FDA Advisory Committee

December 14-15, 2006

KETEK® (telithromycin)

sanofi-aventis US

Overview of FDA Approval Activities for Telithromycin

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Corporate Regulatory Affairs

Overview

- Current status and approval timeline
- Data to support FDA approval
  - clinical pharmacology
  - microbiology
  - clinical efficacy
  - clinical safety
- Postapproval activities

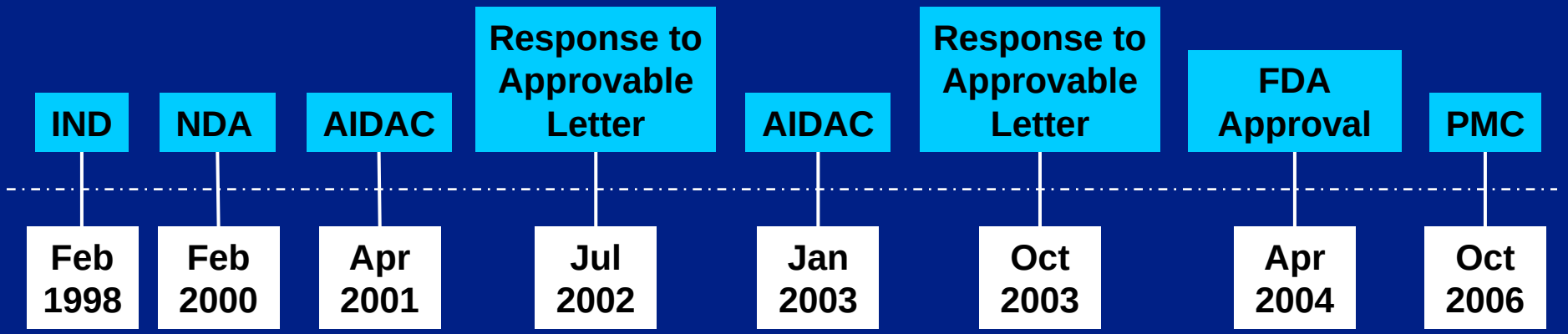
Current Status and Timeline for FDA Approval

Telithromycin: Current Status

- Approved for the following indications (US):
  - community-acquired pneumonia (mild to moderate)
    - *Streptococcus pneumoniae* (including multidrug-resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*
  - acute bacterial exacerbation of chronic bronchitis
    - *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*
  - acute bacterial sinusitis
    - *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *Staphylococcus aureus*

* MDRSP, Multi-drug resistant *S.pneumoniae* includes isolates known as PRSP (penicillin-resistant *S. pneumoniae*), and are isolates resistant to 2 or more of the following antibiotics: penicillin, 2nd generation cephalosporins, eg, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Timeline for FDA Approval of Telithromycin



IND=Investigational New Drug; NDA=New Drug Application; AIDAC=Anti-infective Drugs Advisory Committee; PMC=submitted postmarketing commitment for 18-month visual safety update report.

Timeline for FDA Approval of Telithromycin

- New Drug Application (28-Feb-00)
  - 36 Phase I studies
  - 8 Phase III studies in community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), acute bacterial sinusitis (ABS)
  - 2 Phase III studies in tonsillitis/pharyngitis (T/P)
- Anti-infective Drugs Advisory Committee (26-Apr-01)
  - AIDAC recommended CAP approval, additional data on antibiotic-resistant *S. pneumoniae*, clinical safety
  - FDA “Approvable” for CAP, AECB, ABS (01-Jun-01)

Timeline for FDA Approval of Telithromycin

- Complete response to 1st FDA Letter (24-Jul-02) :
  - clinical trial data:
    - 7 Phase I studies (special populations)
    - 4 Phase III studies (antibiotic-resistant bacteria)
  - ex-US postmarketing data: ~1.5 million exposures
  - additional safety data:
    - large (12,159 safety evaluable) comparative safety study in usual care setting (Study A3014)
- Anti-infective Drugs Advisory Committee (08-Jan-03)
  - AIDAC recommended CAP, AECB, ABS approval
  - FDA “Approvable” for 3 indications (24-Jan-03)
  - FDA briefed AIDAC (06-Mar-03)

