

Summary and Conclusions

Bruno Leroy, MD

Internal Medicine, Global Medical Affairs

Medical Need

- Respiratory tract infections (RTIs) are frequent diseases often associated with morbidity (CAP, AECB, ABS) and mortality (CAP, AECB)
- Optimal therapy for community-acquired RTIs requires antibiotics with a focused spectrum that includes common (*S. pneumoniae* most frequent and invasive) and atypical pathogens
- Increased bacterial resistance to current antibiotics is a growing public health concern
- Physician needs anti-bacterial agents with efficacy against resistant RTI pathogens and focused spectrum

Limitations of Current Therapies

- Decreased in vitro activity against key bacterial RTI pathogens
 - macrolides, β -lactams
 - risk of complications due to inadequately treated infections
- “Bystander effects” on non-respiratory tract pathogens when the antibiotic spectrum is not specifically targeted to RTI pathogens
 - fluoroquinolones, β -lactams
 - decrease therapeutic options for treatment of serious non-RTI infections involving Gram negative pathogens

Telithromycin Microbiology Profile

Unique antibacterial profile:

- Active against key respiratory bacterial pathogens
 - common pathogens and atypicals
- Active against antibiotic-resistant *S. pneumoniae*
 - novel dual binding mechanism
 - low levels of resistance to telithromycin (less than 1% for *S. pneumoniae*)
- Limited activity against non-respiratory pathogens

Efficacy of Telithromycin in CAP

- Efficacy demonstrated in Phase III program
 - effective in CAP due to key common and atypical bacterial pathogens
 - effective in CAP due to multidrug-resistant *S. pneumoniae* (MDRSP)
 - effective in outpatients at risk for complications
 - elderly, bilateral pneumonia, pneumococcal bacteremia
- Efficacy also supported by recently completed Phase IV CAP studies in areas of high *S. pneumoniae* resistance

Efficacy of Telithromycin in AECB

- Efficacy demonstrated in Phase III program
 - consistently effective vs a broad range of comparators
 - effective against key common bacterial pathogens
 - effective in at-risk subgroups
 - elderly, risk factors for co-morbidities, airway obstruction
- Recently completed Phase IV studies show favorable results vs macrolide in AECB due to resistant *S. pneumoniae*

Efficacy of Telithromycin in ABS

- Efficacy demonstrated in Phase III program
 - consistently effective vs standard antibiotic treatments
 - effective against key common bacterial pathogens
 - effective in subgroups of interest
 - severe infection per investigator, documented pathogen at entry, total opacity on sinus x-ray
- Recently completed Phase IV studies show similar or shorter time to symptom resolution vs. antibiotics recognized for their efficacy

Summary:

Safety of Telithromycin (1)

- Extensive safety assessment from clinical trial data and postmarketing experience (~28 million exposures)
 - augmented postmarketing spontaneous reporting
 - pharmacovigilance program for AESIs
 - repeated periodic cumulative safety analyses
 - reporting rate analyses
 - data mining using several methods
 - two large epidemiology studies to evaluate hepatic risk

Summary:

Safety of Telithromycin (2)

- Specific safety pattern characterized
 - most common side effects are gastrointestinal
 - Myasthenia Gravis exacerbation, sometimes life-threatening
 - rare severe hepatic events comparable to other antibiotics in large epidemiologic studies
 - mild to moderate reversible visual events, rarely severe, no documented sequelae
 - infrequent syncope
 - minimal QTc prolongation; no evidence of increased cardiac risk
- Overall risk appears to be comparable to widely prescribed antibiotics used in the same indications

Risk Management Plan Implementation

- Labeling updates
- Patient Package Insert
- “Dear Healthcare Professional” letters
- Communication with disease organizations
- Ketek website for HCP and patients
- Support of CME
- Speaker’s bureau and slide kits
- Sales force training on updated labeling

Other Risk Minimization Activities Under Consideration in the US

- **Professional**
 - revise package insert to new Structured Product Labelling format
 - targeted healthcare communication (eg, “Pharmacy Alert”, “Neurology Alert”)
 - patient chart stickers for Myasthenia Gravis patients
 - support CME for the appropriate use of antibiotics in RTIs
 - contact specific MG centers of excellence
- **Patient**
 - patient educational information:
 - additional alerts regarding AESIs on www.ketek.com
 - evaluate packaging options and Medication Guide
- **Disease Organizations (MGFA, NORD, MDA)**
 - support education programs relevant to drug-induced exacerbations of MG
- **Monitor frequency of use of Ketek among MG patients**
 - through case-matched tracking of pharmacy Rx claims & medical claims

Conclusions (1)

- Benefits of telithromycin:
 - unique antibacterial spectrum, focused on RTI pathogens
 - including common pathogens, atypicals, MDRSP
 - limited activity on non-respiratory pathogens
 - effective in CAP, AECEB, ABS, including in the most vulnerable patients
 - preliminary Phase IV data provide further support for use in patients with resistant *S. pneumoniae* (CAP, AECEB) and in symptom resolution in ABS
- Overall risks associated with telithromycin appear to be comparable to those of other antibiotics prescribed for RTIs
 - 2 large epidemiology studies show comparable risk of acute severe liver injury vs antibiotics used in RTIs

Conclusions (2)

- Telithromycin is an important treatment option for its approved indications: CAP, AECSB, ABS