Pediatric Focused Safety Review
Intuniv® (guanfacine ER)
Pediatric Advisory Committee Meeting
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Outline

- **Background Information**
- Pediatric Studies
- Labeling Changes
- Drug Use Trends
- Safety
- Summary

Background Drug Information
Intuniv® (guanfacine ER)

- **Drug:** Intuniv® (guanfacine ER)
- **Formulation:** extended-release tablets
- **Sponsor:** Shire
- **Original Market Approval:** September 2, 2009
- **Therapeutic Category:** central alpha$_{2A}$-adrenergic receptor agonist
- An immediate-release guanfacine for management of hypertension was approved on October 27, 1986.

Background Drug Information, continued

Intuniv® (guanfacine ER)

Indication

For the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications

Background Drug Information, continued

Intuniv® (guanfacine ER)

Contraindications

History of a hypersensitivity reaction to Intuniv® or its inactive ingredients, or other products containing guanfacine

Warnings and Precautions

- Hypotension, Bradycardia and Syncope: monitor heart rate and blood pressure prior to and during therapy.
- Sedation and Somnolence
- Cardiac Conduction Abnormalities: titrate Intuniv® slowly and monitor vital signs frequently in patients with cardiac conduction abnormalities or patients concomitantly treated with other sympatholytic drugs.
- Rebound Hypertension: taper dose when withdrawing medication and monitor blood pressure and heart rate.

Background Drug Information, continued
Intuniv® (guanfacine ER)

Previous PAC Presentations

May 2011 – review of FAERS reports from September 2, 2009 to September 30, 2010. No new safety concerns identified.

September 2013 – Review of FAERS reports from October 1, 2010 to June 30, 2012. Hallucinations was identified as a safety concern. An additional review of FAERS reports for immediate-release and extended-release guanfacine from October 1986 to October 2012 and a literature search was performed. Thirty-five cases of hallucination-related adverse events were found. Hallucination was added as an adverse event to labeling in 2013.

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Pediatric Studies
Intuniv® (guanfacine ER)

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 years who met DSM-IV® criteria for ADHD.

Safety and efficacy of Intuniv® in pediatric patients less than 6 years of age have not been established.

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Pediatric Labeling Changes
Intuniv® (guanfacine ER)

November 19, 2014 – new weight-based dosing regimen was added.

Table 1: Recommended Target Dose Range for Therapy with INTUNIV®	
Weight	**Target dose range (0.05 - 0.12 mg/kg/day)**
25-33.9 kg	2-3 mg/day
34-41.4 kg	2-4 mg/day
41.5-49.4 kg	3-5 mg/day
49.5-58.4 kg	3-6 mg/day
58.5-91 kg	4-7 mg/day
>91 kg	5-7 mg/day
Doses above 4 mg/day have not been evaluated in children (ages 6-12 years) and doses above 7 mg/day have not been evaluated in adolescents (ages 13-17 years)	

Pediatric Labeling Changes, continued
Intuniv® (guanfacine ER)

March 18, 2015 – information on maintenance treatment was added.

2.4 Maintenance Treatment

- Pharmacological treatment of ADHD may be needed for extended periods. Healthcare providers should periodically re-evaluate the long-term use of INTUNIV®, and adjust weight-based dosage as needed. The majority of children and adolescents reach optimal doses in the 0.05-0.12 mg/kg/day range. Doses above 4 mg/day have not been evaluated in children (ages 6-12 years) and above 7 mg/day have not been evaluated in adolescents (ages 13-17 years)

