Pediatric Focused Safety Review: INTUNIV®
(guanfacine hydrochloride XR)
Pediatric Advisory Committee Meeting
May 16th, 2011

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Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Outline

• Background Information
• Pediatric Studies
• Pediatric Labeling Changes
• Additional Relevant Safety Labeling
• Drug Use Trends
• Adverse Events (including prior OSE reviews)
• Summary
Background Drug Information

• **Drug:** INTUNIV® (guanfacine hydrochloride)

• **Formulation:** extended release tablets: 1, 2, 3 and 4 mg

• **Indication:**
  - Treatment of ADHD as monotherapy and as adjunctive treatment to stimulant medications in children 6-17 years

  **Note:**
  - Efficacy beyond 9 weeks and safety beyond 2 years of treatment have not been established (6 years and older)
  - Safety and efficacy not established less than 6 years of age

• **Therapeutic Category:** selective alpha\textsubscript{2A}-adrenergic receptor agonist. Not a CNS stimulant. Mechanism of action in ADHD unknown

• **Sponsor:** Shire Pharmaceuticals, Inc.
Background Drug Information (continued)

INTUNIV® (guanfacine XR)

• Tenex; NDA 10-032
  – Original Market Approval: October 27, 1986
  – Anti-hypertensive agent
  – 12 years and older

• INTUNIV®; NDA 22-237
  – Original Market Approval: Sept 2, 2009
  – Treatment of ADHD 6-17 years (monotherapy)
  – Feb 25, 2011 Adjunctive treatment of ADHD with stimulant medications (6-17 years of age)
Background Drug Information (continued)  
INTUNIV® (guanfacine XR)

- PREA triggered on Sept 2009 with approval of new indication, dosage form and dosing regimen and additional studies were required:
  - Long-term maintenance safety and efficacy in children 6-17 years
  - Efficacy and safety in adolescent patients 12-17 years
  - Efficacy and safety as adjunctive therapy with psychostimulants in children 6-17 years (PREA requirement fulfilled, per approval Feb 2011)
INTUNIV® (guanfacine XR) Pediatric Studies
Children 6-17 years with ADHD
Monotherapy

Fixed dose, double-blind placebo-controlled trials

– Study 1 evaluated 2, 3, and 4 mg given once daily for 8 weeks (n=345)

– Study 2 evaluated 1, 2, 3, and 4 mg dosed once daily for 9 weeks (n=324)

Patients could be titrated in increments of up to 1 mg/week
INTUNIV® (guanfacine XR) Pediatric Studies
Children 6-17 years with ADHD
Monotherapy (continued)

• Mean reductions in ADHD-RS scores at endpoint were statistically significantly greater for INTUNIV® compared to placebo in both studies for all dose levels

• Subgroup analyses performed: gender and ages 6-12 versus 13-17 years and gender
  – No differential response based on gender
  – Treatment effect observed in ages 6-12 years; limited number (25%) aged 13-17 years: dosing may have been suboptimal based on exposure
INTUNIV® (guanfacine XR): Pediatric Studies
Children 6-17 years with ADHD
Adjunctive therapy

Study 3: Flexible-dose, double-blind, placebo-controlled dose optimization study

- Study 3 evaluated 1, 2, 3 and 4 mg as adjunctive therapy for ADHD patients with a sub-optimal response to stimulants (n=455)
- Patients received 1 mg guanfacine XR and were titrated over 5 weeks to maximum of 4 mg
- Maintained on stable dose for 3 weeks before tapering
- Allowable psychostimulants: Adderall XR®, Vyvanse®, Concerta®, Focalin XR®, Ritalin LA®, Metadate CD® or FDA-approved generics
INTUNIV® (guanfacine XR): Pediatric Studies
Children 6-17 years with ADHD Adjunctive therapy (continued)

- Mean reductions in ADHD-RS scores at endpoint were statistically significantly greater for INTUNIV® in combination with a psychostimulant compared to placebo and psychostimulant

- Nearly 64% of patients reached optimal doses in the 0.05-0.12 mg/kg/day range

Labeling updated February 2011 to include adjunctive therapy indication
INTUNIV® (guanfacine XR)
Relevant Safety Labeling

SECTION 5: WARNINGS AND PRECAUTIONS:

