Pediatric Focused Safety Review: Quillivant XR® (methylphenidate hydrochloride)

Pediatric Advisory Committee Meeting
March 24, 2015

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Outline

• Background Information
• Pediatric Studies
• Pediatric Labeling Changes
• Drug Use Trends
• Adverse Events
• Summary
Background Drug Information: Quillivant XR® (methylphenidate HCl)

- **Therapeutic Category:** central nervous system (CNS) stimulant
- **Sponsor:** NextWave Pharmaceuticals, Inc. (Pfizer subsidiary)
- **Indication:** Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
- **Formulation:** Extended-release oral suspension (after reconstitution with water) 5 mg per mL
- **Dosage and Administration (patients 6 years and older):**
  - starting dose: 20 mg given orally once daily in the morning;
  - increase weekly by increments of 10 mg to 20 mg per day. (maximum recommended dose: 60 mg daily)
Background Drug Information: Quillivant XR® (methylphenidate HCl)

- **Original Market approval/Pediatric labeling changes:**
  - September 27, 2012
  - Safety and effectiveness established in patients 6-17 years of age.
  - Accumulated efficacy data from other methylphenidate products were also considered.
  - Safety and effectiveness have not been established in patients less than 6 years of age.
  - PREA studies waived for ages 0 to 5 years.
Pediatric Studies: Quillivant XR® (methylphenidate HCl)

- Efficacy established in a 2-week, placebo-controlled, laboratory classroom, crossover trial in children aged 6-12 years with ADHD (n=45).
  - Initial open-label dose optimization period of (4-6 weeks) with starting dose of 20 mg once daily in the morning titrated weekly to optimal dose or the maximum dose of 60 mg/day.
  - Attention and behavior evaluated weekly using SKAMP* rating scale.
  - SKAMP-Combined scores were statistically significantly lower (improved) at the primary efficacy endpoint at 4 hours and at all time points (0.75, 2, 4, 8, 10, 12 hours) post-dosing with QUILLIVANT XR® compared to placebo.

*Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale- measures the classroom manifestation of ADHD.
Pediatric Studies: Quillivant XR® (methylphenidate HCl)

• Efficacy partially extrapolated for 12-17-year-olds based on:
  – adequate and well-controlled study of QUILLIVANT XR® in younger pediatric patients
  – additional pharmacokinetic data in adolescents
  – safety information from other methylphenidate containing products.

• Accumulated efficacy data from other methylphenidate products were also considered.
Pediatric Labeling Changes: Quillivant XR® (methylphenidate HCl)

• Pediatric information included throughout labeling.
• 8.4 Use in Specific Populations, Pediatric Use
  – The safety and effectiveness of QUILLIVANT XR® have been established in pediatric patients ages 6 to 17 years.
    • Clinical study conducted in patients ages 6 to 12 years.
    • Efficacy extrapolated in patients ages 12 to 17 years.
  – Safety and efficacy in pediatric patients below the age of 6 years have not been established.
  – The long-term efficacy of methylphenidate in pediatric patients has not been established.
  – Information on long term suppression of growth and juvenile animal data also included.
# Pediatric Drug Utilization: Quillivant XR® (methylphenidate HCl)

<table>
<thead>
<tr>
<th></th>
<th>Patients (N)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quillivant XR®</strong></td>
<td><strong>72,282</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td>0-16 years</td>
<td><strong>67,801</strong></td>
<td><strong>93.8%</strong></td>
</tr>
<tr>
<td>0-1 years</td>
<td><strong>21</strong></td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>2-5 years</td>
<td><strong>10,062</strong></td>
<td><strong>14.8%</strong></td>
</tr>
<tr>
<td>6-11 years</td>
<td><strong>50,835</strong></td>
<td><strong>75.0%</strong></td>
</tr>
<tr>
<td>12-16 years</td>
<td><strong>9,724</strong></td>
<td><strong>14.3%</strong></td>
</tr>
<tr>
<td>17+ years</td>
<td><strong>4,626</strong></td>
<td><strong>6.4%</strong></td>
</tr>
<tr>
<td>Unknown Age</td>
<td><strong>93</strong></td>
<td><strong>0.1%</strong></td>
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</tbody>
</table>

Subtotals may not sum exactly due to rounding. Because of patients aging during the study period, patients may be counted more than once in the individual age categories. For this reason, summing across age groups is not advisable and will result in overestimates of patient counts.

