the AERS search for a DPV pediatric review completed in October 2011. This pediatric review included postmarketing reports of memantine received by the FDA from October 16, 2003 (US approval date of memantine) to September 22, 2011.

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS Reports* from September 23, 2011 to January 31, 2017 with Memantine and Memantine XR

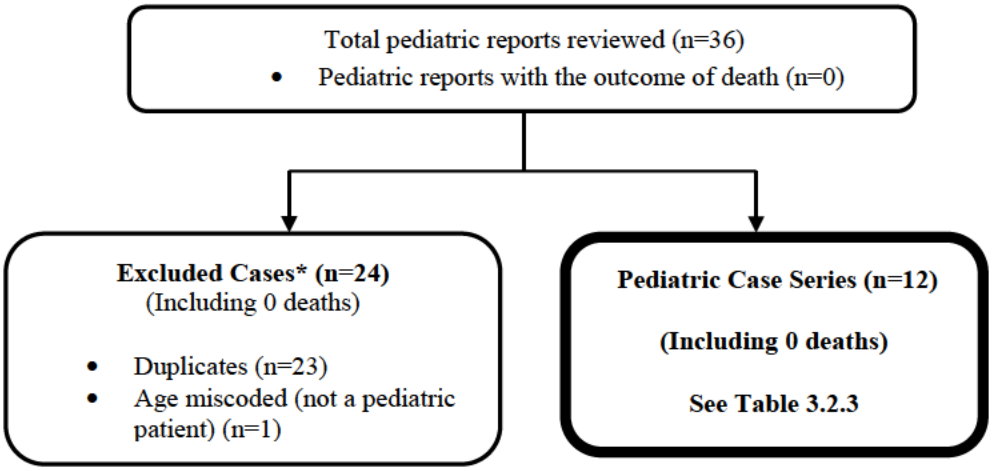
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	1,877 (769)	1,647 (587)	316 (202)
Pediatrics (0 - <17 years)	36 (32)	**36**‡ (32)	0 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡See **Figure 3.2.2**

3.2.2 Selection of Pediatric Cases in FAERS

We identified 36 pediatric reports for memantine or memantine XR, all of which reported a serious outcome (see **Table 3.2.1**). See **Figure 3.2.2** below for the selection of cases to be summarized in **Sections 3.3 - 3.5.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Memantine or Memantine XR



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric case series.

Table 3.2.3 Characteristics of Pediatric Case Series with Memantine or Memantine XR (N=12)

Age	2- < 6 years	4
	6- <12 years	7
	12- < 17 years	1
Sex	Male	10
	Female	2
Year of Initial FDA Receipt	2011	1
	2012	1
	2013	7
	2014	1
	2015	1
	2016	1
Country	United States	9
	Foreign	3
Formulation (n=8)	Memantine tablet	3
	Memantine oral solution	1
	Memantine XR capsule	4
Reported Reason for Use (n=10)[*]	Autism spectrum disorder	8
	"Abnormal brain function"	1
	Obsessive-compulsive disorder and Asperger's disorder	1
Serious Outcome[†]	Hospitalized	5
	Required Intervention	1
	Other serious	7

[*] Not applicable in two cases reporting accidental exposure or overdose.
[†] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no pediatric deaths in the case series.

3.4 SUMMARY OF SERIOUS, PEDIATRIC CASES: UNLABELED ADVERSE EVENTS (N=8)

DPV identified eight non-fatal, pediatric cases reporting an unlabeled, serious adverse event. We did not identify any new pediatric safety signals from the unlabeled adverse events.

3.4.1 Speech disorder, dysphemia (n=2)

Alaghband-Rad et al.[5] reported speech difficulties in two pediatric patients on memantine for the management of autism spectrum disorder. One patient had pre-existing stuttering and experienced an exacerbation of stuttering and new-onset of difficulty in speech. In the second patient, the speech difficulty resolved despite an increase in memantine dose. These two cases are summarized below:

- A 9-year-old male with a 5-year history of autism and baseline stuttering was started on memantine for the management of autism. On the third week of memantine treatment (one week after the memantine dose was increased to 10 mg daily), his stuttering deteriorated and he had difficulty starting to speak. He was only able to speak after a deep, audible breath. Several days after the memantine dose was decreased to 7.5 mg daily, the patient experienced some improvement at the start of speaking, but memantine was eventually discontinued due to the distress from the aggravated stuttering. Three weeks after the discontinuation of memantine, the stuttering was back to baseline.