Timeline for FDA Approval of Telithromycin

- Complete response to 2nd FDA Letter (17-Oct-03)
  - monitoring and auditing documents from Study A3014
  - comprehensive review of visual effects
  - clinical trial data:
    - 2 Phase I drug-drug interaction studies
    - 1 Phase III CAP (antibiotic-resistant *S. pneumoniae*)
    - 1 Phase III AECB
  - ex-US postmarketing data:
    - 29,439 German postmarketing observational survey
    - ~6 million exposures (as of 31-Dec-03)

Timeline for FDA Approval of Telithromycin

- FDA approved telithromycin for CAP, AECB, and ABS (01-Apr-04)

Data to Support FDA Approval of Telithromycin

Clinical Pharmacology

Microbiology

Clinical Efficacy

Clinical Safety

Preapproval Clinical Pharmacology Data

- 90% absorption after oral administration and 57% absolute bioavailability (all ages, no food effect)
- Targeted plasma and respiratory tissue concentrations rapidly achieved
- Multiple pathways of elimination limit potential for increased exposure in special populations
  - no ↑ exposure in mild/moderate hepatic impairment
- Potent CYP3A4 inhibitor; telithromycin (TEL) ↑ concentration of drugs metabolized by CYP3A4

Preapproval Microbiology Data: In Vitro Activity

- Focused spectrum of activity against common and atypical bacterial pathogens that cause respiratory tract infections (RTIs)
- Activity against antibiotic-resistant *S. pneumoniae*
  - novel dual binding mechanism
- Limited activity against nonrespiratory pathogens
  - limited impact on usual bacterial host flora

Preapproval Clinical Efficacy Data: Pivotal Phase III Studies

- Pivotal Phase III efficacy and safety studies in CAP, AECB, and ABS
  - 10 randomized controlled studies
  - 4 open label studies
- Study design and primary efficacy parameters consistent with worldwide regulatory guidelines
  - randomized controlled noninferiority studies

Preapproval Clinical Efficacy Data: CAP

- 2016 TEL subjects in 4 randomized controlled and 4 open label pivotal Phase III CAP studies:
  - effective in CAP due to key common and atypical bacterial pathogens
    - 7 to 10-d TEL vs 10-d amoxicillin-clavulanate (AMC), clarithromycin (CLA), or trovafloxacin (TVA)
  - effective in CAP due to multidrug-resistant *S. pneumoniae* (MDRSP[a])
  - effective in outpatients at risk for complications
    - elderly, bilateral pneumonia, pneumococcal bacteremia

[a] Resistant to ≥2 classes of antibiotics.

CAP: Clinical Cure Rate by Study (All Pivotal Phase III Studies)

	TEL	COMP	95% CI[a]
Comparative CAP pooled	*90.4%*	*90.7%*	*[-4.0; 3.3]*
Study A3001 vs AMX	94.6%	90.1%	[-2.1; 11.1]
Study A3006 vs CLA	88.3%	88.5%	[-7.8; 7. 5]
Study A3009 vs TVA[b]	90.0%	94.1%	[-13.9; 5.2]
Study A4003 (7-day) vs CLA	89.3%	91.8%	[-9.7; 4.7]
Study A4003 (5-day) vs CLA	88.8%	91.9%	[-10.18; 4.26]
All CAP studies 7 to 10-d	*91.0%*		

AMX=amoxicillin; CLA=clarithromycin; TVA=trovafloxacin.

[a] Difference in clinical cure rates.

[b] Study terminated early due to FDA restrictions on trovafloxacin.

CAP: Clinical Cure Rate by Pathogen

	TEL 7 to 10-day	COMP[a] 10-day
Common pathogens		
Streptococcus pneumoniae	93.7%	90%
Haemophilus influenzae	89.3%	95.5%
Moraxella catarrhalis	85.5%	77.8%
Atypical pathogens		
Mycoplasma pneumoniae	97.1%	90.9%
Chlamydophila pneumoniae	94.3%	94.7%

[a] Comparators included amoxicillin (Study A3001), clarithromycin (Studies A3006, A4003), and trovafloxacin (Study A3009; study terminated early due to FDA restrictions on trovafloxacin).

CAP: Clinical Cure Rate for Antibiotic-Resistant *Streptococcus pneumoniae*

Causative pathogen	TEL (n/N, %)	COMP[a] (n/N, %)
All *S. pneumoniae*	312/333 (93.7%)	63/70 (90%)
PEN-R	20/23 (86.9%)	1/1[b]
ERY-R	29/33 (87.9%)	4/5[b]
MDRSP	34/37 (91.1%)	5/6[b]

N=number of subjects; n=number clinically cured; PEN-R=penicillin-resistant; ERY-R=erythromycin-resistant; MDRSP=multidrug-resistant *S. pneumoniae* (resistant to ≥2 classes of antibiotics).