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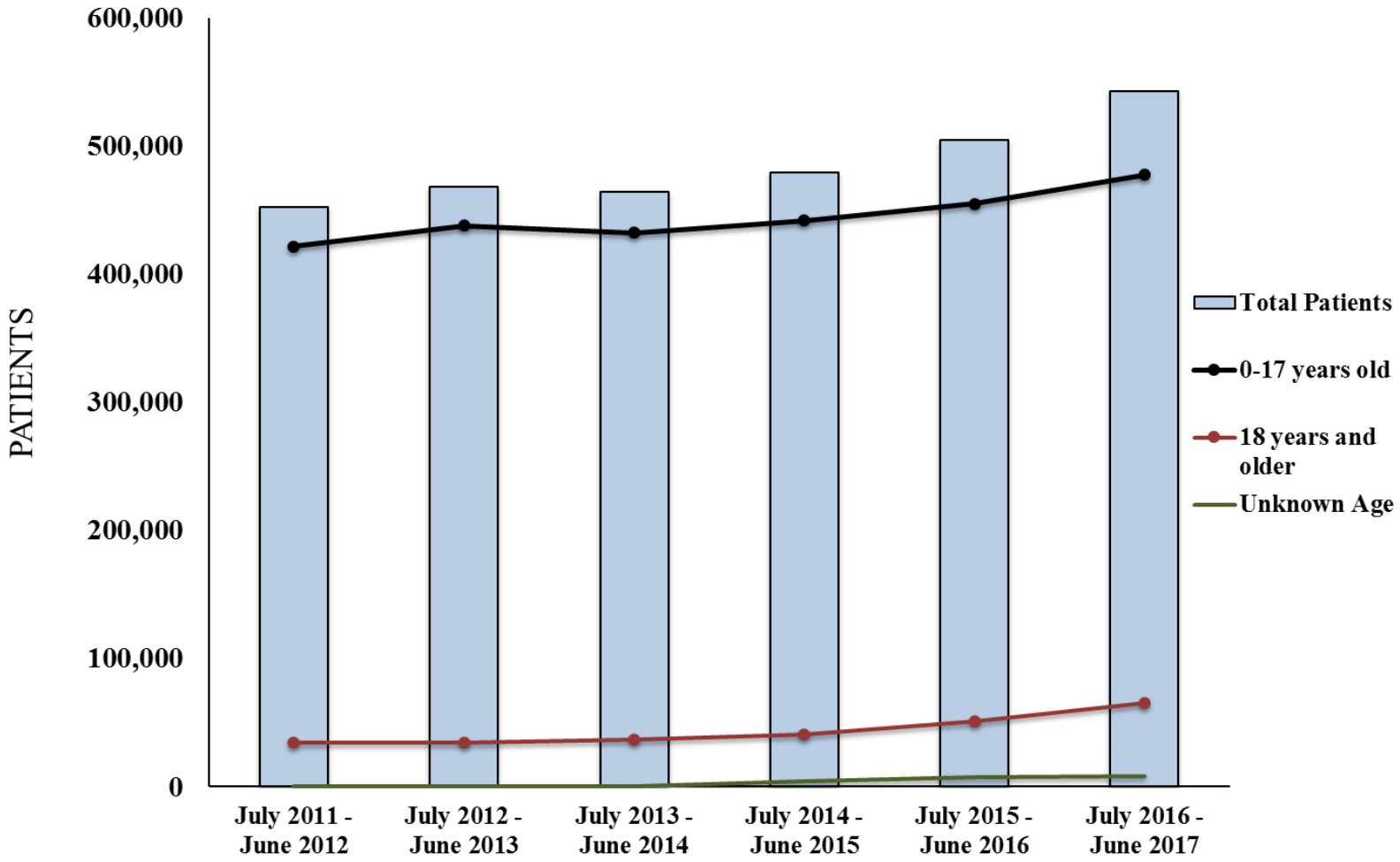
Nationally estimated number of patients* who received prescriptions for guanfacine ER from U.S. outpatient retail pharmacies, stratified by patient age (0-17 years, 18 years and older), July 2011- June 2017, annually**



Source:IQVIA, Total Patient Tracker™. July 2011 – June 2017.
Extracted June 2017. File: TPT L 2017-818 guanfacine ER 8-14-2017.xlsx
* Summing across patient age bands is not done 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

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FDA Adverse Event Reporting System (FAERS) Reports

