

**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: December 1, 2017

Safety Evaluator: Carmen Cheng, PharmD
Division of Pharmacovigilance I (DPV I)

Drug Use Analyst: Shekhar H. Mehta, PharmD, MS
Division of Epidemiology II (DEPI II)

Team Leaders: Vicky Chan, PharmD, BCPS
Safety Evaluator Team Leader, DPV I

Rajdeep Gill, PharmD
Drug Use Analyst Team Leader, DEPI II

(Deputy) Division Directors: Cindy Kortepeter, PharmD
Division Director, DPV I

Grace P. Chai, PharmD
Deputy Director for Drug Utilization, DEPI II

Product Name: Intuniv (guanfacine extended-release)

Pediatric Labeling Approval Date: November 19, 2014 and March 18, 2015

Application Type/Number: NDA: 22037
ANDAs: 200881, 202578, 202568, 201382, 201408

Applicant/Sponsor: NDA: Shire
ANDAs: Actavis Elizabeth; Mylan Pharms, Inc.; Sandoz, Inc.;
Teva Pharms USA; TWI Pharms Inc.

OSE RCM #: 2017-818

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

TABLE OF CONTENTS

Executive Summary	2
1 Introduction.....	3
1.1 Pediatric Regulatory History.....	3
1.2 Highlights of Labeled Safety Issues.....	4
1.3 Previous Office of Surveillance and Epidemiology (OSE) Postmarketing Safety Reviews.....	5
2 Drug Utilization Data.....	6
2.1 Methods and Materials.....	6
2.1.1 Data Sources Used	6
2.2 Results	6
2.2.1 Determining Settings of Care.....	6
2.2.2 Patient Data.....	6
3 Postmarket Adverse Event Reports	7
3.1 Methods and Materials.....	7
3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy.....	7
3.2 Results	8
3.2.1 Total Number of FAERS Reports by Age	8
3.2.2 Selection of Unlabeled, U.S, Serious Pediatric Cases in FAERS.....	8
3.2.3 Characteristics of Pediatric Case Series.....	9
3.3 Summary of Fatal Pediatric Adverse Event Case (N=1)	10
3.4 Summary of Non-Fatal Pediatric Serious Adverse Event Cases (N=32).....	11
3.4.1 Psychiatric Disorders (n=23)	11
3.4.2 Metabolism and Nutrition Disorders (n=2)	13
3.4.3 Miscellaneous (n=7)	14
4 Discussion.....	15
5 Conclusion	16
6 Recommendations.....	16
7 References.....	17
8 Appendices.....	18
8.1 Appendix A. Drug Utilization Database Descriptions.....	18
8.2 Appendix B. FDA Adverse Event Reporting System (FAERS).....	19
8.3 Appendix C. FAERS Case Numbers, FAERS Version Numbers And Manufacturer Control Numbers For The Pediatric Case Series With Guanfacine ER (N=33).....	20
8.1 Appendix D. Ten Leading Causes of Death in 2015 for Ages 0-24 Years Old ⁷	21

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated U.S. postmarketing adverse event reports with a serious outcome and drug utilization data for Intuniv (guanfacine extended-release [ER]) in pediatric patients (0-17 years old). This review focuses on serious, unlabeled adverse events associated with guanfacine ER in pediatric patients.

Guanfacine ER was first approved in 2009 and is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications. The approved pediatric labeling is for the treatment of ADHD in patients 6-17 years old. This BPCA and PREA review was triggered by two pediatric labeling changes. On November 19, 2014, a new weight-based dosing regimen was established for guanfacine ER based on two BPCA and PREA short-term pediatric studies. On March 18, 2015, the guanfacine ER labeling was updated with information on maintenance treatment in patients 6-17 years old based on a PREA study.

The Division of Pharmacovigilance (DPV) identified 33 U.S. pediatric cases in patients 0-17 years old with serious, unlabeled adverse events reported with guanfacine ER, from July 1, 2012 to May 31, 2017, in the FDA Adverse Event Reporting System (FAERS) database. There were no new pediatric safety signals identified, no apparent increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with guanfacine ER. We identified one fatal pediatric case, which did not provide evidence of a causal association with guanfacine ER.

Drug utilization for guanfacine ER was assessed in the U.S. outpatient retail pharmacy setting from July 2011 through June 2017 to provide context for the adverse event reports submitted to the FAERS database. The drug utilization data shows that pediatric patients 0-17 years old accounted for approximately 90% of the total patients annually and utilization of guanfacine ER increased over the study period. The majority of pediatric patients who received a guanfacine ER prescription dispensed were 6 years of age or older. The majority of the U.S. FAERS reports with serious, unlabeled adverse events in the time period reviewed were pediatric patients 6-12 years old, which is consistent with the drug utilization data.

There is no evidence from these data that there are pediatric safety concerns with guanfacine ER at this time. DPV recommends no labeling changes at this time, and will continue to monitor adverse events, including suicidal ideation and behavior, pancreatitis, and medication error involving name confusion, associated with the use of guanfacine ER.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Intuniv (guanfacine extended-release [ER]) is a central alpha_{2A}-adrenergic receptor agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications. Guanfacine ER is available as 1 mg, 2 mg, 3 mg, and 4 mg extended-release tablets.

