

**One Year Post-Exclusivity Adverse  
Event Review:  
Paricalcitol, Zolmitriptan,  
Dorzolamide, and Leflunomide**

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**Solomon Iyasu, M.D., M.P.H.  
Acting Deputy Director  
Division of Pediatric Drug Development  
Center for Drug Evaluation and Research  
Food and Drug Administration**



# Abbreviated Presentations of BPCA-mandated Adverse Event Review

- **No new safety signals**
  - Paricalcitol (Zemplar<sup>®</sup>)
  - Zolmitriptan (Zomig<sup>®</sup>)
  - Dorzolamide (Trusopt<sup>®</sup>)
  - Leflunomide (Arava<sup>®</sup>)

# **Background Drug Information**

**Drug:** Zemplar<sup>®</sup> (paricalcitol)

**Therapeutic Category:** Vitamin D Analog

**Sponsor:** Abbott Laboratories

**Indication:** Prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure

**Original Market Approval:** April 17, 1998

**Pediatric Exclusivity Granted:** December 8, 2003

# Summary:

- No pediatric adverse events were reported through AERS from market approval through January 2005
- It is estimated that approximately 1000 pediatric dialysis patients may be exposed to paracalcitol.<sup>1</sup>
- Safety and effectiveness were examined in a 12 week trial in pediatric patients with end stage renal disease on hemodialysis (described in labeling)
- No patients in the trial developed hypercalcemia

<sup>1</sup> U.S. Renal Data System. 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States [on-line]. Available from URL: <http://www.usrds.org>

# Background Drug Information

**Drug:** Zomig<sup>®</sup> Tablets and Zomig-ZMT<sup>®</sup> Orally Disintegrating Tablets (zolmitriptan)

**Therapeutic Category:** Selective 5-hydroxytryptamine receptor agonist

**Sponsor:** AstraZeneca

**Indication:** Acute treatment of migraine with or without aura in adults. Not recommended for pediatric use (information from exclusivity studies in the label)

**Original Market Approval:** November 25, 1997

**Pediatric Exclusivity Granted:** December 18, 2003

# Zomig<sup>®</sup> (Zolmitriptan )

- Pediatric patients accounted for less than 2% of all claims for Zomig<sup>®</sup> oral tablets and 5% of all claims for Zomig-ZMT<sup>®1</sup>
- Two pediatric adverse event reports identified during the one year post-exclusivity period:
  - Accidental ingestion of 2.5 mg Zomig<sup>®</sup> by a toddler. Hospitalized for observation, no adverse reaction noted.
  - Adolescent with partial seizure after taking Zomig<sup>®</sup>. Patient had history of seizures following astrocytoma removal that were not being treated. Partial seizures are unlabeled but unclear if due to drug or underlying pathology.

# Pediatric Adverse Event Reports: November 25, 1997 – January 18, 2005

All pediatric reports: 24\*

- Deaths: 2 reports, both of the same patient with an intentional overdose of Imitrex<sup>®</sup>, Zomig<sup>®</sup> and Sudafed<sup>®</sup>
- Unlabeled events: dyspnea, drug ineffective, lethargy, accidental exposure, accidental overdose, brain edema\*\* , pupil fixed\*\*

No new concerning unlabeled safety signals identified in pediatric adverse events reported through AERS from market approval through January 2005

Underlined = Unlabeled events in Zomig<sup>®</sup> and Zomig-ZMT<sup>®</sup>

\*Includes duplicate reports

\*\* Only noted in the intentional overdose

# Background Drug Information

**Drug:** Trusopt<sup>®</sup> (dorzolamide ophthalmic solution)

**Therapeutic Category:** carbonic anhydrase inhibitor

**Sponsor:** Merck

**Indication:** Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma

**Original Market Approval:** December 9, 1994

**Pediatric Exclusivity Granted:** January 5, 2004

# Dorzolamide Ophthalmic Solution (Trusopt<sup>®</sup>)

- Minimal use in Pediatrics: 0.5% (472/92,688) prescription claims for dorzolamide hydrochloride, ages 1-16 years<sup>1</sup>
- No adverse events reported during the 1-year post-exclusivity period
- Conclusion: No new safety signal found

# Background Drug Information

**Drug:** Arava<sup>®</sup> (leflunomide)

**Therapeutic Category:** immunomodulator (pyrimidine synthesis inhibitor)

**Sponsor:** Aventis

**Indication:** Treatment of rheumatoid arthritis in adults:

- to reduce signs and symptoms
- to inhibit structural damage as evidenced by X-ray erosions and joint space narrowing
- to improve physical function

**Original Market Approval:** September 10, 1998

**Pediatric Exclusivity Granted:** November 10, 2003

# Leflunomide (Arava<sup>®</sup>)

- No pediatric indication because failed to win on primary endpoint
- Superiority design against high dose methotrexate
- Leflunomide showed activity over historical baseline
- JRA difficult disease/ treated by specialists
- Details/results of trial in PK section of labeling

# Leflunomide (Arava<sup>®</sup>)

- Minimal use in pediatrics: 0.1% (105/74,574) prescription claims for leflunomide, ages 1-16 years<sup>1</sup>
- Two adverse event reports for the 1-year post-exclusivity period:
  - transient elevation of liver enzymes (labeled event), recovered
  - liver failure after an intentional overdose of acetaminophen while on leflunomide, resolved
- Conclusion: No new safety signal found

<sup>1</sup>Caremark Dimension Rx™, Dec 2001 - Nov 2004, Data extracted Jan 2005

# Conclusion

- **This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.**
- **FDA recommends routine monitoring of AEs for Zemplar<sup>®</sup>, Zomig<sup>®</sup>, Trusopt<sup>®</sup> and Arava<sup>®</sup> in all populations.**
- **Does the Advisory Committee concur?**

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