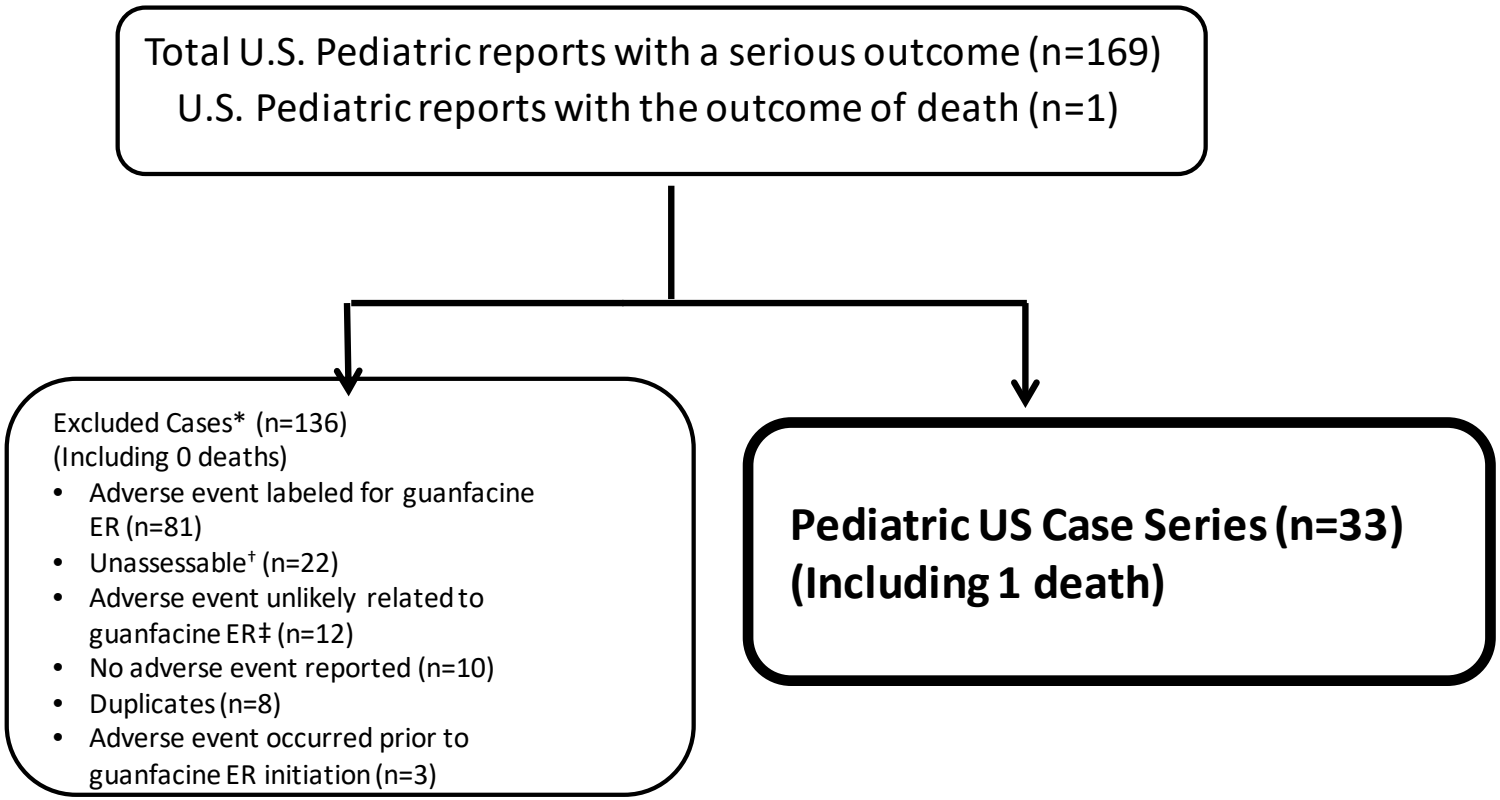
Total US Adult and Pediatric FAERS Reports* From July 1, 2012 to May 31, 2017 with Guanfacine ER

	All reports (US)	Serious† (US)	Deaths (US)
Adults (≥ 18 yrs.)	25 (24)	5 (4)	0 (0)
Pediatrics (0- <18 yrs.)	**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.

