

# Cethromycin: A New Ketolide Antibiotic

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Community-acquired pneumonia (CAP) continues to be a common health challenge worldwide. It is the eighth leading cause of death and affects 5-6 million people in the United States yearly.<sup>1-3</sup> In Medicare patients older than 65 years, the average hospital length of stay due to CAP is 7 days; 15% of this time is spent in the intensive care unit (ICU), and 25% of patients hospitalized with CAP are admitted to the ICU.<sup>4</sup> The cost of admission for 1 episode of CAP is estimated to be \$9749.<sup>4</sup> In addition, the emergence of strains of *Streptococcus pneumoniae* that are resistant to oral antibiotics such as macrolides (40%) and penicillins (20%) makes it more difficult for clinicians to effectively manage treatment for patients with CAP.<sup>5,6</sup> Thus, finding new agents to treat CAP and reduce mortality, morbidity, and the associated hospital admission cost has become a ne-

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**OBJECTIVE:** To review the pharmacology, chemistry, microbiology, in vitro susceptibility, mechanism of resistance, pharmacokinetics, pharmacodynamics, clinical efficacy, safety, drug interactions, dosage, and administration of cethromycin, a new ketolide antibiotic.

**DATA SOURCES:** Literature was obtained through searching PubMed (1950-October 2012), International Pharmaceutical Abstracts (1970-October 2012), and a bibliographic review of published articles. Search terms included cethromycin, ABT-773, ketolide antibiotic, and community-acquired pneumonia.

**STUDY SELECTION AND DATA EXTRACTION:** All available in vitro and preclinical studies, as well as Phase 1, 2, and 3 clinical studies published in English were evaluated to summarize the pharmacology, chemistry, microbiology, efficacy, and safety of cethromycin in the treatment of respiratory tract infections.

**DATA SYNTHESIS:** Cethromycin, a new ketolide, has a similar mechanism of action to telithromycin with an apparently better safety profile. Cethromycin displays in vitro activity against selected gram-positive, gram-negative, and atypical bacteria. The proposed indication of cethromycin is treatment of mild to moderate community-acquired bacterial pneumonia in patients aged 18 years or older. Based on clinical studies, the recommended dose is 300 mg orally once a day without regard to meals. Cethromycin has an orphan drug designation for tularemia, plague, and anthrax prophylaxis. The Food and Drug Administration denied approval for the treatment of community-acquired pneumonia in 2009; a recent noninferiority trial showed comparable efficacy between cethromycin and clarithromycin. Preliminary data on adverse effects suggest that cethromycin is safe and gastrointestinal adverse effects appear to be dose-related.

**CONCLUSIONS:** Cethromycin appears to be a promising ketolide for the treatment of mild to moderate community-acquired pneumonia. It was denied approval by the FDA in 2009 pending more evidence to show its efficacy, with more recent studies showing its noninferiority to antibiotics for the same indication.

*Ann Pharmacother* 2013;47:368-368-79.

Published Online, 5 Mar 2013, *theannals.com*, doi: 10.1345/aph.1R435

cessity. Cethromycin appears to address the resistance issue by providing adequate coverage against *S. pneumoniae* for the treatment of mild to moderate CAP.<sup>7</sup> It is a ketolide antibiotic related to macrolides and is similar to telithromycin, which is currently the only approved ketolide. Telithromycin was originally approved for the treatment of acute sinusitis and acute exacerbation of chronic bronchitis in addition to CAP. However, because of concerns regarding hepatotoxicity, exacerbation of myasthenia gravis, visual disturbances, and loss of consciousness, the Food and Drug Administration (FDA) narrowed its indication to treatment of mild to moderate CAP only and added a black box warning contraindicating its use in myasthenia gravis. Fortunately, cethromycin does not appear to share the toxicity profile of telithromycin. The proposed indication for cethromycin is treatment of mild to moderate community-acquired bacterial pneumonia (CABP) due to susceptible strains of *S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Legionella pneumophila* in patients aged 18 years or older.<sup>8-12</sup>