Pediatric Drug Utilization: Quillivant XR® (methylphenidate HCl)

Prescribing Specialty\textsuperscript{1} and Diagnosis\textsuperscript{2} September 2012 through June 2014, Aggregate

- Top prescribing specialties
  - Pediatrics (49.5%)
  - Psychiatry (23%)
  - Nurse Practitioner (9%)

- Attention Deficit Disorder (ICD-9 code 314.0) was the only diagnosis captured in pediatric patients across all age groups

\textsuperscript{1}IMS, National Prescription Audit (NPA). September 2012-June 2014. Extracted October 2014.

Total Number* of Quillivant XR® Adverse Event Reports Since Approval  
(September 27, 2012- July 31, 2014)

<table>
<thead>
<tr>
<th></th>
<th>All reports</th>
<th>Serious**</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 yrs.)</td>
<td>28(28)</td>
<td>12(12)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pediatrics (0-&lt;17 yrs.)</td>
<td>156 (155)</td>
<td>32 (31)</td>
<td>2† (2)</td>
</tr>
</tbody>
</table>

*May include duplicates and transplacental exposures, and have not been assessed for causality

**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

†No additional cases of pediatric deaths were identified among cases not reporting an age.
Selection of Serious Pediatric FAERS Cases

Total Pediatric reports with a serious outcome (n=32)
• Pediatric reports with the outcome of death (n=2)

Excluded Reports (n=9) (Including 2 deaths)
• Methylphenidate product other than Quillivant XR® (n=7)*
• Non-serious outcome (n=1)†
• Adverse event reported when not on Quillivant XR® (n=1)

Pediatric serious cases (n=23) (Including 0 deaths)

* First death case: Literature report of a 14-year-old male who died of intentional overdose of bupropion, clonidine, and methylphenidate (not Quillivant XR®).

† Second death case: Division of Pharmacovigilance followed up with the reporter who stated that death was reported in error. The case was corrected to a non-serious outcome.
Demographics of Serious Adverse Events: Quillivant XR® (methylphenidate HCl) (n=23)

- **Age**
  - 12-<17 years (n=2)
  - 6-<12 years (n=14)
  - 2-<6 years (n=7)

- **Gender**
  - Male (n=18)
  - Female (n=5)

- **Reported Reason for Use**
  - ADHD (n=18)
  - Unknown (n=5)
Serious Non-Fatal Labeled Adverse Events: Quillivant XR® (methylphenidate HCl) (n=12)

Events occurred only once unless otherwise specified

4 Contraindications
Swollen tongue, pharyngeal edema (captured under hypersensitivity reactions)*

5 Warnings and Precautions
Psychotic disorder
Visual hallucination*
Tachycardia and blood pressure increased
Syncope

6 Adverse Reaction
Palpitations
Vision blurred, mydriasis
Generalized rash
Tics (n=2)

9 Drug Abuse and Dependence
Homicidal Ideation

10 Overdosage
Agitation*

*Also classified as an Adverse Reaction
Serious Non-Fatal **Unlabeled** Adverse Events: Quillivant XR® (methylphenidate HCl) (n=11)

- **Medication Error** (n=3)
- **Psychiatric events** (n=3)
  - Anger
  - Autism
  - Obsessive-compulsive disorder, onychophagia
- **Drug effect incomplete** (n=1)
- **Respiratory depression** (n=1)
- Melena (n=1)
- Hemorrhage, contusion, wound (n=1)
- Anisometropia, amblyopia, strabismus (n=1)