Guanfacine ER was first approved by the FDA on September 2, 2009 as monotherapy for the treatment of ADHD in patients 6-17 years. In February 2011, guanfacine ER was approved as adjunctive treatment with long-acting oral psychostimulants for the treatment of ADHD.

This Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) review was triggered by two pediatric labeling changes. On November 19, 2014, a new weight-based dosing regimen was established for guanfacine ER based on two BPCA and PREA short-term pediatric studies. Study SPD503-312 was a 15-week, double-blind, randomized, placebo-controlled, dose-optimization study conducted in adolescents aged 13-17 years (n=314) to evaluate the efficacy and safety of guanfacine ER in the treatment of ADHD. Study SPD503-316 was a 12-week (for children aged 6-12) or 15-week (for adolescents aged 13-17), randomized, double-blind, parallel-group, placebo-and active-reference, dose-optimization study (n=337) to assess the efficacy and safety of once-daily dosing in the treatment of ADHD.¹ The adverse events reported in these two studies were consistent with the known safety profile of guanfacine ER.²

On March 18, 2015, the guanfacine ER labeling was updated with information on maintenance treatment in patients 6-17 years old based on a PREA study, SPD503-315. This was a long-term, double-blind, placebo-controlled monotherapy maintenance trial in patients 6-17 years old for the treatment of ADHD. Additional safety information was added in Section 6.1 Clinical Trials Experience under “Discontinuation of Treatment” regarding increases in mean systolic and diastolic blood pressure upon the discontinuation of guanfacine ER.¹

In addition, on November 27, 2017, the guanfacine ER labeling for the brand product was updated with the risk of withdrawal blood pressure increase/rebound hypertension and heart rate increase, and hypertensive encephalopathy upon the abrupt discontinuation of guanfacine ER. The following sections of the guanfacine ER labeling in the prescribing information were updated: 2 Dosage and Administration, 5 Warnings and Precautions, 6.1 Adverse Reactions, and 17 Patient Counseling Information, as well as the Patient Information section. In this review, we identified cases that reported rebound hypertension; we excluded six of these cases from further discussion because they only reported labeled events (captured in Figure 3.2.2 within the 81 excluded cases with labeled adverse events for guanfacine ER).

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current approved labeling for guanfacine ER provides the following safety information in the Highlights of Prescribing Information:¹

-----CONTRAINDICATIONS-----

History of hypersensitivity to INTUNIV[®], its inactive ingredients, or other products containing guanfacine (4).

----- WARNINGS AND PRECAUTIONS-----

- Hypotension, bradycardia, syncope: Titrate slowly and monitor vital signs frequently in patients at risk for hypotension, heart block, bradycardia, syncope, cardiovascular disease, vascular disease, cerebrovascular disease or chronic renal failure. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Avoid concomitant use of drugs with additive effects unless clinically indicated. Advise patients to avoid becoming dehydrated or overheated (5.1).
- Sedation and somnolence: Occur commonly with INTUNIV[®]. Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to INTUNIV[®] (5.2).
- Cardiac Conduction Abnormalities: May worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. Titrate slowly and monitor vital signs frequently (5.3).

----- ADVERSE REACTIONS -----

Most common adverse reactions (≥5% and at least twice placebo rate) in fixed-dose monotherapy ADHD trials in children and adolescents (6 to 17 years): hypotension, somnolence, fatigue, nausea, and lethargy (6.1)

Flexible dose-optimization ADHD trials in children (6 to 12 years) and adolescents (13 to 17 years): somnolence, hypotension, abdominal pain, insomnia, fatigue, dizziness, dry mouth, irritability, nausea, vomiting, and bradycardia (6.1).

Adjunctive treatment to psychostimulant ADHD trial in children and adolescents (6 to 17 years): somnolence, fatigue, insomnia, dizziness, and abdominal pain (6.1).

-----DRUG INTERACTIONS-----

- Strong and moderate CYP3A4 inhibitors increase guanfacine exposure. Decrease INTUNIV[®] to 50% of target dosage when coadministered with strong and moderate CYP3A4 inhibitors (2.7).
- Strong and moderate CYP3A4 inducers decrease guanfacine exposure. Based on patient response, consider titrating INTUNIV dosage up to double the target dosage over 1 to 2 weeks (2.7).

Additionally, the guanfacine ER labeling contains the following safety information in Section 8.4 Pediatric Use:

8.4 Pediatric Use

Safety and efficacy of INTUNIV[®] in pediatric patients less than 6 years of age have not been established. The efficacy of INTUNIV[®] was studied for the treatment of ADHD in five controlled monotherapy clinical trials (up to 15 weeks in duration), one randomized withdrawal study and one controlled adjunctive trial with psychostimulants (8 weeks in duration) in children and adolescents ages 6-17 who met DSM-IV[®] criteria for ADHD [see Adverse Reactions (6) and Clinical Studies (14)].

1.3 PREVIOUS OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (OSE) POSTMARKETING SAFETY REVIEWS

The following is a summary of completed OSE reviews that included pediatric cases, ordered by completion date:

December 22, 2010: A **pediatric postmarketing review** conducted in accordance with PREA summarized 47 serious pediatric cases reported with guanfacine ER. This review included FDA Adverse Event Reporting System (FAERS) reports received by the FDA from September 2, 2009 (U.S. approval date of guanfacine ER) to September 30, 2010. The Division of Pharmacovigilance (DPV) did not identify any new safety concerns in children 0-16 years old. FDA presented this evaluation to the Pediatric Advisory Committee (PAC) in May 2011.

