Pediatric Focused Safety Review: Revatio® (sildenafil)
Pediatric Advisory Committee Meeting
March 24, 2015

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Office of New Drugs/ ODE IV
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Outline

• Background Information
• Pediatric Studies
• Labeling Changes
• Drug Use Trends
• Safety
• Summary
Background Drug Information
Revatio® (sildenafil)

- **Drug:** Revatio®
- **Formulations:** Oral tablet, oral suspension and intravenous
- **Sponsor:** Pfizer
- **Original Market Approval:** June 3, 2005
- **Therapeutic Category:** phosphodiesterase-5 inhibitor

Sildenafil is also marketed as Viagra® oral tablet
Revatio® (sildenafil)

Indication:

- Treatment of pulmonary arterial hypertension (WHO Group 1) in adults to improve exercise ability and delay clinical worsening.
Pediatric Study
Revatio®(sildenafil)

A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study of 234 patients aged 1 to 17 years with pulmonary arterial hypertension (PAH). Patients were randomized on the basis of body weight to three dose levels of Revatio® or placebo for 16 weeks of treatment. After completing the 16 week controlled study, patients originally randomized to Revatio®, remained on his/her dose or, if originally randomized to placebo, were randomized to low, medium or high dose. After all patients completed 16 weeks of follow-up, the blind was broken and doses were adjusted as clinically indicated. Patients were followed for a median of 4 years.

Administration of Revatio® did not result in a statistically significant improvement in the primary endpoint of exercise capacity. Revatio® does not have an approved pediatric indication.
Pediatric Study
Revatio® (sildenafil)

Kaplan-Meier Plot of Mortality by Revatio® Dose

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Number at Risk</th>
<th>0 Years</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>100</td>
<td>95</td>
<td>85</td>
<td>79</td>
<td>51</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Medium dose</td>
<td>74</td>
<td>73</td>
<td>68</td>
<td>65</td>
<td>40</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Low dose</td>
<td>55</td>
<td>54</td>
<td>51</td>
<td>47</td>
<td>33</td>
<td>22</td>
<td>12</td>
</tr>
</tbody>
</table>
5 WARNINGS AND PRECAUTIONS
5.1 Mortality with Pediatric Use

In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing Revatio® dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of Revatio®, particularly chronic use, is not recommended in children.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

The pediatric study and results are described. A Kaplan-Meier plot of mortality by Revatio® dose is presented and the increase in mortality is described.
Sildenafil Pediatric Utilization

U.S. Non-Federal Hospital Setting

Nationally estimated number of pediatric patients (0-16 years) with an inpatient or outpatient ER hospital discharge billing for sildenafil from U.S. non-federal hospitals, July 2005 through June 2014

# Sildenafil Drug Utilization
## U.S. Non-Federal Hospital Setting

Nationally estimated number of patients with an inpatient or outpatient ER hospital discharge billing for sildenafil from U.S. non-federal hospitals, stratified by patient age*, July 2013 through June 2014, aggregate

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Patients (N)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients**</td>
<td>36,427</td>
<td>100.0%</td>
</tr>
<tr>
<td>0-16 years</td>
<td>4,537</td>
<td>12.5%</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>2,798</td>
<td>61.7%</td>
</tr>
<tr>
<td>1-16 years</td>
<td>1,922</td>
<td>42.4%</td>
</tr>
<tr>
<td>17 years and older</td>
<td>31,829</td>
<td>87.4%</td>
</tr>
<tr>
<td>Unspecified age</td>
<td>85</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).

**Unique patient counts may not be added across time periods or products due to the possibility of double counting those patients who are receiving treatments over multiple periods in the study. Patient age subtotals may not sum exactly due to patients aging during the study, 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.

Sildenafil Pediatric Utilization
U.S. Outpatient Retail Pharmacy Setting

Nationally estimated number of pediatric patients (0-16 years) that received a dispensed prescription for sildenafil from U.S. outpatient retail pharmacies, July 2005 through June 2014

# Sildenafil Drug Utilization

**U.S. Outpatient Retail Setting**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Patients (N)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients**</td>
<td>2,645,454</td>
<td>100.0%</td>
</tr>
<tr>
<td>0-16 years</td>
<td>3,909</td>
<td>0.2%</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>430</td>
<td>11.0%</td>
</tr>
<tr>
<td>1-16 years</td>
<td>3,550</td>
<td>90.8%</td>
</tr>
<tr>
<td>17 years and older</td>
<td>2,640,778</td>
<td>99.8%</td>
</tr>
<tr>
<td>Unspecified age</td>
<td>3,828</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).

**Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatments over multiple periods in the study. Patient age subtotals may not sum exactly due to patients aging during the study, 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.

Sildenafil Drug Utilization
Prescriber Specialty and Diagnosis

• Top prescribing specialty for all sildenafil products was General Practice/Family Medicine/Doctor of Osteopathy (42% of prescriptions) in the outpatient retail pharmacy setting¹
  – Pediatrics accounted for <1% of sildenafil prescriptions

• Chronic pulmonary heart disease was the only diagnosis reported for pediatric use of sildenafil² by U.S. office-based physician surveys

## Total Adult and Pediatric Sildenafil Cases in the FDA Adverse Event Reporting System (FAERS) June 3, 2005 to June 30, 2014

<table>
<thead>
<tr>
<th></th>
<th>All reports (US)</th>
<th>Serious(^\d) (US)</th>
<th>Deaths(^\S) (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 yrs.)</td>
<td>9947 (7680)</td>
<td>6770 (4539)</td>
<td>1977 (1330)</td>
</tr>
<tr>
<td>Pediatrics (0- &lt;17 yrs.)</td>
<td>236(92)</td>
<td>213 (72)</td>
<td>56 (3)</td>
</tr>
</tbody>
</table>

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

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

Pediatric reports with a serious outcome including life threatening, hospitalization, disability and death (n=132)
- Pediatric reports with the outcome of death (n=56)

Excluded
- Duplicates (n=6)
  (including 1 death)

Pediatric Case Series (126)
( Including 55 deaths)
55 Total Fatal Pediatric Cases, Domestic (n=3), Non-Domestic (n=52)

- Overall, nearly half of the fatal pediatric cases were infants, with a median age of 1 year (mean of 4 years). Twenty-nine death cases were reported from clinical studies, including 21 cases from the Long-Term Use of Revatio® study. There were 2 cases of death temporally related to sildenafil use where the relationship to sildenafil cannot be ruled out
  - Accidental ingestion by 6 year old (domestic case)
  - Autopsy-confirmed pulmonary hemorrhage (labeled, non-domestic)
Domestic Fatal Pediatric Cases (n=3)

- 6 year old with accidental ingestion and died of unknown cause
- 18 month old with sepsis and multi-organ failure
- 2 week old with unknown cause of death
Non-Domestic Fatal Pediatric Cases Grouped by Reported Cause of Death by Organ System (n=52)

- Respiratory (n=24)
- Cardiac (n=8)
- Infections (n=5)
- Nervous system (n=3)
- Surgeries (n=2)
- Renal (n=1)
- Multi-organ failure (n=1)
- Congenital (n=1)
- Shunt malformation (n=1)
- Unknown (n=6)
Non-Domestic Fatal Pediatric Cases, continued

Respiratory (n=24)
- Pulmonary hypertension (n=14)
- Pulmonary hypertension crisis (n=3)
- Pulmonary hemorrhage (n=2)
- Respiratory failure (n=2)
- Emphysema (n=1)
- Hypoxia (n=1)
- Pneumothorax (n=1)
Non-Domestic Fatal Pediatric Cases, continued

Cardiac disorders (n=8)
• Cardiac failure (n=4)
• Total anomalous pulmonary venous connection (n=2)
• Cardiopulmonary insufficiency (n=1)
• “Pericardium stroke” (n=1)
Non-Domestic Fatal Pediatric Cases, continued

Infections and Infestations (n=5)
- Sepsis (n=1)
- Cytomegalovirus (n=1)
- Candida (n=1)
- Meningitis (n=1)
- Norovirus (n=1)

Nervous system disorders (n=3)
- Acute cerebral infarction (n=1)
- Brain trauma (n=1)
- Cerebral hemorrhage (n=1)
Non-Domestic Fatal Pediatric Cases, continued

Surgeries (n=2)
• Post-surgery (n=1)
• Scoliosis surgery (n=1)