- A 4-year-old male without a history of speech disorder who was started on memantine 5 mg daily for autism. While on memantine, he developed a speech disorder; like the first patient, he was only able to speak after a deep, audible breath. The patient tolerated this adverse event, and the memantine dose was gradually increased to 7.5 mg daily. The speech disorder eventually resolved, despite continuation of memantine.

3.4.2 Accidental exposure to product by child, overdose (n=2)

Two cases reported in the literature described accidental exposure or overdose in 2-year-old toddlers. Both patients co-ingested memantine and donepezil. Unlabeled adverse events for both memantine and donepezil included tachycardia and encephalopathy. The remaining events reported in these cases were consistent with the labeling for memantine and donepezil (with the exception of central nervous system depression which is only labeled for memantine). These two cases are summarized below:

- Thornton and Clark[6] reported a 2-year-old female who experienced agitation and visual hallucinations after an unwitnessed ingestion of donepezil and memantine, as confirmed by elevated blood levels. The patient was hospitalized and presented with hypotension, tachycardia, and encephalopathy. She was discharged after 3 days of hospital admission.

- Thorton et al.[7] performed a retrospective review of a state-wide poison control system's database of pediatric exposures to antidementia drugs over an 11-year period in California. One case highlighted was mild central nervous system depression in a 2-year-old male after ingestion of memantine (maximum dose of 120 mg) and donepezil (maximum dose of 60 mg). The mild central nervous system depression resolved without intervention following observation in the emergency department.

*Reviewer's Comment: Tachycardia and encephalopathy are unlabeled events for memantine, memantine XR and donepezil. The memantine and donepezil labeling for the other events reported in these two cases are shown in **Table 3.4.2** below:*

Table 3.4.2. Labeling of Adverse Events in Memantine, Memantine XR, and Donepezil		
Adverse Event	**Memantine, Memantine XR**	**Donepezil**
Agitation	8.4 Pediatric Use, 10 Overdosage	6.2 Postmarketing Experience
Visual hallucinations	10 Overdosage	Hallucinations – 6.1 Clinical Trials Experience, 6.2 Postmarketing Experience
Hypotension	Memantine XR only – 6.1 Clinical Trials Experience	10 Overdosage
CNS depression	Captured under related terms in 10 Overdosage (coma, loss of consciousness, somnolence)	(not labeled)

3.4.3 Miscellaneous (n=4)

Four cases reported unlabeled adverse events for memantine or memantine XR. Two of the four cases did not provide enough information for assessment: chromaturia (n=1) and serotonin level increased (n=1). In the third case, a literature article[8] reported drug ineffective when memantine was prescribed to control aggression or self-injurious behaviors in a pediatric patient with autism.

Reviewer's Comment: Memantine failed to demonstrate efficacy for autism spectrum disorders in clinical trials and therefore the event of drug ineffective is expected.

The fourth case reported mood dysphoria, behavioral disinhibition, aggression, suicidal ideation, and homicidal ideation in a patient who was enrolled in a phase 2 pediatric clinical trial for memantine XR. This single case of homicidal ideation occurred after a precipitating event in a patient with a history of behavioral problems and newly diagnosed psychotic disorder and ADHD. The events resolved with counseling and medication adjustments. We did not identify any additional cases of homicidal ideation in the pediatric case series. This case is summarized below:

- An 8-year-old male with a history of behavioral problems and Asperger's disorder was a participant in an open-label extension study for memantine XR for autism spectrum disorders. His concomitant medications included quetiapine for autism spectrum disorder (more than 2 years) and mirtazapine for sleep (more than 1 year). Prior to this study, he completed 2 study protocols totaling about 13 weeks of memantine XR treatment. On Day 42 of memantine XR treatment in the extension study, the patient began to experience "mood dysphoria." Over the next few weeks, the patient had increasing symptoms of mood dysphoria and behavioral disinhibition. He held a knife and