December 13, 2012: A **pediatric postmarketing review** conducted in accordance with PREA summarized 124 serious pediatric cases reported with guanfacine ER. This review included FAERS reports received by the FDA from October 1, 2010 to June 30, 2012. DPV identified hallucinations, an unlabeled event at the time of the review for both guanfacine ER and guanfacine immediate-release (IR) (Tenex) as a safety concern. DPV recommended conducting a FAERS search for hallucination-related adverse events reported with all formulations of guanfacine, across all ages, to assess whether this may be a safety concern.

- February 6, 2013: Addendum to the guanfacine ER pediatric postmarketing review presented details on each of the 124 cases regarding concomitant medications. DPV did not identify a consistent pattern between concomitant medications and adverse events reported in the case series.
- March 26, 2013: A **pharmacovigilance review of hallucinations and guanfacine IR and guanfacine ER** conducted as a follow-up to the December 2012 pediatric review, prior to the presentation to the PAC in September 2013. This review included FAERS reports received by the FDA from October 27, 1986 (U.S. approval date for guanfacine IR) to October 2, 2012. DPV identified 35 cases of hallucination-related adverse events reported with the use of guanfacine from FAERS and the literature search. The findings from this review supported the association of hallucinations with guanfacine use, across multiple indications. Thus, DPV recommended adding hallucinations to the Postmarketing Experience section of all guanfacine product labels.
 - As a result of this review, the labeling for both guanfacine products was subsequently updated. In July 2013, the statement “Hallucinations have been reported in pediatric patients receiving Tenex for treatment of attention-deficit hyperactivity disorder” was added to Pediatric Use under PRECAUTIONS for guanfacine IR. In August 2013, “hallucinations” was added to Section 6.2 Postmarketing Experience for guanfacine ER.

FDA presented this pediatric postmarketing review to the PAC in September 2013.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed descriptions and limitation of the databases are included in the **Appendix A**.

2.1.1 Data Sources Used

Sales Distribution Data

The QuintilesIMS, National Sales Perspectives™ database was used to obtain the nationally estimated number of units (packages) sold for guanfacine ER from manufacturers to all U.S. channels of distribution in 2016. The sales distribution data represent the amount of product sold from manufacturers to pharmacies and other settings of care; it does not reflect what is being sold to or administered to patients directly.

Outpatient Retail Settings

The IMS Health Total Patient Tracker (TPT) database was used to provide the nationally estimated number of patients who received a dispensed prescription for guanfacine ER from U.S. outpatient retail pharmacy settings stratified by patient age (0-5 years, 6-12 years, 13-17 years, 18 years and older) from July 2011 through June 2017, annually.

2.2 RESULTS

2.2.1 Determining Settings of Care

Sales data for guanfacine ER by the number of packages sold from manufacturers to all U.S. settings of distribution indicated that approximately 88% of sales were to outpatient retail pharmacies, 9% to non-retail settings and 4% to mail-order/specialty pharmacies during 2016.^a Accordingly, only U.S. outpatient retail pharmacy utilization patterns were examined for guanfacine ER. Data from mail-order/specialty pharmacies and non-retail settings, such as clinics and hospitals, were not included in this review.

2.2.2 Patient Data

Table 2.2.2 shows the nationally estimated number of patients who received guanfacine ER prescriptions dispensed from U.S. outpatient retail pharmacies, stratified by patient age from July 2011 through June 2017, annually.

^a Source: QuintilesIMS, National Sales Perspective (NSP) January 2016 – December 2016. Extracted July 2017. File: NSP 2017-818 Intuniv BPCA 9-28-2017.xlsx

Table 2.2.2. Nationally estimated number of patients who received prescriptions for guanfacine ER from U.S. outpatient retail pharmacies, stratified by patient age†, July 2011 through June 2017, annually.

	July 2011 - June 2012		July 2012 - June 2013		July 2013 - June 2014	
	Patients	Share(%)	Patients	Share(%)	Patients	Share(%)
Grand Total	452,558	100%	468,096	100%	464,224	100%
0-17 years	421,713	93%	437,661	93%	432,231	93%
0 - 5 years	21,749	4.8%	19,889	4.2%	16,872	3.6%
6-12 years	300,872	66.5%	311,230	66.5%	302,943	65.3%
13 - 17 years	118,857	26.3%	130,022	27.8%	136,583	29.4%
18 years and older	34,167	7.5%	34,168	7.3%	36,464	7.9%
Unknown Age	2	<0.2%	220	<0.2%	762	0.2%
	July 2014 - June 2015		July 2015 - June 2016		July 2016 - June 2017	
	Patients	Share(%)	Patients	Share(%)	Patients	Share(%)
Grand Total	479,367	100%	504,419	100%	542,941	100%
0-17 years	441,800	92%	454,683	90%	477,566	88.0%
0 - 5 years	13,400	2.8%	13,122	2.6%	14,169	2.6%
6-12 years	305,765	63.8%	309,752	61.4%	318,792	58.7%
13 - 17 years	146,335	30.5%	156,233	31.0%	170,783	31.5%
18 years and older	40,886	8.5%	51,364	10.2%	65,485	12.1%
Unknown Age	4,442	0.9%	7,489	1.5%	8,219	1.5%

Source: IMS Health, Total Patient Tracker™. July 2011 – June 2017.

