Pediatric Focused Safety Review Update – Exjade (deferasirox)

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FDA Update

Outline

- September 2015 Pediatric Advisory Committee presentation and request
- Safety issues under evaluation
  - Fever
  - Dehydration/ Hypovolemia
  - Kidney injury
  - Liver injury
- Data sources

Case presented at Sept. 2015 PAC

- Death of a 2 11/12 y.o. girl in association with an acute illness and respiratory syncytial virus (RSV) while receiving deferasirox (DFS) for β-thalassemia and iron overload.
- The patient presented with acute renal and hepatic failure, along with metabolic acidosis. Her immediate cause of death was cerebral edema with herniation.

PAC request and FDA interpretation

- The Pediatric AC members requested that FDA review "any data regarding safety of continued medication to children who have fever, and report back to the PAC"
- FDA ongoing comprehensive review plan
  - Focus broadened to fever and hypovolemia
  - Identify cases from available sources
  - Examine adverse events, possible predisposing factors, and potentially preventable causes
  - Analyze role of interrupting or continuing DFS during acute illness

Acute illness events

Fever

- At least 1 fever occurred among 45% of children (ages 2-15, all indications) in clinical trials (Exjade Investigator Brochure)
- Viral infection, hypovolemia, anorexia, and liver injury may occur without fever
- Is fever a reliable indicator for interrupting DFS dosing?

Acute illness events

Hypovolemia

- Potential for acute volume loss to produce labeled renal criteria for dose modification
- Potential for volume loss to produce excess exposure
- Limitations to methods of volume status assessment from data sources

Safety issues under evaluation for continuation of DFS with acute illness

- Acute illness events
  - Fever
  - Hypovolemia or dehydration
- Associated adverse effects
  - Kidney Injury
  - Liver Injury

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Data sources

- A 5 year observational study (registry) of children aged 2 to less than 6 years at enrollment with transfusional hemosiderosis treated with deferasirox (ENTRUST)
  FDA receipt of data: January 29, 2016
- Pooled analysis of safety data from 17 pediatric clinical trials with Exjade (age <16 years)
- FAERS (FDA Adverse Event Reporting System)
- Published literature

Conclusion

- Final report to PAC expected March 2017 meeting
- Presentation will include discussion of possible label changes