

Drug Benefit’s Complexities Offer Political Fodder

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WASHINGTON — Does your Medicare patient need a prescription for a drug not on his or her drug plan formulary? Be warned: You may have to fill out pages of forms.

“There continue to be widespread reports of drug plans requiring prior authorization for beneficiaries to receive needed medication,” Sen. Hillary Clinton

(D-N.Y.) said during a hearing of the U.S. Senate Special Committee on Aging. “Some reports have plans requiring forms for each drug, while others are requiring doctors to fill out forms as long as 14 pages for drugs that a beneficiary has been taking for years.”

Addressing her remarks to Dr. Mark B. McClellan, administrator of the Centers for Medicare and Medicaid Services and the hearing’s first witness, Sen. Clinton continued, “Your agency’s request that plans

discontinue this practice does not seem to be working, based on the information we have. I hope that you will require, not request, require that the plans cease this practice and enforce that requirement.”

In his prepared testimony, Dr. McClellan told the committee that CMS has “developed specific procedures for timely exceptions and appeals. Using those procedures, a Medicare beneficiary can get coverage for a drug that is not on a plan’s established formulary.”

He also acknowledged, however, that the plan rollout was not without problems. “We make no excuses for these problems,” he told committee members. “They are important, they are ours to solve, and we are finding and fixing them.”

Many of the problems with getting prescriptions filled occurred in the dual-eligible population—patients who qualified for both Medicare and Medicaid. “These often are the poorest and most vulnerable Americans who rely on medications to manage their chronic physical and mental illnesses,” noted committee chairman Gordon Smith (R-Ore.). “We knew there would be challenges associated with their transition from Medicaid into the new Medicare drug benefit, but

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it seems that perhaps not enough was done to ensure a seamless transition.”

As a result of the problems with the drug benefit, “pharmacists are not getting paid on time and have to take out

loans to pay their bills and keep their doors open,” said committee member Blanche Lincoln (D-Ark.). “These problems could have been avoided.”

Sen. Clinton said the problems were so bad that she was ready to give up. “I for one believe we should scrap this and start over. We are spending hundreds of billions of dollars on an inefficient delivery of a plan that could be done in a much more cost-effective way,” she said.

But Sen. Rick Santorum (R-Pa.) disagreed. “Throwing it out would doom seniors to a situation where they would be getting less care than they are today,” he said. “We should not be flippant about casting out babies with bathwaters. The idea that we’re going to once again play politics with prescription drugs . . . is below the dignity of this committee.”

Committee member Conrad Burns (R-Mont.) also weighed in. “We Americans are in this business that everything has to be instant—tea, coffee, everything that we do, and we’re supposed to have a new program put in place and all at once it’s perfect,” he said. “I would ask my colleagues [to just] get the program in place; that serves our purpose, and then we know what to fix. Right now, we don’t know what to fix.”

One thing Sen. Smith said he wants to change about Medicare is the program’s requirement that dual-eligible patients living at home or in an assisted living facility pay copayments for drugs received under the program; currently, only dual-eligible patients in nursing homes are exempt from copayments. Sen. Smith introduced a bill eliminating such copayments for dual-eligible patients in home- or community-based care; the measure, cosponsored by Sen. Jeff Bingaman (D-N.M.) was still being considered at press time.

Brief Summary of Prescribing Information Rev. October 2005

KETEK®
(telithromycin) Tablets

To reduce the development of drug-resistant bacteria and maintain the effectiveness of KETEK and other antibacterial drugs, KETEK should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

INDICATIONS AND USAGE

KETEK tablets are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years old and above.

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*.

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP[†]]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, or *Mycoplasma pneumoniae*.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of KETEK and other antibacterial drugs, KETEK should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

KETEK is contraindicated in patients with a history of hypersensitivity to telithromycin and/or any components of KETEK tablets, or any macrolide antibiotic. Concomitant administration of KETEK with cisapride or pimozide is contraindicated. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions** and **PRECAUTIONS**.)

WARNINGS

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including telithromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agents.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that toxin-producing strains of *Clostridium difficile* are the primary cause of “antibiotic-associated colitis”.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS**.)

Telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, telithromycin should be avoided in patients with congenital prolongation of the QTc interval, and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (e.g., quinidine and procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents.

No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with telithromycin treatment in 4780 patients in clinical efficacy trials, including 204 patients having a prolonged QTc at baseline.

Exacerbations of myasthenia gravis have been reported in patients with myasthenia gravis treated with telithromycin. This has sometimes occurred within a few hours after intake of the first dose of telithromycin. Reports have included life-threatening acute respiratory failure with a rapid onset in patients with myasthenia gravis treated for respiratory tract infections with telithromycin. Telithromycin is not recommended in patients with myasthenia gravis unless no other therapeutic alternatives are available. If other therapeutic alternatives are not available, patients with myasthenia gravis taking telithromycin must be closely monitored. Patients must be advised that if they experience exacerbation of their symptoms, they should discontinue treatment of KETEK and immediately seek medical attention. Supportive measures should be instituted as medically necessary.