Extracted August 2017. File: TPT 2017-818 guanfacine ER 8-14-2017 age xls; and TPT L 2017-818 guanfacine ER 8-14-2017 to tage 0-17 xls

† Summing across patient age bands is not advisable because this will result in overestimates of patient counts, patient age subtotals do not sum exactly (>100%) due to patients aging during the study period. Patients may be counted more than once in the individual age categories.

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	June 15, 2017
Time Period of Search	July 1, 2012* - May 31, 2017
Search Type	FBIS Quick Query
Product Terms	Product Name: Intuniv NDA: 022037
Search Parameters	All ages, all outcomes, worldwide

Abbreviation: FBIS = FAERS Business Intelligence Solution

* Guanfacine ER has been presented to the PAC previously. The most recently completed pediatric postmarketing review included FAERS reports through June 30, 2012.

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS Reports* From July 1, 2012 to May 31, 2017 with Guanfacine ER

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	25 (24)	5 (4)	0 (0)
Pediatrics (0 to <18 years)	370 (307)	231 (169 [‡])	3 (1)

* 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.

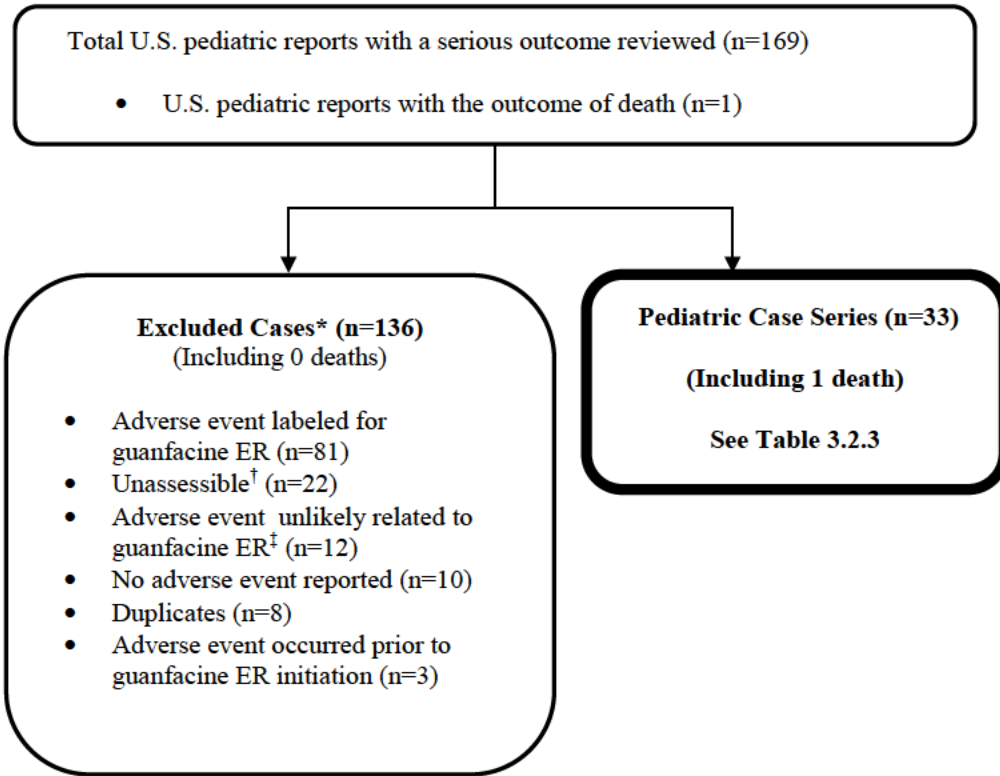
[‡] See **Figure 3.2.2**

3.2.2 Selection of Unlabeled, U.S, Serious Pediatric Cases in FAERS

We identified 169 U.S. pediatric reports of guanfacine ER reporting a serious outcome from July 1, 2012 to May 31, 2017 (see **Table 3.2.1**). Our pediatric case series included 34 cases, including one death.

Figure 3.2.2 presents the specific selection of cases to be summarized in **Sections 3.3 and 3.4**.

Figure 3.2.2 Selection of Unlabeled, Serious Pediatric Cases with Guanfacine ER



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

[†] Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

[‡] Adverse event unlikely related to guanfacine ER: For example, gynecomastia and hyperprolactinemia reported with risperidone, infection reported during guanfacine ER use, or adverse event resolved without treatment and the continuation of guanfacine ER.

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 Guanfacine ER

(N=33)		
Age	2- < 6 years	2
	6- <13 years	23
	13- < 18 years	8
Sex	Male	24
	Female	9

Table 3.2.3 Characteristics of Pediatric Case Series with Guanfacine ER

(N=33)		
Reported Reason for Use*	ADHD	22
	ADHD and ASD	2
	ADHD and anxiety	1
	Anxiety	1
	Disruptive behavior disorder	1
	“Impulsivity control”	1
	Tourette's	1
	Unknown	4
Serious Outcome [†]	Death	1
	Life-threatening	2
	Hospitalized	8
	Disability	1
	Other serious	27

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; ASD = autism spectrum disorder

* Not applicable in three cases reporting accidental exposure.

[†] 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.

In **Sections 3.3-3.4** below, the unlabeled adverse events for guanfacine ER are emphasized in *italics* and underline.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASE (N=1)

DPV identified one fatal pediatric case reported with guanfacine ER whose autopsy reported the cause of death was *portal and splenic vein thromboses*. This case did not provide evidence of a causal association with guanfacine ER. Therefore, no new safety signal was identified. The case is summarized below.