• 5.1 Hypotension, Bradycardia, and Syncope
  – Dose dependent and usually asymptomatic; 7% hypotension in the INTUNIV® group in the pediatric studies compared to 3% placebo

• 5.2 Sedation and Somnolence
  – 38% patients taking INTUNIV® versus 12% for placebo (monotherapy)
  – 18% patients taking INTUNIV® versus 7% for placebo (adjunctive)

• 5.3 Other Guanfacine containing products
  – Avoid guanfacine-containing products such as Tenex
Outpatient Utilization Data (all ages): guanfacine

Source: SDI Vector One®: National and Total Patient Tracker. Extracted Nov 2010

Sept 2009 to Sept 2010

- 2 million guanfacine prescriptions dispensed
  - 67% generic guanfacine
  - 33% INTUNIV® (guanfacine XR)

- 476,000 projected unique patients received a dispensed prescription for guanfacine
Outpatient Utilization Data (all ages):
INTUNIV® (guanfacine XR)
Source: SDI Vector One®: National and Total Patient Tracker. Extracted Nov 2010
Sept 2009 to Sept 2010

• 676,000 Intuniv® prescriptions dispensed:
  – 65% (436,000 prescriptions) patients aged 6-12 years
  – 24% (164,000 prescriptions) patients aged 13-17 years
  – 5% (30,000 prescriptions) patients aged 0-5 years

• 208,000 projected unique patients received a dispensed prescription for Intuniv®
  – 63% (132,000 patients) aged 6-12 years
  – 25% (53,000 patients) aged 13-17 years
  – 5% (11,000 patients) aged 0-5 years
Total number of dispensed prescriptions for brand INTUNIV® stratified by age through U.S. outpatient retail pharmacies, Sept 2009-Sept 2010

Source: SDI: Vector One®: National. Extracted 11-10. Files: VONA 2010-2089 Guanfacine Products TRx by Age 11-8-10.xls
Outpatient Utilization Data: INTUNIV® (guanfacine XR) Sept 2009 to Sept 2010

- Top Prescribing Specialties:
  Source: SDI Vector One®: National. Extracted Nov 2010
  - Psychiatry (49%)
  - Pediatrics (24%)
  - Nurse Practitioners (6%)

- Top Diagnosis Code:
  SDI Physician Drug and Diagnosis Audit. Extracted Nov 2010
  “Attention Deficit Disorder”
Previous OSE Post-Marketing Safety Reviews for guanfacine IR

• June 12, 2000: Update of use and safety in pediatric and adolescent populations with ADHD; most frequent AEs in pediatric patients: CNS disorders (convulsions, sedation), psychiatric disorders (mania), cardiac disorders (bradycardia) and injury & poisoning

• Aug 1, 2000: Update of cases reporting sudden death or serious cardiovascular events with concomitant use of guanfacine and psychostimulant; no serious adverse cardiac events or death associated with combination
Previous OSE Post-Marketing Safety Reviews for guanfacine IR (continued)

- April 9, 2001: Review of mania and aggressive behavior; Labeling for guanfacine IR updated (postmarketing AEs)
- June 6, 2007: Review in response to the pending guanfacine ADHD NDA; no new signals for significant AEs identified, confirmed syncope signal
# Crude Counts for Adverse Events

**INTUNIV® (guanfacine XR)**

**September 2, 2009 to September 30 2010**

<table>
<thead>
<tr>
<th></th>
<th>All reports (US)²</th>
<th>Serious³ (US)</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 yrs.)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pediatrics (0-16 yrs.)</td>
<td>39 (38)</td>
<td>35 (34)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown Age (Null values)</td>
<td>37 (36)</td>
<td>32 (31)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>All Ages</td>
<td><strong>79 (77)</strong></td>
<td><strong>70 (68)</strong></td>
<td><strong>3 (3)</strong></td>
</tr>
</tbody>
</table>

¹ May include duplicates  
² US counts in parentheses  
³ Serious adverse drug experiences per regulatory definition (CFR 3414.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.
Total Crude Count AEs* since INTUNIV® Approval (Sept. 2, 2009 – Sept. 30, 2010)

Total crude count reports: all ages (n=79)

Duplicate reports (n=6)

Unduplicated reports (n=73)

Excluded Reports (n=26)
  - Adult patients (n=5)
  - Non-serious (n=9)
  - Null age (n=12)

Pediatric serious cases (n=47, 2 fatalities)