Selection of Pediatric FAERS Cases guanfacine ER



*These 136 reports were reviewed and excluded from the case series.
†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.

Fatal case guanfacine ER (n=1)

A 15-year-old female prescribed guanfacine ER (4 mg/day) and lisdexamfetamine (50 mg/day for > 2 years) for "abnormal" and "impulsive" behavior and disruptive behavior disorder died at home from complications of portal and splenic vein thromboses. Past medical history includes intellectual and developmental delay, congenital hypoplasia of corpus callosum, migraine, Crohn's disease, colitis, and obesity. Concomitant medication included propranolol. She presented to the emergency department (ED) for evaluation of the abdominal pain. She was 'severely anemic' (value not reported). She was transfused and discharged to home with instructions for medical follow-up; however, she died later that day.

The reporting physician stated the thromboses were not related to the patient's medications, but possibly due to a "transfusion reaction."

This case did not provide evidence of a causal association with guanfacine ER.

Unlabeled events are underlined

Serious Non-Fatal Unlabeled Adverse Events guanfacine ER (n=32)

Psychiatric Disorders (n=23)

Aggression and Self-injurious behavior (n=9)

- confounded by patient's medical history (autism spectrum disorder, history of aggression) (n=6)
- occurred after 1 missed dose of guanfacine and lisdexamfetamine (n=1)
- reported after use of generic guanfacine, resolved upon resumption of brand name (n=1)
- aggression after increase of guanfacine dose from 1 to 2 mg, diminished after decreasing dose to 1 mg (n=1)

Unlabeled events are underlined

Serious Non-Fatal Unlabeled Adverse Events guanfacine ER (n=32)

Psychiatric Disorders (n=23), continued

Suicidal ideation, suicide attempt, homicidal ideation (n=7)

- Cases reported either a long latency to onset from start of guanfacine and/or were confounded by concomitant medications or medical history.

Background Information on Suicide in Elementary School-Aged Children and Early Adolescents*

- 0.17 per 100,000 persons in youth between the ages of 5 and 11 years
- 5.18 per 100,000 among adolescents aged 12 to 17 years

*Sheftall AH, Asti L, Horowitz LM, et al. Suicide in Elementary School-Aged Children and Early Adolescents. Pediatrics.2016;138(4):e20160436

Unlabeled events are underlined

Serious Non-Fatal Unlabeled Adverse Events guanfacine ER (n=32)

Psychiatric Disorders (n=23), continued

Paranoia (n=3)

- Also reported hallucinations.
- All had positive dechallenge.

Tics (n=3)

- Confounded by history of tics, continued after discontinuation of guanfacine or resolved while on guanfacine with a decrease in risperidone dose.

Withdrawal syndrome (n=1)

- Reported wanting to eat, fatigue, pain in his legs and abdomen after discontinuing guanfacine.

Unlabeled events are underlined

Serious Non-Fatal Unlabeled Adverse Events guanfacine ER (n=32)

Metabolism and Nutrition Disorders (n=2)

Abnormal weight gain/ weight increased (n=2)

Miscellaneous (n=7)

Pancreatitis (n=2)

Drug dispensing error (n=2)

– Invega® (paliperidone) dispensed instead of the prescribed Intuniv®

Brain neoplasm/brain edema (n=1)

Blepharospasm (n=1)

Lichenoid drug eruptions (n=1)

Unlabeled events are underlined

Summary of Safety Review
Intuniv® (guanfacine ER)

- This concludes the pediatric focused safety review of FAERS reports.
- No new safety signals were identified.
- FDA recommends continuing routine, ongoing post-marketing safety monitoring, including:
  - monitoring for suicidal ideation and behavior
  - pancreatitis
  - medication error involving name confusion
- Does the committee concur?

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