FAERS Case #8785400: A 15-year-old female was prescribed guanfacine ER and lisdexamfetamine for “abnormal” and “impulsive” behavior, as well as for disruptive behavior disorder. Additional medical history included mild intellectual delay, developmental delay, congenital hypoplasia of corpus callosum, migraine, Crohn’s disease, colitis, and obesity. The patient’s concomitant medication included propranolol for migraine. She had been on lisdexamfetamine for more than two years and guanfacine ER for approximately two months when she complained of abdominal pain for several days. She was taking lisdexamfetamine 50 mg daily and guanfacine ER 4 mg daily. She presented to the emergency department (ED) for evaluation of the abdominal pain. The patient was “severely anemic” (the hemoglobin count was not reported). After treatment with a blood transfusion, she was discharged home with instructions to follow-up with a

gastroenterologist. Later that day, the patient expired at home. The autopsy revealed that the “patient died of *portal and splenic vein thromboses*.” The reporting physician stated the thromboses were not related to the patient’s medications, but possibly due to a “transfusion reaction.”

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=32)

3.4.1 *Psychiatric Disorders (n=23)*

- **Self-injurious behavior, aggression (n=9):** Nine cases reported *aggression* (n=7), *self-injurious behavior* (n=1), or *both aggression and self-injurious behavior* (n=1). The two cases of *self-injurious behavior* did not report suicidal intent (a 9-year-old male bit his clothes and himself, and an 8-year old male placed his head outside or attempted to get out of a moving car). Six of the eight cases were confounded by the patient’s medical history (autism spectrum disorder, history of aggression). The seventh case is possibly related to the underlying ADHD, because aggression and other behavioral disturbances were reported following the drug dose omission of the patient’s ADHD medications (guanfacine ER and lisdexamfetamine). The eighth case reported the onset of *aggression* reported with generic guanfacine ER; the aggression resolved upon resumption of the brand product. The remaining case reported the onset of *aggression* in a 5-year-old male shortly after an increase in guanfacine ER dose from 1 mg to 2 mg daily (he had been on the 1 mg dose for one year). Guanfacine ER was prescribed for “impulsivity control” and no other medical history was reported. As a result, the guanfacine ER dose was decreased to 1 mg daily, and the aggression was diminishing but persistent at the time of reporting.
- **Suicidal ideation, suicide attempt, homicidal ideation (n=7):** Seven cases reported either *suicide attempt* (n=3), *suicidal ideation* (n=2), or *both suicidal and homicidal ideation* (n=2). The median age of the patients was 13 years old (range 9-13 years old). The reported reasons for guanfacine ER use were ADHD (n=6), or ADHD and anxiety (n=1). The time to onset of the suicidal behavior following initiation of treatment with guanfacine ER was: 2 weeks (n=1), 5 weeks (n=1), 5 months (n=1), >9 months (n=1), and >2 years (n=3).

Two cases reported a resolution of *suicidal ideation* after the discontinuation of guanfacine ER alone; however, both cases reported a medical history of anxiety. The third case reported a resolution of *suicidal attempt* after the discontinuation of three ADHD medications including guanfacine ER; the patient had been on guanfacine ER and the concomitant ADHD medications for more than three years. A summary of these three cases are provided below:

- A 10-year-old male experienced gradual changes (“more withdrawn, lethargic, depressed, and had bad thoughts”) after starting guanfacine ER for ADHD and anxiety. His concomitant medication included vitamin C. About five months after starting guanfacine ER, the patient had panic attacks, increased aggression, anger, suicidal ideation, and suicidal behavior. Guanfacine ER was discontinued by the patient’s mother, against the doctor's recommendations. The patient had immediate improvement, with complete recovery after a few months.
- A 13-year-old male with ADHD and general anxiety disorder experienced severe depression and suicidal ideation after being on guanfacine ER 3 mg daily for five weeks. His concomitant medications included lisdexamfetamine 70 mg daily and sertraline 125 mg (frequency unspecified). A psychiatric evaluation done prior to the initiation of guanfacine ER did not demonstrate such behavior. The reporter noted that the “event abated after use stopped” (without further details).
- A 12-year-old male with ADHD experienced suicide attempt, impulsive behavior, and anger after three to four years on guanfacine ER, lisdexamfetamine, and mixed amphetamine salts ER. The patient tried to harm himself, choke himself, and jump off a bridge. He was also described as “out of control, jumping, yelling and punching walls.” As a result, guanfacine ER and both concomitant medications were discontinued. About three weeks later, the patient was hospitalized with acute psychosis. The patient’s mother stated that the patient may be bipolar. The outcome of suicide attempt was reported as resolved; other adverse events were reported as ongoing.

The four remaining cases either reported a long latency in the time to onset of the suicidal behavior and/or were confounded by concomitant medications labeled for suicidal ideation (e.g. sertraline) or medical history (e.g. depression, oppositional defiant disorder, or anxiety). Two of the cases reported a suicide attempt by intentional overdose of 1) guanfacine ER in a 14-year-old female or 2) guanfacine ER and ibuprofen in a 13-year-old female; both patients recovered after treatment in the hospital. In addition, one of the four cases reported the suicidal and homicidal ideation resolved after the sertraline dose was increased and with the continuation of guanfacine.