*Adverse Event Reports
Characteristics of Serious Pediatric Cases
INTUNIV® (n=47)

- Gender
  - Male (n=34)
  - Female (n=13)

- Age
  - 2-5 years (n=4)
  - 6-11 years (n=28)
  - 12-16 years (n=15)

- Dosing
  - Mean: 2.5 mg; Median: 2 mg
  - Range: 1 mg to 21 mg
Fatal Adverse Events (2 cases)  
INTUNIV® (guanfacine XR)

9 year old boy experienced sudden death 6 days after starting guanfacine XR 1 mg for unspecified reason

- Concomitant medications: mometasone, lamotrigine, topiramate, lisdexamfetamine and quetiapine
- Missed 3 days of all his medications and found deceased prone in bed
- Post mortem toxicology: seizure medications were subtherapeutic
- Autopsy reported cause of death as sudden unexpected death in epilepsy (SUDEP)
Serious Fatal Adverse Events cont’d
INTUNIV® (guanfacine XR)
(2 cases)

16 year old male took unknown dose of guanfacine XR for unspecified indication

- Found unresponsive and pronounced dead at the scene
- Patients blood was positive for morphine, dextromethorphan, nordextromethorphan, carisoprodol, meprobamate, and olanzapine
  - Unknown if guanfacine present in the patients’ blood
- Medical examiner reported cause of death as accidental acute “poly-drug toxicity” involving the combined effects of dextromethorphan and morphine
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Total Cases (n=45)

- Syncope (n=17)
- Cardiovascular, non-syncopal (n=7)
- Neurologic (n=10)
- Psychiatric (n=9)
- Miscellaneous (n=2)

Note: 6 cases also reported Gastrointestinal AEs
*a case may have more than one event
Serious Non-Fatal Labeled Adverse Events
INTUNIV® (guanfacine XR)
Syncope (17 cases)

• Types of events:
  – syncope (n=13) - pre-syncope and syncope (n=1)
  – pre-syncope (n=2) - depressed level of consciousness (n=1)

• Gender: 11 males and 6 females

• Age: 7-15 years; median age 11 years

• Dosing: 1-4 mg; median dose 2 mg.
Serious Non-Fatal Labeled Adverse Events
INTUNIV® (guanfacine XR)
Syncope (17 cases)
(continued)

• 12/17 cases reported time of onset
  – Range 1-28 days; median time to onset 9 days

• 4 cases reported concomitant medications also labeled for syncope (methylphenidate, escitalopram, fluticasone/salmeterol, trazodone, and clonidine)

Labeling: Warnings & Precautions

5.1 Hypotension, Bradycardia and Syncope
Serious Non-Fatal Labeled Adverse Events
INTUNIV® (guanfacine XR)
Cardiovascular Events, Non-syncope (7 cases)

- Types of events:
  - heart rate decreased (n=2)
  - bradycardia and hypotension (n=2)
  - bradycardia and arrhythmia (n=1)
  - QT prolongation (n=1)
  - hypotension (n=1)

- Gender: 7 males
- Age: 4-15 years; median age of 8 years
- Dose: 1-4 mg; median 2 mg
Serious Non-Fatal Labeled Adverse Events
INTUNIV® (guanfacine XR)
Cardiovascular Events, Non-syncope (7 cases) (continued)

- Potential contributing factors:
  - Congenital QTc prolongation (n=1)
  - Concomitant medication: divalproex sodium (n=1), which is labeled for bradycardia

**Labeling:**

5.1 Hypotension, Bradycardia and Syncope (Warnings & Precautions)

6.1 Effects on Heart Rate and QT interval (Clinical Trial Experience)
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Neurologic Events (10 cases)

• Gender: 7 males and 3 females
• Age: 4-14 years; median age 7 years
• Dose: 1-3 mg daily; median 1.5 mg
• Time to onset of event: 1-21 days; median 4.5 days
• Reasons for use: ADHD (n=6), tic (n=1), impulse control (n=1) and unknown (n=2)

* a case may have more than one adverse event
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Neurologic Events (10 cases, 13 events)

Labeled (n=7)
• convulsion (n=3)
• somnolence/hypersomnia (n=3)
• headache (n=1)

Unlabeled (n=6)
• unresponsive to stimuli (n=3)
• muscle twitching (n=2)
• dyskinesia (n=1)