attempted to kill his sister; he also had suicidal ideation. These thoughts occurred when he was upset. Additionally, he was aggressive at school and suspended for bullying. On Day 126 of memantine XR treatment, memantine XR was discontinued secondary to the severe mood dysphoria and he was withdrawn from the study. The following day, the patient was hospitalized for treatment. In the hospital, the patient was diagnosed with psychotic disorder and ADHD. He attended individual and family counseling sessions. His quetiapine dose was increased and he was started on fluoxetine for depression as well as methylphenidate for hyperactivity. However, the investigator considered the discharge diagnoses to be errors, because the patient had not previously exhibited ADHD symptoms and the investigator thought the reported symptoms were related to autism. The investigator additionally reported that the patient had an anxious attachment to his mother, and the event that precipitated the patient's behavioral change was a change in his mother's job where she could no longer be home in the evenings. The patient's behavior improved at discharge, without further aggression or suicidal and homicidal thoughts.

Reviewer's Comment: While memantine XR is labeled for aggression and irritability in Section 8.4 Pediatric Use as a result of the pediatric clinical trials, memantine XR is also labeled for aggression, depression, anxiety, and suicidal ideation in Section 6 Adverse Reactions.

3.5 SUMMARY OF SERIOUS, PEDIATRIC CASES: LABELED ADVERSE EVENTS (N=4)

Although memantine and memantine XR are not indicated for use in the pediatric population, the pediatric labeling for memantine XR indicated that the overall safety profile of memantine in pediatric patients was generally consistent with the known safety profile in adults. Therefore, for the purpose of this review, we considered labeled adverse events those listed in the labeling for one or more of the memantine products, even if pediatric patients were not specifically mentioned. Four cases reported one or more labeled adverse events for memantine or memantine XR. We did not identify new risks or labeled events reported in unusual numbers in pediatric patients.

Two of the four cases reported behavioral disorders, including behavioral disinhibition and aggression, in patients with autism spectrum disorder. The patients in these two cases were participants in one of the phase 2 pediatric clinical trials for the safety and tolerability of memantine XR in pediatric patients with autism spectrum disorder. The first case reported disruptive and combative behavior, including aggression, in an 8-year-old male with autism and anxiety. He was on sertraline and memantine XR. The patient's behavior returned to baseline after memantine XR was discontinued (positive dechallenge). In the second case, a 7-year-old male with PDD-NOS, ADHD, depression, and a history of suicidal threat experienced severe behavioral disinhibition, including aggression while on memantine XR. His complicated psychiatric and social history potentially confounded the events. The patient's concomitant medications included sertraline, dexmethylphenidate, and risperidone. The patient was

hospitalized and his medications were adjusted (discontinued memantine XR and dexmethylphenidate, along with decreased doses of sertraline and risperidone). He was diagnosed with depressive disorder, anxiety disorder, and mild intellectual disability. The psychologist stated that the patient's decreased intellectual functioning contributed to the patient's "aggressive way of dealing with problems and to low frustration tolerance." The patient recovered following treatment in the hospital.

Reviewer's Comment: Aggression and irritability are labeled for memantine XR in Section 8.4 Pediatric Use as a result of the findings from the pediatric clinical trials.

The third and fourth cases reported labeled events, but with confounding factors. A patient with a history of occasional constipation reported worsening constipation on the second day of memantine XR treatment.

Reviewer's Comment: Constipation is labeled under Section 6 Adverse Reactions for the three memantine formulations.

The last case was a literature report[9] of increased appetite and weight gain in a patient on fluoxetine, aripiprazole, and memantine. The authors of the literature article attributed these adverse events to aripiprazole.

Reviewer's Comment: Weight increased is labeled for memantine XR in Section 6 Adverse Reactions, as well as for aripiprazole in Warnings and Precautions (Section 5.6 Metabolic Changes). In addition, increased appetite is labeled for aripiprazole in Section 6 Adverse Reactions.[10]

4 DISCUSSION

Although memantine and memantine XR are not indicated for use in the pediatric population, DPV identified 12 pediatric cases of memantine or memantine XR reporting a serious outcome, received by the FDA from September 23, 2011 to January 31, 2017 in the FAERS database. Off-label usage was reported in 6 of the 12 cases. The remaining 6 cases included 2 cases of accidental exposure to memantine, and 4 cases from the clinical trials for the safety and tolerability of memantine XR in pediatric patients with autism spectrum disorder. There were no new pediatric safety signals identified, no apparent increase in the severity or frequency of any labeled adverse events, and there were no pediatric deaths reported with memantine or memantine XR.