*Unlabeled events are underlined.*
Serious Non-Fatal Unlabeled Adverse Events: Quillivant XR® (methylphenidate HCl) Medication Errors (n=3)

- 10-year-old male with autism, Down syndrome, and ADHD received 10 mL (50 mg) of Quillivant XR® (per pharmacist’s instructions) instead of the prescribed dose of 10 mg (2 mL). Two days later, he was hospitalized due to agitation, tachycardia, insomnia, and loss of appetite, and discharged on the same day.

- 4-year-old male with ADHD mistakenly given 5 mL (25 mg) of Quillivant XR® by his mother instead of the prescribed dose of 1 mL (5 mg), and experienced “random arm movements” and “strange movements of mouth and tongue”. Despite treatment with diphenhydramine, he was admitted to the intensive care unit for continued involuntary movements, rapid speech, and being “hot” and “sweaty”. He returned to baseline after 5 hours, and was discharged home.

- 9-year-old female received an incorrect dose of Quillivant XR® because the patient’s parent reconstituted Quillivant XR® with an incorrect amount of water. The patient was admitted to the hospital for supportive therapy and observation.

*Unlabeled events are underlined.*
Serious Non-Fatal Unlabeled Adverse Events: Quillivant XR® (methylphenidate HCl) Medication Errors, continued (n=3)

Comment: The Division of Medication Error Prevention and Analysis (DMEPA) conducted a review on medication errors related to Quillivant XR® on October 9, 2014 which identified 17 cases of improper technique, storage, dose and quantity dispensed. The addition of the following statements to carton labeling were recommended to decrease wrong technique/storage errors:

• “Pharmacist: Quillivant XR® must be reconstituted with ___ mL prior to dispensing.”

• “Check and make sure that the Quillivant XR® bottle contains liquid medicine. If Quillivant XR® is in powder form, do not use it. Return it to your pharmacist.”

*Unlabeled events are underlined.
Serious Non-Fatal Unlabeled Adverse Events: Quillivant XR® (methylphenidate HCl) Psychiatric Disorders (n=3)

Anger

- 6-year-old male was prescribed Quillivant XR® 5 mg daily for ADHD. Dose was increased to 10 mg daily and he became “angry and violent”. Dose then decreased back to 5 mg daily, but symptoms persisted. Medication was eventually discontinued. The physician correlated the events to Quillivant XR®; however, he stated that the patient’s behavior was attributed to methylphenidate in general (not specific to the brand product).

Comment: Anger is labeled in the Adverse Reactions section (6.2) of the Concerta® (methylphenidate extended-release) label.

*Unlabeled events are underlined.
Serious Non-Fatal **Unlabeled** Adverse Event: Quillivant XR® (methylphenidate HCl) Psychiatric Disorders (n=3)

**Autism**

- 5-year-old male previously on methylphenidate transdermal patch and started on Quillivant XR® on an unknown date. Patient given diagnosis of autism, but timing of diagnosis relative to methylphenidate use is unclear. No other information on medical history, concomitant medications or outcome provided.

*Comment: This case lacks sufficient information to make an assessment.*

*Unlabeled events are underlined.*
Serious Non-Fatal Unlabeled Adverse Events: Quillivant XR® (methylphenidate HCl) Psychiatric Disorders (n=3)

Obsessive-compulsive disorder, onychophagia

- 5-year-old male with history of nasal allergies, on no other medications, started Quillivant XR® 10 mg daily. Approximately 3 weeks later, he was chewing and biting his fingers and toes. 6 ½ weeks later, he had “no pads on ends of fingers” and he was seen in the emergency department. Due to concern for possible infection, an antibiotic ointment was prescribed as treatment. Quillivant XR® was discontinued, and the patient recovered.