Renal disorders (n=1)
• Acute renal failure

Multi-organ failure (n=1)
• Multi-organ failure

Congenital disorders (n=1)
• Trisomy 18
Non-Domestic Fatal Pediatric Cases, continued

Shunt malformation (n=1)
• Shunt malformation

Unknown cause (n=6)
• 3 cases confounded by underlying disease and complex medical history including congenital disorders
• 3 cases reported by consumers and media and did not provide relevant clinical information. One case was associated with accidental intravenous administration of oral sildenafil.
Serious Non-Fatal Labeled Adverse Events
Revatio® (sildenafil)(n=28)

5 Warning and Precautions
5.2 Hypotension (n=5)
5.3 Pulmonary veno-occlusive disease (n=1)
5.3 Vasodilatation (n=1)
5.4 Epistaxis (n=2)
5.5 Vision loss (n=1)
   – Visual acuity reduced (n=1)
5.6 Hearing loss (n=2)
Serious Non-Fatal Labeled Adverse Events, continued Revatio® (sildenafil)

6 Adverse Events
6.1 Clinical Trials
• Flushing (n=1)
• Pyrexia (n=1)
• Dyspnea (n=1)
6.2 Post-marketing
• Hypertension (n=1)
• Convulsions (n=3)
• Cerebrovascular Accident (n=1)
• Intracerebral hemorrhage (n=1)
• Retinal hemorrhage (n=1)

17 Patient Counseling
• Pneumonia (n=4)
• Respiratory tract Infection (n=3)
Serious Non-Fatal Unlabeled Adverse Events, Revatio® (sildenafil) (n= 43)

Gastrointestinal disorders (n=7)
- Abdominal distension (n=2)
- Enterocolitis (n=1)
- Necrotizing enterocolitis (n=1)
- Pancreatitis (n=1)
- Swollen tongue (n=1)
- Volvulus (n=1)

General disorders and administration site conditions (n=6)
- Chest pain (n=2)
- Malaise (n=1)
- Medical device complication (n=1)
- Drug ineffective (n=1)
- Hyperhidrosis (n=1)
Serious Non-Fatal Unlabeled Adverse Events, continued Revatio® (sildenafil)

Respiratory, thoracic and mediastinal disorders (n=5)
- Hypoxia (n=2)
- Respiratory distress (n=1)
- Respiratory failure (n=1)
- Pulmonary edema (n=1)

Injury, poisoning, and procedural complications (n=4)
- Accidental exposure to product (n=1)
- Overdose (n=1)
- Wound dehiscence (n=1)

Hepatobiliary disorders (n=3)
- Liver function test abnormal (n=2)
- Autoimmune hepatitis (n=1)

Blood and lymphatic system disorders (n=3)
- Immune thrombocytopenic purpura (n=1)
- Leukopenia (n=1)
- Methemoglobinemia (n=1)
Serious Non-Fatal Unlabeled Adverse Events, continued Revatio® (sildenafil)

Surgical and medical procedures (n=2)
- Colostomy (n=1)
- Surgery (n=1)
Cardiac disorders (n=2)
- Cardiac failure (n=1)
- Bradycardia (n=1)
Skin and subcutaneous tissue disorders (n=2)
- Stevens-Johnson Syndrome (n=1)
- Pruritic rash (n=1)
- Wrong technique used in drug administration (n=1)
Psychiatric disorders (n=2)
- Impulsive behavior (n=1)
- Noctiphobia (n=1)
Serious Non-Fatal Unlabeled Adverse Events, continued *Revatio®* (sildenafil)

Renal and urinary disorders (n=1)
- Acute renal failure (n=1)

Reproductive system and breast disorders (n=1)
- Clitoral engorgement (n=1)

Infections and infestations (n=1)
- Gastroenteritis (n=1)
Serious Non-Fatal Adverse Events
Revatio® (sildenafil)

Many of the non-fatal serious pediatric cases were probably related to or confounded by underlying disease, congenital disorders and comorbidities. Because many unlabeled events consisted of one single report with limited clinical information, it was difficult to determine whether these reports documented new safety issues with sildenafil use.
Summary of Safety Reviews
Revatio® (sildenafil)

• This concludes the pediatric focused safety review of FAERS reports
• No potential safety signals were identified
• FDA recommends continued routine monitoring
• Does the committee concur?
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