PRECAUTIONS

General

Prescribing KETEK in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

KETEK may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported.

There have been post-marketing adverse event reports of syncope usually associated with vagal syndrome.

Patients should be cautioned about the potential effects of these visual disturbances and syncope on driving a vehicle, operating machinery or engaging in other potentially hazardous activities. (See **ADVERSE REACTIONS, CLINICAL STUDIES**.)

Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of KETEK. These events were generally reversible.

Caution should be used in patients with a previous history of hepatitis/jaundice associated with the use of KETEK. (See **ADVERSE REACTIONS, Liver and biliary system**.) Telithromycin is principally excreted via the liver and kidney. Telithromycin may be administered without dosage adjustment in the presence of hepatic impairment. In the presence of severe renal impairment (CL_{CR} < 30 mL/min), a reduced dosage of KETEK is recommended. (See **DOSAGE AND ADMINISTRATION**.)

Information for patients

The following information and instructions should be communicated to the patient. KETEK may cause problems with vision particularly when looking quickly between objects close by and objects far away. These events include blurred vision, difficulty focusing, and objects looking doubled. Most events were mild to moderate; however, severe cases have been reported. Problems with vision were reported as having occurred after any dose during treatment, but most occurred following the first or second dose. These problems lasted several hours and in some patients came back with the next dose. (See **PRECAUTIONS, General** and **ADVERSE REACTIONS**.) If visual difficulties occur:

- patients should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.
- avoiding quick changes in viewing between objects in the distance and objects nearby may help to decrease the effects of these visual difficulties.
- patients should contact their physician if these visual difficulties interfere with their daily activities.

Patients should be aware of the possibility of experiencing syncope (fainting), and its impact on the ability to drive, especially if they are experiencing vagal symptoms (severe nausea, vomiting, and/or lightheadedness).

If patients experience these symptoms, they should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.

Patients should also be advised:

- that antibacterial drugs including KETEK should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When KETEK is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by KETEK or other antibacterial drugs in the future.
- that KETEK has the potential to produce changes in the electrocardiogram (QTc interval prolongation) and that they should report any fainting occurring during drug treatment.
- that KETEK should be avoided in patients receiving Class 1A (e.g., quinidine, procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents.
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as uncorrected hypokalemia, or clinically significant bradycardia.
- that telithromycin is not recommended in patients with myasthenia gravis. Patients should inform their physician if they have myasthenia gravis.
- that simvastatin, lovastatin, or atorvastatin should be avoided in patients receiving KETEK. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be stopped during the course of treatment.
- that KETEK tablets can be taken with or without food.
- to inform their physician of any other medications taken concurrently with KETEK, including over-the-counter medications and dietary supplements.

Drug interactions

Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system. Co-administration of KETEK tablets and a drug primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentration of the drug co-administered with telithromycin that could increase or prolong both the therapeutic and adverse effects. Therefore, appropriate dosage adjustments may be necessary for the drug co-administered with telithromycin.

The use of KETEK is contraindicated with cisapride. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY, Drug-drug interactions**.)

The use of KETEK is contraindicated with pimozide. Although there are no studies looking at the interaction between KETEK and pimozide, there is a potential risk of increased pimozide plasma levels by inhibition of CYP 3A4 pathways by KETEK as with macrolides. (See **CONTRAINDICATIONS**.)

In a pharmacokinetic study, simvastatin levels were increased due to CYP 3A4 inhibition by telithromycin. (See **CLINICAL PHARMACOLOGY, Other drug interactions**.) Similarly, an interaction may occur with lovastatin or atorvastatin, but not with pravastatin or fluvastatin. High levels of HMG-CoA reductase inhibitors increase the risk of myopathy. Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of treatment.

Monitoring of digoxin side effects or serum levels should be considered during concomitant administration of digoxin and KETEK. (See **CLINICAL PHARMACOLOGY, Drug-drug interactions**.)

Patients should be monitored with concomitant administration of midazolam and dosage adjustment of midazolam should be considered if necessary. Precaution should be used with other benzodiazepines, which are metabolized by CYP 3A4 and undergo a high first-pass effect (e.g., triazolam). (See **CLINICAL PHARMACOLOGY, Drug-drug interactions**.)

Concomitant treatment of KETEK with rifampin, a CYP 3A4 inducer, should be avoided. Concomitant administration of other CYP 3A4 inducers such as phenytoin, carbamazepine, or phenobarbital is likely to result in subtherapeutic levels of telithromycin and loss of effect. (See **CLINICAL PHARMACOLOGY, Other drug interactions**.)