Drug utilization findings showed use of memantine and memantine XR in pediatric patients aged 0-16 years accounted for less than 1% (approximately 5,500 pediatric patients) of total patient use in the U.S. outpatient retail pharmacy setting. Although memantine and memantine XR are not indicated for use in the pediatric population, our analyses show prescriptions were dispensed

to pediatric patients. However, utilization could not be validated due to lack of access to patient medical records.

5 CONCLUSION

Overall, we found limited use of memantine or memantine XR among pediatric patients and no new patterns of FAERS cases or trends suggestive of new or unexpected adverse events attributable to the use of the memantine or memantine XR were identified.

6 RECOMMENDATIONS

DPV recommends no labeling changes at this time, and will continue to monitor adverse events associated with the use of memantine and memantine XR.

7 REFERENCES

1. Namenda XR (memantine hydrochloride) extended release capsules [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; September 2014.

2. Namenda (memantine HCl) tablets, solution [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; October 2013.

3. Namenda (memantine HCl) solution [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; August 2014.

4. Diak I. Namenda (memantine) and pediatric safety profile. FDA Postmarketing Safety Review. RCM 2011-3475. October 5, 2011.

5. Alaghband-Rad J, Nikvarz N, Tehrani-Doost M, Ghaeli P. Memantine-induced speech problems in two patients with autistic disorder. Daru. 2013 Jul 2;21(1):54.

6. Thornton SL, Clark RF. Encephalopathy from unintentional donepezil and memantine ingestion. Pediatr Emerg Care. 2014 Sep;30(9):649-50.

7. Thornton SL, Pchelnikova JL, Cantrell FL. Characteristics of pediatric exposures to antidementia drugs reported to a poison control system. J Pediatr. 2016 May;172:147-50.

8. Haq AU, Ghaziuddin N. Maintenance electroconvulsive therapy for aggression and self-injurious behavior in two adolescents with autism and catatonia. J Neuropsychiatry Clin Neurosci. 2014 Winter;26(1):64-72.

9. Bernhardt EB, Walsh KH, Posey DJ, McDougle CJ. Memantine for comorbid obsessive-compulsive disorder and Asperger disorder suggests a link in glutamatergic dysregulation. J Clin Psychopharmacol. 2011 Oct;31(5):673-5.

10. Abilify (arpiprazole) tablets [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; February 2017.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

National Sales Perspectives (NSP)

The QuintilesIMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS, Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the VectorOne® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. VectorOne® receives over 2.1 billion prescription claims per year.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.1 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS (N=12)

FAERS Case #	Version #	Manufacturer Control #
8178870	1	AUR-APL-2011-05142
8846870	1	USA/USA/12/0026211
8778123*	1	US-EISAI INC-E2020-11287-SPO-US
8846052*	1	US-FRI-1000039413
8909285*	1	AUR-APL-2012-04615
10154041*	2	US-INDICUS PHARMA-000251
10156611*	2	US-ACCORD-023498
10454276*	2	US-FRI-1000070565
10463054*	2	US-CIPLA LTD.-2014US01319
10472080*	2	US-DRREDDYS-USA/USA/12/0026211
11080495*	1	PHHY2015US051204
11094733*	1	US-TEVA-560954USA
11097633*	1	US-APOTEX-2015AP008970
11099572*	2	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2015US-96651
11101189*	1	US-FRI-1000076364
11112010*	1	US-H14001-15-00694
11114434*	1	US-AUROBINDO-AUR-APL-2015-04210
11120977*	1	US-LUPIN PHARMACEUTICALS INC.-2015-01365
11121082*	1	US-ZYDUS-008060
11130749*	1	2015/048
11139511*	1	2015PRN00026
11144820*	1	2015JUB00131
11169034*	1	US-ROXANE LABORATORIES, INC.-2015-RO-00913RO
11195444*	1	US-ACTAVIS-2015-11522
9053262	4	US-FRI-1000042362
9143623	5	US-FRI-1000042999
9239392	3	HU-FRI-1000044177
9408106	6	US-FRI-1000046633
9506764	1	2013/164
9506912	1	2013/165
9573484	1	US-FRI-1000049210
10269387	2	US-DRREDDYS-USA/USA/14/0041354
9922719*	1	PHHY2014US018135
10709572	1	(blank)
12444813	2	US-FRI-1000084692

*Duplicate case

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