[a] Comparators included amoxicillin (Study A3001), clarithromycin (Studies A3006, A4003), and trovafloxacin (Study A3009; study terminated early due to FDA restrictions on trovafloxacin).

[b] The numbers of isolates are too small for percentages to be meaningful.

CAP: Clinical Cure Rate by Risk Subgroup

	TEL (n/N, %)	COMP[a] (n/N, %)
Blood culture positive		
All *S. pneumoniae* bacteremia	67/76 (88.1%)	15/19 (78.9%)
PEN-R	5/7 (71.4%)	1/1
ERY-R	8/10 (80%)	4/5 (80%)
MDRSP	11/13 (84.6%)	5/6 (83.3%)
≥65 years old	295/335 (88%)	83/96 (86.5%)
PORT score ≥III	306/342 (89.5%)	83/110 (84.5%)

N=number of subjects; n=number clinically cured; PEN-R=penicillin G-resistant (MIC≥2.0 mg/mL); ERY-R=erythromycin A- (macrolide-) resistant (MIC≥1.0 mg/mL); MDRSP=multidrug-resistant *S. pneumoniae* (resistant to ≥2 classes of antibiotics); PORT=Pneumonia Patient Outcomes Research Team prediction rule based on age, coexisting disease, abnormal physical, abnormal laboratory findings.

[a] Comparators included amoxicillin (Study A3001), clarithromycin (Studies A3006, A4003), and trovafloxacin (Study A3009; study terminated early due to FDA restrictions on trovafloxacin).

Preapproval Clinical Efficacy Data: AECB

- 480 TEL subjects in 3 randomized controlled pivotal Phase III AECB studies:
  - effective in AECB due to key common bacterial pathogens
    - 5-d TEL vs 10-d amoxicillin-clavulanate (AMC), cefuroxime (CEF), or CLA
  - effective in outpatients at risk for complications
    - elderly, risk factors for morbidity[a], airway obstruction

[a] Respiratory insufficiency, congestive heart failure, diabetes mellitus, alcoholism, sickle cell disease, liver disease, coronary artery disease (Studies A3003, A3007), nonpulmonary cancer, cerebrovascular disease, COPD, allergy to antibiotics, IV drug use, inhaled corticosteroid use (Study A3007).

AECB: Clinical Cure Rate by Study (All Pivotal Phase III Studies)

	TEL	COMP	95% CI[a]
Study A3003 vs AMC	86.1%	82.1%	[-6.4; 14.3]
Study A3007 vs CEF	86.4%	83.1%	[-5.8; 12.4]
Study A3013 vs CLA	85.8%	89.2%	[-9.9;3.1]
All AECB studies	*86.0%*	*85.8%*	*[-4.3; 4.9]*

AMC=amoxicillin-clavulanate; CEF=cefuroxime; CLA=clarithromycin.

[a] Difference in clinical cure rates.

AECB: Clinical Cure Rate by Pathogen

	TEL 5-d	COMP[a] 10-d
Common pathogens		
Streptococcus pneumoniae	81.5%	78.9%
Haemophilus influenzae	73.3%	84.9%
Moraxella catarrhalis	93.1%	85.3%

[a] Comparators included AMX, CEF, and CLA.

AECB: Clinical Cure Rate by Risk Subgroup (Comparative Studies)

	TEL	COMP[a]
≥65 years old (N=184)	85.3%	83.3%
Risk factors for morbidity[b]		
at least 1 (N=338)	85.8%	85.5%
at least 2 (N=171)	83.0%	84.0%
FEV_1/FVC <60% (N=149)	78.5%	82.2%

FEV_1=forced expiratory volume at 1 minute; FVC=forced vital capacity.

[a] Comparators included amoxicillin-clavulanate (Study A3003), cefuroxime (Study A3007), and clarithromycin (Study A3013).

[b] Respiratory insufficiency, congestive heart failure, diabetes mellitus, alcoholism, sickle cell disease, liver disease, coronary artery disease (Studies A3003, A3007), nonpulmonary cancer, cerebrovascular disease, COPD, allergy to antibiotics, IV drug use, inhaled corticosteroid use (Study A3007).