Reviewer’s comment: These seven cases either reported a long latency in the time to onset of the suicidal behavior and/or were confounded by concomitant medications labeled for suicidal ideation or medical history. It is a challenge to assess the reported suicidal adverse events from the limited information provided

in postmarketing reports (potential missing psychiatric or social history as possible triggers). The high background rate of coexisting conditions with ADHD may potentially be risk factors for suicidal behaviors in this patient population. However, DPV will continue to monitor for unconfounded cases of suicidal ideation and behavior reported with guanfacine ER.

- **Paranoia (n=3):** The three cases of *paranoia* also reported hallucinations and all three cases reported a positive dechallenge. However, in one of the positive dechallenge cases, the role of guanfacine ER to the onset of paranoia (described as the patient “became paranoid and would have nothing to do with his grandfather who had always been his buddy”) is less likely; the onset of paranoia was reported after the patient had been on guanfacine ER and methylphenidate for more than three years.

Reviewer’s comment: Hallucinations is labeled for guanfacine ER in Section 6.2 Postmarketing Experience.

- **Tics (n=3):** Three cases reported *tics* while the patients were taking guanfacine ER. The cases were either confounded by a history of tics, tics were ongoing following the discontinuation of guanfacine ER (negative dechallenge), or the tics resolved with the continuation of guanfacine ER and decreased risperidone dose.
- **Withdrawal syndrome (n=1):** One case reported *withdrawal syndrome* in a 16-year-old male who had an abrupt discontinuation of guanfacine ER after being on guanfacine ER 2 mg twice daily (prescribing error) for two to three years. The withdrawal symptoms were reported by the patient’s mother as wanting to eat, fatigue, pain in his legs, and abdominal pain. The events were ongoing at the time of the report (about four days off guanfacine ER).

3.4.2 *Metabolism and Nutrition Disorders (n=2)*

Two cases reported *abnormal weight gain or weight increased*, while the patients were taking guanfacine ER. The first case, reported in the published literature³, described a 7-year-old male who experienced rapid weight gain after starting guanfacine ER 2 mg daily. Despite diet and physical exercise, the patient continued to have an *increased appetite* and increased food consumption. He gained 35 pounds in the 12-month period since the initiation of guanfacine ER (his baseline weight was 68 pounds). Therapy with guanfacine ER was continued and the event was ongoing. The second case reported an 8-year-old male who experienced an unintentional weight gain of 20-25 pounds, from a baseline of 75-80 pounds in the same year that guanfacine ER was started. The patient’s concomitant medication included mixed amphetamine salts. The patient had decreased appetite in the morning and at lunchtime, but he would be hungry from 3 pm to 10 pm. Other pertinent adverse events reported included *elevated cholesterol* (no laboratory values reported) and *gynecomastia* (described as “developed breasts”).

Reviewer's comment: Although guanfacine ER is labeled for "increased weight" in Section 6.1 Clinical Trials, the labeling also states that patients in the clinical trials had a mean increase in weight of 0.5 kg compared to those taking placebo. In the open-label studies where patients received guanfacine ER for at least 12 months, the patients on guanfacine ER gained an average of 8 kg in weight. Therefore, these cases reported an unexpected and significant weight gain while the patients were taking guanfacine ER. In the second case, there were no diagnostic evaluations to confirm gynecomastia; the event was reported as the development of breasts, which could possibly be related to the patient's weight gain.

3.4.3 **Miscellaneous (n=7)**

The remaining seven unlabeled adverse events with two or fewer cases are summarized here. Based on the limited number of reports received for each of these events, no conclusions can be made regarding an association between the reported adverse event and guanfacine ER.

Two cases reported pancreatitis while the patients were taking guanfacine ER. The first case reported the onset of pancreatitis in a 13-year-old male after being on guanfacine ER 1 mg daily for one week and the dose was titrated to 2 mg daily. The patient was not taking any concomitant medications but his medical history was not reported. The patient was seen in the ED; guanfacine ER was on hold and the event was ongoing at the time of the report. The second case reported the onset of pancreatitis on the second day of treatment with guanfacine ER 2 mg daily (not titrated from 1 mg) in a 7-year-old male. Guanfacine ER was discontinued. The patient was admitted to the pediatric intensive care unit and required parental nutrition. He had necrosis of a large part of the pancreas and developed pleural effusion secondary to the pancreatitis. At the time of the report, the event was resolving.

Reviewer's comment: Both cases demonstrated a possible role for guanfacine ER with a short time to onset of pancreatitis after the initiation of the medication. Therefore, DPV searched the FAERS database for guanfacine reports received through August 18, 2017, using the PTs: pancreatitis, acute pancreatitis, and pancreatitis necrotising. We identified eight additional cases of pancreatitis reported with guanfacine, including seven cases reported with guanfacine ER and one case reported with guanfacine IR. There were seven pediatric patients (≤ 17 years old) and one adult patient. The majority of the cases provided very limited information for assessment. We did not identify a safety signal for pancreatitis from the current FAERS cases. DPV will continue to monitor for cases of pancreatitis reported with guanfacine ER.