In patients treated with metoprolol for heart failure, the increased exposure to metoprolol, a CYP 2D6 substrate, may be of clinical importance. Therefore, co-administration of KETEK and metoprolol in patients with heart failure should be considered with caution. (See **CLINICAL PHARMACOLOGY, Drug-drug interactions**.)

Spontaneous post-marketing reports suggest that administration of KETEK and oral anticoagulants concomitantly may potentiate the effects of the oral anticoagulants. Consideration should be given to monitoring prothrombin times/INR while patients are receiving KETEK and oral anticoagulants simultaneously.

No specific drug interaction studies have been performed to evaluate the following potential drug-drug interactions with KETEK. However, these drug interactions have been observed with macrolide products.

Drugs metabolized by the cytochrome P450 system such as carbamazepine, cyclosporine, tacrolimus, sirolimus, hexobarbital, and phenytoin: elevation of serum levels of these drugs may be observed when co-administered with telithromycin. As a result, increases or prolongation of the therapeutic and/or adverse effects of the concomitant drug may be observed.

Ergot alkaloid derivatives (such as ergotamine or dihydroergotamine): acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia has been reported when macrolide antibiotics were co-administered. Without further data, the co-administration of KETEK and these drugs is not recommended.

Laboratory test interactions

There are no reported laboratory test interactions.

Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals to determine the carcinogenic potential of KETEK have not been conducted.

Telithromycin showed no evidence of genotoxicity in four tests: gene mutation in bacterial cells, gene mutation in mammalian cells, chromosome aberration in human lymphocytes, and the micronucleus test in the mouse.

No evidence of impaired fertility in the rat was observed at doses estimated to be 0.61 times the human daily dose on a mg/m² basis. At doses of 1.8-3.6 times the human daily dose, at which signs of parental toxicity were observed, moderate reductions in fertility indices were noted in male and female animals treated with telithromycin.

Pregnancy

Teratogenic effects: Pregnancy Category C. Telithromycin was not teratogenic in the rat or rabbit. Reproduction studies have been performed in rats and rabbits, with effect on pre-post natal development studied in the rat. At doses estimated to be 1.8 times (900 mg/m²) and 0.49 times (240 mg/m²) the daily human dose of 800 mg (492 mg/m²) in the rat and rabbit, respectively, no evidence of fetal terata was found. At doses higher than the 900 mg/m² and 240 mg/m² in rats and rabbits, respectively, maternal toxicity may have resulted in delayed fetal maturation. No adverse effects on prenatal and postnatal development of rat pups were observed at 1.5 times (750 mg/m²/d) the daily human dose.

There are no adequate and well-controlled studies in pregnant women. Telithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

Telithromycin is excreted in breast milk of rats. Telithromycin may also be excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when KETEK is administered to a nursing mother.

Pediatric use

The safety and effectiveness of KETEK in pediatric patients has not been established.

Geriatric use

In all Phase III clinical trials (n=4,780), KETEK was administered to 694 patients who were 65 years and older, including ≥ 35 patients who were 75 years and older. Efficacy and safety in elderly patients ≥ 65 years were generally similar to that observed in younger patients; however, greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is required based on age alone. (See **CLINICAL PHARMACOLOGY, Special populations, Geriatric** and **DOSAGE AND ADMINISTRATION**.)

ADVERSE REACTIONS

In Phase III clinical trials, 4,780 patients (n=2702 in controlled trials) received daily oral doses of KETEK 800 mg once daily for 5 days or 7 to 10 days. Most adverse events were mild to moderate in severity. In the combined Phase III studies, discontinuation due to treatment-emergent adverse events occurred in 4.4% of KETEK-treated patients and 4.3% of combined comparator-treated patients. Most discontinuations in the KETEK group were due to treatment-emergent adverse events in the gastrointestinal body system, primarily diarrhea (0.9% for KETEK vs. 0.7% for comparators), nausea (0.7% for KETEK vs. 0.5% for comparators).

All and possibly related treatment-emergent adverse events (TEAEs) occurring in controlled clinical studies in ≥ 2.0% of all patients are included below:

Table 5

All and Possibly Related Treatment-Emergent Adverse Events Reported in Controlled Phase III Clinical Studies (Percent Incidence)				
Adverse Event*	All TEAEs		Possibly-Related TEAEs	
	KETEK n= 2702	Comparator† n= 2139	KETEK n= 2702	Comparator† n= 2139
Diarrhea	10.8%	8.6%	10.0%	8.0%
Nausea	7.9%	4.6%	7.0%	4.1%
Headache	5.5%	5.8%	2.0%	2.5%
Dizziness (excl. vertigo)	3.7%	2.7%	2.8%	1.5%
Vomiting	2.9%	2.2%	2.4%	1.4%
Loose Stools	2.3%	1.5%	2.1%	1.4%
Dysgeusia	1.6%	3.6%	1.5%	3.6%

* Based on a frequency of all and possibly related treatment-emergent adverse events of ≥ 2% in KETEK or comparator groups.