The development of cethromycin began in 1997 when Abbott Laboratories, in collaboration with Taisho Pharmaceuticals, initiated the investigational process.<sup>13</sup> Phase 3 studies started in 2001 with these 2 laboratories, and Advanced Life Sciences continued the investigational process in 2005. Advanced Life Sciences named the drug Restanza and completed Phase 3 trials for the treatment of CAP and for the prevention of postexposure inhalation of anthrax. A New Drug Application was submitted to the FDA on September 30, 2008, seeking approval for use of cethromycin in treatment of mild to moderate CAP. In 2009, the FDA's Anti-Infective Drugs Advisory Committee voted in favor of the cethromycin safety profile but against its efficacy for treatment of CAP. The FDA has designated it as an orphan drug for the prophylactic treatment of inhalation anthrax postexposure.<sup>14,15</sup> In 2011, Advanced Life Sciences declared its liquidation and has been searching for additional investments in the cethromycin development program.<sup>16</sup> The patent for cethromycin will expire in 2016.<sup>13</sup> Despite the freeze in the approval process for mild to moderate pneumonia, studies continued to compare cethromycin to drugs marketed for the treatment of CAP, such as clarithromycin, and to study the efficacy of cethromycin against non-CAP-related pathogens.<sup>17,18</sup> A recently published study showed an increase in cardiovascular deaths in patients receiving azithromycin, which is used frequently for the treatment of pneumonia.<sup>19</sup> Under these circumstances, the search for new anti-infective agents directed against pneumonia is more warranted than ever before.

## Pharmacology

Cethromycin is a 3-keto, 11,12 carbamate derivative of erythromycin A with an O-6 linked aromatic ring. It binds

strongly to the 50S ribosomal subunit and inhibits bacterial protein synthesis.<sup>20</sup> It binds specifically to the 23S ribosomal RNA (rRNA) of the 50S ribosomal subunit.<sup>21,22</sup> As a ketolide, cethromycin has affinity to domains II and V of the 23S rRNA, unlike macrolides that have affinity to domain V.<sup>23</sup> Since the wall of the polypeptide exit tunnel is built mainly from nucleotides of domains I through V of the 23S rRNA, this binding blocks the exit tunnel and prevents the departure of the nascent polypeptide halting protein synthesis.<sup>22</sup> As a ketolide, and similar to erythromycin, clarithromycin, and azithromycin, cethromycin interacts with the large ribosomal subunit through hydrophobic interactions of the lactone ring and hydrogen bonding of its sugar moiety with the ribosome.<sup>22</sup> Also, these compounds can interact with ribosomes that possess short or vacant chains without touching ribosomes with large chains.<sup>24</sup> Macrolides, azalides, and ketolides possess different abilities to inhibit bacterial protein synthesis by halting the translation of growing peptide chains. For instance, with erythromycin, terminated peptide chains contain 6-8 residues, whereas, with telithromycin, those formed peptide chains contain 9-10 residues.<sup>25</sup> Cethromycin is expected to have the same mechanism of action as telithromycin.<sup>26</sup>

## Chemistry

Cethromycin (Figure 1),<sup>27</sup> formerly known as ABT-773, is a ketolide that possesses a chemical structure similar to that of macrolides. The macrolides' basic structure consists of a large 12- to 16-membered lactone ring with sugar moieties attached by glycosidic bonds. Azithromycin is a 15-membered ring, also known as an azalide compound, with a tertiary amino compound. Ketolides are 14-membered rings, like erythromycin and clarithromycin, where a keto group is present at the C3 position of the lactone ring and an 11,12 carbamate group.<sup>28</sup> Cethromycin has a quinolylallyl side chain at the C6 position of the lactone ring; telithromycin has an extended alkyl-aryl group that branches from 11,12 carbamate group.<sup>25</sup>

## Microbiology

In vitro activity of cethromycin against selected organisms is summarized in Table 1.<sup>29-45</sup>

### GRAM-POSITIVE BACTERIA

Cethromycin displays in vitro activity against streptococci, including strains of *S. pneumoniae* that are resistant to penicillins and macrolides.<sup>29-33</sup> It was shown to be more potent than its predecessor telithromycin against macrolide-resistant streptococci and more potent than macrolides and fluoroquinolones against penicillin-resistant strepto-

cocci.<sup>30,32,34</sup> The susceptibility to penicillin was determined using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (Table 1).<sup>35</sup> Although cethromycin displays in vitro activity against methicillin- and macrolide-susceptible *S. aureus*, this activity is greatly diminished in the presence of genes that confer resistance to clindamycin.<sup>30,31</sup> Cethromycin does not seem to have reliable in vitro activity against enterococci except strains of *Enterococcus faecalis* that are susceptible to vancomycin.<sup>31</sup> It also displays in vitro activity against *Bacillus anthracis* and was given an orphan status by the FDA in 2007 for the prophylactic treatment of patients exposed to inhalation anthrax.<sup>29</sup>