Two cases reported a drug dispensing error where the outpatient pharmacy dispensed paliperidone (Invega) 3 mg instead of the prescribed "Intuniv" 3 mg. The first case reported that a 10-year-old male took two doses of paliperidone and experienced headache and sweating. The second case reported that a 7-year-old female took three doses of paliperidone and experienced an acute dystonic reaction and anticholinergic effects. Both patients were treated in the ED and the adverse events were ongoing at the time of the report.

Reviewer's comment: In September 2014, the Division of Medication Error Prevention and Analysis (DMEPA) conducted a postmarket medication memorandum and reviewed the cases of wrong drug errors between the product names: Intuniv and Invega. At the time of the review, DMEPA identified five cases (including one of the cases identified in this review) of medication errors involving the name confusion. The name pair was added to Institute for Safe Medication Practices (ISMP) List of Confused Drug Names in May 2012. DMEPA determined there are sufficient differences between the container labels to minimize the risk for selection error. In this memo, DMEPA recommended continuing to monitor for wrong drug errors between the product names: Invega and Intuniv. DPV, along with DMEPA, will continue to monitor for cases of medication error involving name confusion reported with guanfacine ER.

The remaining three cases reported brain neoplasm/brain edema, blepharospasm, or lichenoid drug eruptions. A non-cancerous brain tumor and fluid around the brain was detected in an asymptomatic 11-year-old female undergoing an investigational study for Tourette syndrome; the tumor almost five years after the initiation of guanfacine ER. Treatment with guanfacine ER continued in this patient. Another case reported the onset of blepharospasm (described as an “eye tic/heavy blink”) causing visual impairment in an 11-year-old male on the sixth day of treatment with guanfacine ER 1 mg daily for anxiety; the event was ongoing for more than one week after the discontinuation of guanfacine ER. The remaining case was a literature report⁴ of lichenoid drug eruptions in a 5-year-old male after being on guanfacine 1.5 mg daily for three months. Two weeks after the discontinuation of guanfacine, the pruritus improved. Further improvement was seen after treatment with topical hydrocortisone ointment for six weeks. Three months after stopping guanfacine, there was no active lesion or pruritus.

Reviewer's comment: It is likely that the case of lichenoid drug eruptions pertained to the guanfacine IR formulation based on the reported guanfacine dose. DPV searched the FAERS database for guanfacine reports received through August 30, 2017 and did not identify any additional cases of lichenoid drug eruption.

4 DISCUSSION

DPV identified 33 U.S. pediatric cases (patients 0-17 years old) with serious, unlabeled adverse events reported with guanfacine ER from July 1, 2012 to May 31, 2017 in the FAERS database. There were no new pediatric safety signals identified, no apparent increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with guanfacine ER. We identified one fatal pediatric case reported with guanfacine ER, which did not provide evidence of a causal association with guanfacine ER.

Of the 32 non-fatal, serious cases, the most frequently reported adverse events were psychiatric adverse events such as aggression and suicidal ideation or behavior. However, some cases were confounded by the patient's medical history or concomitant medications, or reported a long time to onset of the event since the initiation of guanfacine ER. In the general population, about half

of the children with ADHD may have coexisting conditions such as behavior or conduct problems, anxiety disorders, depression, and difficult peer relationships.⁵ Therefore, in some of the FAERS cases, the aggression or suicidal ideation or behavior may possibly be disease-related, either with the underlying ADHD or its comorbidities.⁶ Additionally, it is a challenge to perform a causality assessment of suicide-related events and guanfacine ER from the postmarketing cases, because of the comorbid conditions, limited information regarding the patients' psychiatric history or social stressors, and the prevalence of youth suicides. According to the Centers for Disease Control and Prevention, suicide was the third leading cause of death for youths aged 10 to 14 years old and the second leading cause of death for youths aged 15 to 24 years old in the U.S. in 2015 (see **Appendix D** for the top ten leading causes of death in 2015).⁷

In order to capture pediatric use of guanfacine ER and to provide context for the adverse event reports submitted to the FAERS database, drug utilization patterns were assessed. Pediatric patients 0-17 years old accounted for approximately 90% of the total patients annually and utilization increased slightly over the study period. The majority of pediatric patients who received a dispensed prescription for guanfacine ER were 6 years of age or older. Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that guanfacine ER was distributed primarily to the outpatient setting based on the QuintilesIMS, National Sales Perspectives™ database. Accordingly this review was focused on outpatient retail pharmacy utilization. These data are based on dispensed prescription claims, and do not undergo chart validation for accuracy of abstracted information from prescription level data. Furthermore, our analyses were only focused on the outpatient retail setting and might not apply to other settings of care such as inpatient setting and clinics where guanfacine ER may be used.

5 CONCLUSION

Pediatric utilization of guanfacine ER increased over the examined time period and the majority of pediatric use occurred in patients 6 years or older. The majority of the U.S. FAERS reports with serious, unlabeled adverse events in the time period reviewed were pediatric patients 6-12 years old, which is consistent with the drug utilization data. There is no evidence from these data that there are pediatric safety concerns with guanfacine ER at this time.

6 RECOMMENDATIONS

DPV recommends no labeling changes at this time, and will continue to monitor adverse events, including suicidal ideation and behavior, pancreatitis, and medication error involving name confusion, associated with the use of guanfacine ER.