Other factors possibly contributed
e.g. seizure disorder, cerebral palsy, incorrect dosing

Labeling
5.2 Sedation and Somnolence (Warnings and Precautions)
6 Discontinuation due to adverse events includes headache
(Clinical trial Experience)
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Psychiatric Events (9 cases)

- Gender: 6 males and 3 females
- Age: 5-15 years; median age 11 years
- Dose: 1-21 mg daily; median 2 mg
- Time to onset of event: 1-40 days; median 22 days
- Reasons for use: ADHD (n=8) and hyperactivity, aggression, and opposition (n=1)

*a case may have more than one adverse event*
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Psychiatric Events: Labeled

- Agitation (n=4)
- Anxiety (n=1)
- Irritability (n=1)
- Nightmare and Sleep Terror (n=1)

Labeling:

6.1 Clinical trial experience
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Psychiatric Events: Unlabeled

• Aggression (n=2)
  – possible contributing factors: use of medication labeled for aggression (lisdexamfetamine and methylphenidate)

• Intentional overdose (n=2)
  – 15 year old male an hour after administering first dose, reported drug was ineffective and took remaining 21 mg. He became anxious, agitated, angry; seen in ER and released. Stable on 4 mg
  – 15 year old female took a “handful” of guanfacine XR; experienced nausea, dizziness and 5 fainting episodes; CT, EEG, unspecified blood tests negative. Treated with hospitalization and IV fluids
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Psychiatric Events: Unlabeled (continued)

• **Suicidal and homicidal ideation (n=1)**
  – 8 year old girl who after 31 days on 1 mg, increased to 2 mg and threatened to kill herself and others
  – The event resolved without intervention

• **Suicidal and self-injurious ideation (n=1)**
  – 12 year old girl with ADHD participating in placebo-controlled dose optimization study. Upset after loss of cell phone and Facebook privileges
  – Study drug titrated down, patient withdrawn from study and adverse event resolved (unclear which treatment group)
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Psychiatric Events: Unlabeled (continued)

• Visual hallucination (n=1)
  – 5 year old female treated for hyperactivity, aggression, and opposition experienced hallucinations 4 days after starting guanfacine XR (dose=1 mg/day); these symptoms abated with discontinuation
  – Concomitant medication: multivitamin

• Impulsive behavior and negativism (n=1)
  – Patient with ADHD and Oppositional Defiant Disorder

• Mania and grandiosity (n=1)
  – 8 year old male on fluoxetine experience pressured speech, grandiosity, and motor agitation after 40 days on guanfacine XR; stable on fluoxetine and guanfacine IR
  – Diagnosis: ADHD, oppositional defiant disorder and mild tics
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Gastrointestinal events (6 cases)

- 6 cases classified as psychiatric or syncopal events, also reported GI adverse events
- 9 events
  - abdominal pain or discomfort (n=3)
  - decreased appetite (n=2)
  - vomiting (n=2)
  - abdominal pain with constipation (n=1)
  - nausea (n=1)

Labeling:

Highlights includes abdominal pain as a common adverse reaction
6.1 Clinical trial experience
Serious Non-Fatal Adverse Events
INTUNIV® (guanfacine XR)
Miscellaneous (2 cases)

• **Rash**: 10 year old female was hospitalized after unclear duration of therapy; guanfacine XR discontinued; 1 day later developed flushing, irregular HR, abnormal BP; outcome unknown

• **Product quality issue**: insurance company mandated substitution of guanfacine IR in place of guanfacine XR.
Summary Pediatric Focused Safety Review
INTUNIV® (guanfacine XR)

• This concludes the pediatric focused safety review

• No new safety signals were identified

• The FDA recommends continued routine monitoring.

• Does the Committee concur?
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Figure 1: Total number of dispensed prescriptions for guanfacine stratified by age through U.S. outpatient retail pharmacies, Sept 2009-Sept 2010

Source: SDI: Vector One® National. Extracted 11-10. Files: VONA 2010-2009 Guanfacine TRx by Age 11-8-10.xls
Total number of dispensed prescriptions for generic guanfacine stratified by age through U.S. outpatient retail pharmacies, Sept 2009-Sept 2010

Source: SDI: Vector One®: National. Extracted 11-10. Files: VONA 2010-2089 Guanfacine Products TRx by Age 11-8-10.xls