Pediatric focused safety evaluation

Active ingredient: deferasirox

Peter Waldron, MD
Outline

• Background
• Division of Pharmacovigilance
• Office of Clinical Pharmacology
• Division of Pediatric and Maternal Health
• Division of Epidemiology
Background
US regulatory history: deferasirox (DFS)

• 2005 approved for transfusional iron overload age ≥ 2 years
• 2009 maximum Exjade dose increased from 30 mg/kg/day to 40 mg/kg/day
• 2010 Boxed Warning added for renal failure, hepatic failure, and gastrointestinal hemorrhage
• 2013 Exjade approved for non-transfusion dependent thalassemia age 10 years and older, maximum dose 20 mg/kg/day
• 2015 Jadenu tablet, film coated, and 2017 granule approved; 7 mg of Jadenu is equivalent to 10 mg of Exjade
2015 Pediatric Focused Safety Review

• January, 2015 pediatric focused safety review (PFSR) was triggered two years after approval of sNDA S-015: chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia (NTDT)

• September, 2015 PFSR was presented to Pediatric Advisory Committee
Case with fatal outcome presented to FDA Pediatric Advisory Committee Sept. 2015

- A 35 month (2 yr, 11 mo) old girl with transfusion dependent thalassemia
- RBC transfusion started at 7 mo. (28 mo. earlier)
- Chelation started at 24 mo. (11 mo. earlier)
- Concomitant medications: MVI, vitamin D, folic acid
Case Summary

• High dose (32 mg/kg/day) Exjade, with lower serum ferritin (SF) (655 mcg/L 42 days before the acute presentation)
• Acute hypovolemia and fever with RSV infection
• Acute kidney injury (AKI)/renal failure and acute liver failure (coagulopathy and encephalopathy)
• Later (12 hour), overt shock and respiratory failure
• Death due to cerebral herniation
Pediatric safety evaluation timeline

• Sept. 2015 Exjade PFSR presented to PAC
  – Testimony from the mother of the girl who died
  – Cooley Anemia Foundation testified about its membership's concern for use of Exjade during febrile illnesses, and requested that a Warning, to stop the use of Exjade for children who develop a fever, be added to the product information

• November 2015 Division of Pharmacovigilance (DPV) consulted, based on the request from PAC: “to acquire any data regarding safety of continued medication (administration) to children who have fever, and report back to the PAC”

• April 2016 Tracked Safety Issue opened: pediatric fever and dehydration

• March 2017 interim report to PAC

• April 2018 evaluation completed; May 2018 deferasirox labels updated
Questions identified by the Safety Issues Team

• Are there features of childhood illnesses, such as hypovolemia, that could interact with DFS use, to produce severe toxicity?

• Could continued drug use during periods of decreased glomerular function result in increased drug exposure?

• Is there an interaction between drug dose and body iron burden (BIB), such that at a high body iron burden a given dose may be associated with a lower rate of adverse reactions (AR), whereas that same dose at a lower BIB will be associated with an increased rate of AR?
Division of Pharmacovigilance

Fever and dehydration
Acute hepatic failure
### FAERS Cases Of Renal Impairment After Episode Of Fever or/and Dehydration

<table>
<thead>
<tr>
<th></th>
<th>No renal impairment (%)</th>
<th>Renal impairment (%)</th>
<th>N total = 149</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever only</strong></td>
<td>95</td>
<td>5</td>
<td>58</td>
</tr>
<tr>
<td><strong>Dehydration only</strong></td>
<td>75</td>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td><strong>Fever and dehydration</strong></td>
<td>52</td>
<td>48</td>
<td>23</td>
</tr>
</tbody>
</table>
### Summary of FAERS and literature cases of acute hepatic failure

<table>
<thead>
<tr>
<th></th>
<th>Encephalopathy (E); Coagulopathy (C)</th>
<th>AKI</th>
<th>Hypovolemia</th>
<th>Overchelation</th>
<th>Causality</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAERS N=13</strong></td>
<td>E: 13</td>
<td>Yes: 10</td>
<td>Yes: 11</td>
<td>Yes: 7</td>
<td>Probable: 8</td>
<td>Recovery: 10</td>
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<tr>
<td></td>
<td>C: 4; NR: 7</td>
<td>NR: 3</td>
<td>NR: 2</td>
<td>NR: 6</td>
<td>Possible: 5</td>
<td>Death: 3</td>
</tr>
<tr>
<td><strong>Literature N=3</strong></td>
<td>E: 2</td>
<td>Yes: 2</td>
<td>Yes: 3</td>
<td>Yes: 3</td>
<td>Probable: 3</td>
<td>Recovery: 3</td>
</tr>
<tr>
<td></td>
<td>C: 3</td>
<td>NR: 1</td>
<td></td>
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</tbody>
</table>

NR: no result reported
Summary of DPV findings

• There was a high frequency of indicators of renal impairment among children with dehydration risk, with or without fever

• An association between risk factors for hypovolemia and incidence of renal impairment indicators

• Reports of acute hepatic failure were associated with
  – Severe, acute kidney injury
  – Risk factors for hypovolemia
  – Overchelation
Introduction to next speakers

• Clinical Pharmacology: Olanrewaju Okusanya, Pharm D, MS
• DPMH: Mona Khurana, MD
• DEPI Nested Case Control Study: Steve Bird, Pharm D, PhD
• DEPI Clinical Trials analysis: Kate Gelperin, MD, MPH