7 REFERENCES

1. Intuniv (guanfacine) extended-release tablets [package insert]. Lexington, MA: Shire US, Inc.; July 2016.
2. Zhang J. Cross Discipline Team Leader Review NDA 22037/S-010. Intuniv (guanfacine extended-release tablet), Indication: Attention deficit/hyperactivity disorder in children and adolescents aged 6 to 17 years old. November 3, 2014.
3. Siddiqi SU, Giordano BP, Dedlow ER. Excessive Weight Gain With Guanfacine: 16.1 Kilograms in 12 Months. *Clin Pediatr (Phila)*. 2015 Jul;54(8):793-5.
4. Romanelli M, Rhodes A. Guanfacine-induced lichenoid drug eruption in a child with autism and attention deficit hyperactivity disorder. *Pediatr Dermatol*. 2014 Sep-Oct;31(5):614-5.
5. Centers for Disease Control and Prevention – Attention-Deficit/Hyperactivity Disorder (ADHD). <http://www.cdc.gov/ncbddd/adhd/conditions.html>. Accessed January 10, 2016.
6. Patel BD, Barzman DH. Pharmacology and pharmacogenetics of pediatric ADHD with associated aggression: a review. *Psychiatr. Q*. 2013; 84: 407-415.
7. Centers for Disease Control and Prevention – Injury Prevention & Control: Data & Statistics (WISQARS™). http://www.cdc.gov/injury/wisqars/leading_causes_death.html. Accessed October 4, 2017.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS

IMS Health, National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS 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.

IMS Health, 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 Vector One® 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. Vector One® receives over 2.1 billion prescription claims per year.

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.

8.3

APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH GUANFACINE ER (N=33)

FAERS Case #	Version #	Manufacturer Control #
8719456	3	US-SHIRE-ALL1-2012-03753
8756276	1	(blank)
8785400	3	US-SHIRE-ALL1-2012-04323
8835525	1	US-SHIRE-ALL1-2012-04735
8862793	1	US-JNJFOC-20121007619
8901938	1	(blank)
8926987	2	US-SHIRE-ALL1-2012-05656
9069570	1	US-SHIRE-ALL1-2013-00868
9097683	1	US-SHIRE-ALL1-2013-00760
9336612	1	US-SHIRE-ALL1-2013-02841
9350290	2	US-SHIRE-ALL1-2013-03880
9443608	1	US-SHIRE-ALL1-2013-05201
10143200	1	(blank)
10578505	1	ALL1-2014-00328
10678211	1	US-SHIRE-US201409257
10709500	1	(blank)
10884396	1	US-SHIRE-US201501561
10930084	1	(blank)
10934888	1	US-SHIRE-US201502220
11067965	1	(blank)
11292271	2	US-SHIRE-US201508124
11422784	1	US-SHIRE-US201510553
11810029	1	(blank)
11819237	3	US-JNJFOC-20151126087
12140953	1	(blank)
12206938	1	(blank)
12317902	1	US-SHIRE-US201604770
12431769	1	(blank)
13141003	1	US-SHIRE-US201700666
13268637	1	(blank)
13373089	1	(blank)
13564956	1	US-SHIRE-US201711000
13596390	1	US-SHIRE-US201711345

APPENDIX D. TEN LEADING CAUSES OF DEATH IN 2015 FOR AGES 0-24 YEARS OLD⁷

**10 Leading Causes of Death, United States
2015, All Races, Both Sexes**

Rank	Age Groups					
	<1	1-4	5-9	10-14	15-19	20-24
1	Congenital Anomalies 4,825	Unintentional Injury 1,235	Unintentional Injury 755	Unintentional Injury 763	Unintentional Injury 3,919	Unintentional Injury 8,595
2	Short Gestation 4,084	Congenital Anomalies 435	Malignant Neoplasms 437	Malignant Neoplasms 428	Suicide 2,061	Suicide 3,430
3	SIDS 1,568	Homicide 369	Congenital Anomalies 181	Suicide 409	Homicide 1,587	Homicide 3,146
4	Maternal Pregnancy Comp. 1,522	Malignant Neoplasms 354	Homicide 140	Homicide 158	Malignant Neoplasms 583	Malignant Neoplasms 886
5	Unintentional Injury 1,291	Heart Disease 147	Heart Disease 85	Congenital Anomalies 156	Heart Disease 306	Heart Disease 691
6	Placenta Cord Membranes 910	Influenza & Pneumonia 88	Chronic Low. Respiratory Disease 80	Heart Disease 125	Congenital Anomalies 195	Congenital Anomalies 191
7	Bacterial Sepsis 599	Septicemia 54	Influenza & Pneumonia 44	Chronic Low. Respiratory Disease 93	Influenza & Pneumonia 72	Diabetes Mellitus 144
8	Respiratory Distress 462	Perinatal Period 50	Cerebro-vascular 42	Cerebro-vascular 42	Chronic Low. Respiratory Disease 63	Chronic Low. Respiratory Disease 139
9	Circulatory System Disease 428	Cerebro-vascular 42	Benign Neoplasms 39	Influenza & Pneumonia 39	Cerebro-vascular 61	Complicated Pregnancy 120
10	Neonatal Hemorrhage 406	Chronic Low. Respiratory Disease 40	Septicemia 31	Two Tied 33	Diabetes Mellitus 52	Influenza & Pneumonia 112

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARMEN CHENG
12/01/2017

SHEKHAR H MEHTA
12/01/2017

RAJDEEP K GILL
12/05/2017

VICKY C CHAN
12/05/2017

GRACE CHAI
12/05/2017

CINDY M KORTEPETER
12/05/2017