Comment: although there is a temporal relationship and positive dechallenge between Quillivant XR and nail biting, obsessive-compulsive disorder commonly co-occurs with other psychiatric disorders such as ADHD or anxiety.

*Unlabeled events are underlined.
Serious Non-Fatal Unlabeled Adverse Events: Quillivant XR® (methylphenidate HCl)
General disorders (n=1)

Drug Effect Incomplete

• 16-year old male with history of a congenital “disability” and ADHD on clonidine, quetiapine, and guanfacine extended-release was started on Quillivant XR® 30 mg daily. About two months later, he became aggressive when the methylphenidate wore off in the afternoon. Subsequently, the dose of Quillivant XR® was increased to 40 mg daily with an unknown effect. The manufacturer investigated the product quality complaint; all results were found to be within specifications.

*Unlabeled events are underlined.
Serious Non-Fatal Unlabeled Adverse Events: Quillivant XR® (methylphenidate HCl) Respiratory/thoracic/mediastinal disorders (n=1)

Respiratory Depression

- 5-year-old male with unknown medical history on clonidine, montelukast, and desmopressin nasal spray started Quillivant XR® 20 mg daily for ADHD. Two days later, the patient experienced “respiratory depression/respiratory distress”, and was admitted to the hospital, requiring intubation. The patient also had vomiting, altered mental status, and seizure. The patient recovered and methylphenidate was permanently discontinued.

Comment: Although no medical history was provided, montelukast use suggests a potential history of asthma or allergy. With the limited information provided, determining methylphenidate’s role in the adverse events is challenging.

*Unlabeled events are underlined.
Serious Non-Fatal Unlabeled Adverse Events: Quillivant XR® (methylphenidate HCl)
Gastrointestinal Disorder (n=1)/Vascular Disorder (n=1)

**Melena**
- 9-year-old male had “black tarry stools” while on Quillivant XR®. No further information provided.
Comment: Insufficient information provided to assess causality.

**Hemorrhage, contusion, wound**
- 7-year-old male titrated to 30 mg Quillivant XR® daily. About three days later, bruising without local trauma was noted. Five months later, a big bruise appeared on his leg that bled without trauma. On an unspecified date, the dose was changed to twice daily (unspecified dose) due to ineffectiveness. Hematology labs normal. No concomitant medications. The medication was discontinued and the bruising resolved.
Comment: Thrombocytopenia is a labeled event for methylphenidate but in this case, the patient’s platelet count was normal. An alternative etiology for the bruising and unusual bleeding cannot be ruled out.

*Unlabeled events are underlined.*
Serious Non-Fatal Unlabeled Adverse Events: Quillivant XR® (methylphenidate HCl)

Eye Disorders (n=1)

Anisometropia, amblyopia, strabismus

- 6-year-old male with history of a decreased visual acuity (20/30) and ADHD started Quillivant XR® 25 mg twice daily. About four months later, his vision worsened (became 20/100), and he was diagnosed with anisometropic amblyopia and strabismus. He did not recover, and the reporting physician stated there was a low possibility that the events were related to Quillivant XR®.

Comment: The patient had pre-existing vision impairment. Concerta® (methylphenidate extended-release) labeling includes vision disturbance (difficulties with accommodation and blurring of vision reported with stimulant treatment) Warnings and Precautions, and Concerta® and Quillivant XR® labeling include blurred vision in Adverse Reactions.

*Unlabeled events are underlined.
Summary Pediatric Focused Safety Review: Quillivant XR® (methylphenidate HCl)

- This concludes the pediatric focused safety review.
- Quillivant XR® is approved for the treatment of ADHD in patients 6 -17 years of age.
- Many events had single cases, confounding factors or limited information from which to draw causality.
- The safety review identified no new safety signals other than those already identified regarding medication errors.
- FDA recommends continuing ongoing surveillance.
- Does the Committee concur?
ACKNOWLEDGEMENTS

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Grace Chai, PharmD
Justin Mathew, PharmD