Preapproval Clinical Efficacy Data: ABS

- 458 TEL subjects in 3 randomized controlled pivotal Phase III ABS studies:
  - effective in ABS due to key common bacterial pathogens
    - 5-d TEL vs 10-d AMC or CEF
  - effective in outpatients at risk for complications
    - investigator-assessed severe infection, pathogen at entry, opacity on sinus X-ray

ABS: Clinical Cure Rate by Study (All Pivotal Phase III Studies)

	TEL 5-day	TEL 10-day	COMP	95% CI[a]
Study A3005 vs AMC	75.3%	72.9%	74.5%	[-9.9; 11.7]
Study A3011 vs CEF[b]	85.2%	NA	82.0%	[-7.1; 13.4]
All ABS studies	*80.9%*	*72.9%*	*77.4%*	*[-3.8; 10.7]*
Study A3002[b,c]	91.1%	91.0%	NA	

AMC=amoxicillin-clavulanate; CEF=cefuroxime.

[a] Difference in clinical cure rates with 5-day TEL.

[b] Included bacteriologic cultures by sinus puncture aspirate or endoscopy.

[c] Telithromycin (5-day vs 10-day).

ABS: Clinical Cure Rate by Risk Subgroup

	TEL 5-day	COMP 10-day
Investigator-assessed severe infection	80.0%	77.8%
Pathogen at entry	87.5%	77%
Total opacity on sinus X-ray	85.7%	76.7%

Summary of Preapproval Clinical Efficacy Data for Telithromycin

- Effective in 14 pivotal Phase III efficacy studies for CAP (7 to 10-day treatment) as well as AECB and ABS (5-day treatment)
- Effective in CAP due to key common – including MDRSP – and atypical bacterial pathogens
- Effective in outpatients at risk for complications

Preapproval Safety Data: Steps Taken to Establish Safety of Telithromycin

- Conducted comprehensive clinical development program
- Collected and evaluated data from postmarketing surveillance
  - AE case definitions and data collection forms developed with FDA and external expert input
- Developed and implemented risk management plan

Preapproval Safety Data: Data Submitted to Support FDA Approval (31-Dec-03)

Source	TEL-treated
Phase I studies	1252
Phase III studies	4780
Randomized controlled[a]	2702
Ex-US postmarketing[b]	6 million
Other studies	2405
German survey	29,439
Study A3014[c]	12,159

[a] Including 2 Phase III randomized controlled T/P studies
[b] Based on Intercontinental Medical Statistics (IMS) data.
[c] Data not relied upon for FDA approval; number reflects safety evaluable subjects.

Most Frequent Treatment-Emergent Adverse Events in Phase III Studies

	TEL N=2702	COMP N=2139	TEL open label N=2078
Subjects (%) with AEs	1348 (49.9)	1035 (48.4)	738 (35.5)
Diarrhea	292 (10.8)	185 (8.6)	129 (6.2)
Nausea	213 (7.9)	99 (4.6)	92 (4.4)
Headache	148 (5.5)	126 (5.9)	55 (2.6)
Dizziness	99 (3.7)	57 (2.7)	22 (1.1)
Vomiting	79 (2.9)	48 (2.2)	41 (2.0)
Loose stools	63 (2.3)	33 (1.5)	16 (0.8)
Dysgeusia	43 (1.6)	77 (3.6)	14 (0.7)

Adverse Events Leading to Discontinuation and Serious Adverse Events in Phase III

Subjects (%) with AEs	TEL N=2702	COMP N=2139	TEL open label N=2078
AEs leading to discontinuation	119 (4.4)	92 (4.3)	48 (2.3)
All SAEs	59 (2.2)	61 (2.9)	69 (3.3)
All treatment-related SAEs	9 (0.3)	6 (0.3)	7 (0.3)
Deaths[a]	9 (0.3)	9 (0.4)	10 (0.5)

[a] No treatment-related deaths (as assessed by Investigator).