† Includes comparators from all controlled Phase III studies.

The following events judged by investigators to be at least possibly drug related were observed infrequently (≥ 0.2% and < 2%), in KETEK-treated patients in the controlled Phase III studies.

Gastrointestinal system: abdominal distension, dyspepsia, gastrointestinal upset, flatulence, constipation, gastroenteritis, gastritis, anorexia, oral candidiasis, glossitis, stomatitis, watery stools.

Liver and biliary system: abnormal liver function tests: increased transaminases, increased liver enzymes (e.g., ALT, AST) were usually asymptomatic and reversible. ALT elevations above 3 times the upper limit of normal were observed in 1.6%, and 1.7% of patients treated with KETEK and comparators, respectively. Hepatitis, with or without jaundice, occurred in 0.07% of patients treated with KETEK, and was reversible. (See **PRECAUTIONS, General**.)

Nervous system: dry mouth, somnolence, insomnia, vertigo, increased sweating

Body as a whole: abdominal pain, upper abdominal pain, fatigue

Special senses: Visual adverse events most often included blurred vision, diplopia, or difficulty focusing. Most events were mild to moderate; however, severe cases have been reported. Some patients discontinued therapy due to these adverse events. Visual adverse events were reported as having occurred after any dose during treatment, but most visual adverse events (65%) occurred following the first or second dose. Visual events lasted several hours and recurred upon subsequent dosing in some patients. For patients who continued treatment, some resolved on therapy while others continued to have symptoms until they completed the full course of treatment. (See **PRECAUTIONS, General** and **PRECAUTIONS, Information for patients**.)

Females and patients under 40 years old experienced a higher incidence of telithromycin-associated visual adverse events. (See **CLINICAL STUDIES**.)

Urogenital system: vaginal candidiasis, vaginitis, vaginosis fungal

Skin: rash

Hematologic: increased platelet count

Other possibly related clinically-relevant events occurring in <0.2% of patients treated with KETEK from the controlled Phase III studies included: anxiety, bradycardia, eczema, elevated blood bilirubin, erythema multiforme, flushing, hypotension, increased blood alkaline phosphatase, increased eosinophil count, paresthesia, pruritus, urticaria.

Post-Marketing Adverse Event Reports:

In addition to adverse events reported from clinical trials, the following events have been reported from worldwide post-marketing experience with KETEK.

Allergic: face edema, rare reports of severe allergic reactions, including angioedema and anaphylaxis.

Cardiovascular: atrial arrhythmias, palpitations

Gastrointestinal system: pancreatitis

Liver and biliary system: Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with telithromycin. This hepatic dysfunction may be severe and is usually reversible.

Musculoskeletal: muscle cramps, rare reports of exacerbation of myasthenia gravis. (See **WARNINGS**.)

Nervous system: syncope usually associated with vagal syndrome.

OVERDOSAGE

In the event of acute overdose, the stomach should be emptied by gastric lavage. The patient should be carefully monitored (e.g., ECG, electrolytes) and given symptomatic and supportive treatment. Adequate hydration should be maintained. The effectiveness of hemodialysis in an overdose situation with KETEK is unknown.

DOSAGE AND ADMINISTRATION

The dose of KETEK tablets is 800 mg taken orally once every 24 hours. The duration of therapy depends on the infection type and is described below. KETEK tablets can be administered with or without food.

Table 6

Infection	Daily dose and route of administration	Frequency of administration	Duration of treatment
Acute bacterial exacerbation of chronic bronchitis	800 mg oral (2 tablets of 400 mg)	once daily	5 days
Acute bacterial sinusitis	800 mg oral (2 tablets of 400 mg)	once daily	5 days
Community-acquired pneumonia	800 mg oral (2 tablets of 400 mg)	once daily	7-10 days

KETEK may be administered without dosage adjustment in the presence of hepatic impairment.

In the presence of severe renal impairment (CL_{CR} < 30 mL/min), including patients who need dialysis, the dose should be reduced to KETEK 600 mg once daily. In patients undergoing hemodialysis, KETEK should be given after the dialysis session on dialysis days. (See **CLINICAL PHARMACOLOGY, Renal insufficiency**.)

In the presence of severe renal impairment (CL_{CR} < 30 mL/min), with coexisting hepatic impairment, the dose should be reduced to KETEK 400 mg once daily. (See **CLINICAL PHARMACOLOGY, Multiple insufficiency**.)

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