FDA Advisory Committee

December 14-15, 2006

KETEK® (telithromycin)

sanofi-aventis US

Postapproval Safety Experience

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Postapproval Safety Experience

- Introduction
- Pharmacovigilance initiatives
- Overview of postapproval safety experience
- Specific postapproval safety experience:
  - hepatic events
  - visual events
  - syncopal events
  - exacerbation of myasthenia gravis
- Conclusions

The Postmarketing Team
Internal and External Experts

- Global Pharmacovigilance
- Global Epidemiology
- Hepatology
- Cardiology
- Neurology
- NeuroOphthalmology

Postmarketing Experience

- First approved in Europe in July 2001
  - approved in United States April 2004
- ~ 28 million postmarketing exposures to telithromycin worldwide
  - ~ 6 million in United States

Spontaneous Reports Strengths/Weaknesses

- Cornerstone of postmarketing safety surveillance:
  - identify serious, rare events
  - better characterize uncommon events
  - additional information about subpopulations
- Reporting rates are measures of reporting intensity, not incidence and are affected by:
  - severity of AE
  - time since launch/ Weber effect
  - stimulated reporting
  - secular trends
  - health care provider inclination to report

Reporting Rate Calculation

- Since treatment with telithromycin is short term (5-10 days):
  - Reporting rates are expressed in number of cases per million prescriptions

Overview of Postmarketing Reports

- Most frequently reported adverse events:
  - gastrointestinal: nausea, vomiting, diarrhea
  - visual: blurred vision, visual disturbance, diplopia
  - nervous: dizziness, headache
  - skin: pruritus, urticaria, rash
  - general: malaise

Reporting Rates 29 months Postapproval ex-US vs US

	Ex-US ($\times 10^6$ exposures) (July 01 to Dec 03)	US ($\times 10^6$ exposures) (Apr 04 to Sep 06)
Gastrointestinal		
Nausea	23.5	26.8
Diarrhea	14.1	17.0
Vomiting	10.9	14.2
Visual		
Blurred vision	45.0	45.5
Visual disturbance	12.8	18.5
Accommodation disorder	6.5	1.6
Diplopia	6.2	12.3

Reporting Rates 29 months Postapproval ex-US vs US

	Ex-US (x 10^6 exposures) (July 01 to Dec 03)	US (x 10^6 exposures) (Apr 04 to Sep 06)
Nervous		
Dizziness	20.3	25.6
Headache	13.9	11.1
Skin		
Pruritus	8.6	5.7
Urticaria	6.2	6.2
Rash	7.7	10.0
General		
Malaise	7.2	6.6

Pharmacovigilance Initiatives: Risk Identification

- Individual case safety reports (ICSR)
  - pre-US approval (May 2003): standardized questionnaires designed to collect detailed information on hepatic, cardiac and visual events
  - intensive follow-up of adverse events (including phone contact)
  - pre-US approval (Aug 2003): expedited reporting of all serious hepatic events

Pharmacovigilance Initiatives: Risk Assessment

- Preapproval
  - routine aggregate reviews of ICSRs
  - cumulative postmarketing report (Jan 2003)
  - monthly postmarketing cumulative analyses (Dec 2003)
  - comparative analyses based on FDA FOI extracted data

Pharmacovigilance Initiatives: Risk Assessment

- Postapproval
  - ad hoc aggregate safety analyses
  - postmarketing visual commitment study
  - preclinical studies
  - comparative analyses based on FDA FOI extracted data
  - two epidemiologic claims database studies for hepatic events

Risk Communication

- Safety information component of physician and patient communication, delivered through a variety of methods:
  - sales representative presentations and handouts
  - mailings to physicians
  - Ketek.com web site
  - educational programs
  - Myasthenia Gravis organizations