Adverse Events of Special Interest

- Several safety topics identified as adverse events of special interest (AESIs)
  - hepatic and cardiac (QTc-related)
    - review of preclinical, clinical pharmacology and/or clinical data
    - known effects of related macrolide class
  - visual AEs
    - Phase III randomized controlled studies
  - exacerbation of myasthenia gravis
    - postmarketing surveillance

Adverse Events of Special Interest: Hepatic Adverse Events

- Preclinical studies: ↑ hepatic enzymes, histologic changes
- Clinical studies:
  - hepatic AEs; incidence similar to comparators
  - 1 report of hepatitis with biopsy that showed granulomatous hepatitis with eosinophil granulocytes
- Ex-US postmarketing (n≈6 million as of 31-Dec-03)
  - moderate reversible hepatic injury
  - infrequent reports of Acute Severe Liver Injury (ASLI)
  - no reports of drug-related hepatic failure, death, transplantation

Adverse Events of Special Interest: Hepatic Adverse Events

- Hepatic safety comparable to other antibiotics prescribed for similar treatment indications
- Appropriate characterization of hepatic effects in initial labeling, including statement in Precautions section

Adverse Events of Special Interest: Cardiac (QTc-Related) Adverse Events

- Preclinical studies:↑ QTc; similar to macrolides
- Clinical pharmacodynamic studies (Phase I and III):
  - 1.5-ms mean ↑ QTc at therapeutic dose
  - QTc outlier values uncommon; similar frequency to CLA and non-macrolide antibiotics
  - no excess risk for significant QTc prolongation
- Ex-US postmarketing: isolated reports (torsades de pointes, ventricular fibrillation), lacked information or confounded
- Appropriate characterization of QTc prolongation in initial labeling, including statement in Warnings section

Adverse Events of Special Interest: Visual Adverse Events

- Clinical studies
  - incidence higher in TEL than COMP (1.1% vs 0.4%)
  - most visual AEs mild or moderate in severity
  - mild, transient, fully reversible blurred vision (0.5%)
  - Phase I studies – transient delay in accommodation
- Ex-US postmarketing
  - consistent with clinical trial reports
  - very rare reports of severe visual AEs; no objective eye injury or persistent ocular sequelae
- Appropriate characterization of visual effects in initial labeling, including statement in Precautions section

Adverse Events of Special Interest: Exacerbation of Myasthenia Gravis

- Clinical studies: no subjects with myasthenia gravis
- Ex-US postmarketing data:
  - rare reports of exacerbation of myasthenia gravis, including respiratory failure
  - generally occurred within a few hours of first dose and resolved with discontinuation of telithromycin
- Appropriate characterization of exacerbation of myasthenia gravis in initial labeling, including statement in Warnings section

Summary of Preapproval Safety Data

- Large experience prior to FDA approval[a]
  - 4780 subjects in pivotal Phase III studies
  - ~6 million postmarketing exposures
- Overall safety profile similar to marketed antibiotics
  - gastrointestinal events most common
  - low discontinuation rate
- AESIs characterized in initial labeling

[a] An additional 12,159 safety evaluable TEL subjects were enrolled in Study A3014, but these data were not used as a basis for FDA approval or referenced in the USPI.

Comparison of USPI for Adverse Events Reported in Warnings/Precautions Section

	TEL	ERY	CLA	AZI	AMX	AMC	CEF	LEV	MOX
Hepatic disorders	✖	✖				✖		✖	✖
QT prolongation/TdP	✖			✖				✖	✖
Exacerbation of myasthenia gravis	✖	✖							
Tendon effects								✖	✖
Osteochondrosis								✖	✖
Rhabdomyolosis		✖							
Allergic reactions				✖	✖	✖	✖	✖	✖
Syncope	✖							✖	✖
Visual disorders	✖								
Convulsions and psychoses								✖	✖
Peripheral neuropathy								✖	✖
Phototoxicity								✖	

Postapproval Activities

Status of Postmarketing Commitments

- Completed 18-month visual safety update report
  - characterized worldwide postmarketing spontaneous reports of visual AEs
  - results of analysis consistent with preapproval findings

Status of Postmarketing Commitments

- Experience in pediatric population
  - completed 10 Phase I, 3 Phase II studies
  - initiated 5 Phase III studies; safety data reviewed by Independent Data Monitoring Committee – no safety signal identified
  - voluntarily paused 08-Jun-06, pending final confirmation that pediatric development program consistent with current thinking of FDA

Risk Management Plan

- Telithromycin Risk Management Plan developed, continuously updated, and implemented to:
  - detect unexpected and rare AEs, regularly update TEL safety profile, and facilitate access to information
  - continually monitor AESIs to further characterize in clinical practice environments
  - compare occurrence of AESIs with other antibiotics prescribed for similar indications
  - provide ongoing microbiologic surveillance of antibiotic resistance patterns

Conclusions

- Completed comprehensive clinical development program
- Followed up on postmarketing commitments
- Continue to monitor and assess safety profile using multiple data sources and methods
- Perform microbiologic surveillance studies