### GRAM-NEGATIVE BACTERIA

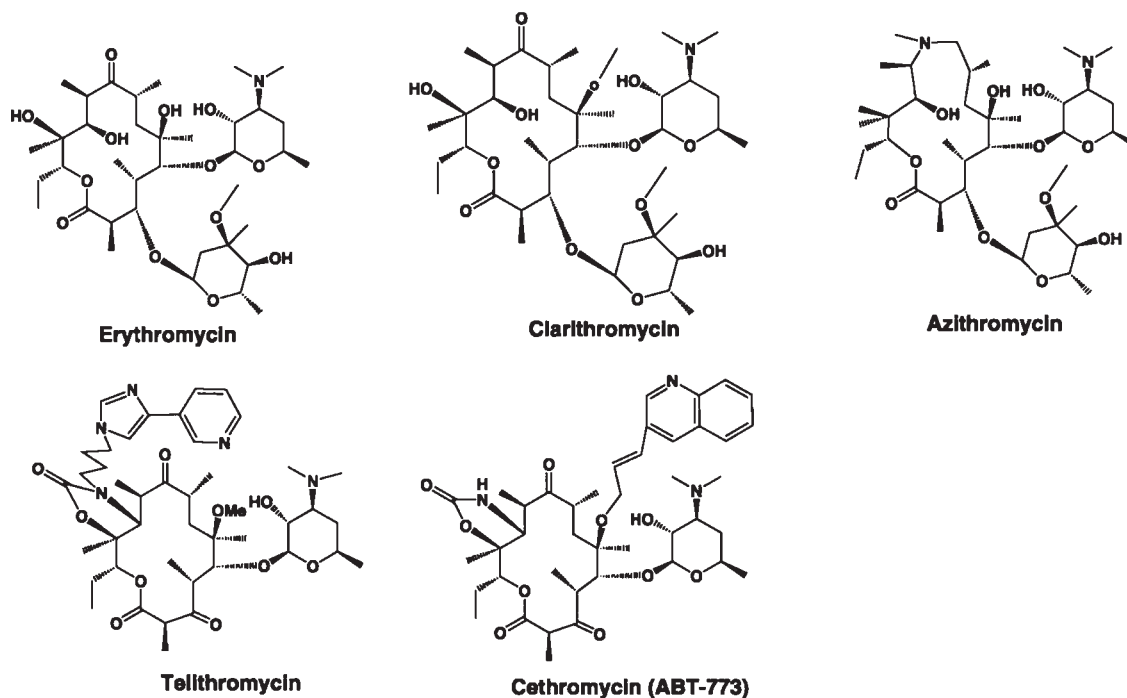
Cethromycin displays comparable in vitro activity to azithromycin against respiratory gram-negative organisms including  $\beta$ -lactamase-producing *H. influenzae* and *M. catarrhalis*.<sup>31,33</sup> It was shown to be more potent than erythromycin and clarithromycin but less potent than fluoroquinolones against  $\beta$ -lactamase-producing *H. influenzae*.<sup>32</sup> It showed similar potency against  $\beta$ -lactamase-producing *M. catarrhalis*.<sup>32</sup> In addition, cethromycin possesses in vitro activity against *Francisella tularensis* and *Yersinia pestis* and was given orphan drug status by the FDA in 2009 for the prophylactic treatment of plague and tularemia.<sup>29,36</sup>

### ATYPICAL AND ANAEROBIC BACTERIA

Cethromycin is active against the 3 organisms commonly associated with atypical pneumonia: *Chlamydomphila* spp., *Legionella* spp., and *Mycoplasma* spp.<sup>37-41</sup> It was shown to be more potent than telithromycin and the macrolides against *Chlamydomphila pneumoniae*.<sup>37,39</sup> The intracellular activity of cethromycin against *L. pneumophila* serogroup 1 was greater than that of macrolides but lower than that of fluoroquinolones.<sup>40</sup> The activity of cethromycin was comparable to that of macrolides but greater than that of fluoroquinolones and doxycycline against *Mycoplasma pneumoniae*.<sup>41</sup> While cethromycin is active against several anaerobic organisms associated with sinusitis and bites, it lacks significant activity against gram-negative anaerobes such as *Bacteroides* spp. and *Fusobacterium* spp.<sup>42-45</sup>

### Resistance

Strains of *S. pneumoniae* usually develop resistance to macrolides by either expressing efflux pumps or by alteration of the 50S ribosomal subunit.<sup>46,47</sup> The first mechanism of resistance is mediated by the *mefA* gene and results in phenotype M.<sup>47</sup> It affects only macrolides and is most prevalent in North America.<sup>46</sup> The second mechanism of resistance is mediated primarily by the *ermB* gene and occurs after methylation of adenine 2058 in 23S rRNA, resulting in phenotype MLS<sub>B</sub>. It affects macrolides, lin-



**Figure 1.** Chemical structures of related macrolide, azalide, and ketolide antibiotics.<sup>26</sup> Permission granted by the American Society for Microbiology through Copyright Clearance Center's RightsLink service, August 30, 2012.

Table 1. In Vitro Activity of Cethromycin

Organism	Isolates, n <sup>a</sup>	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)
<b>Gram-positive</b>			
<i>Bacillus anthracis</i> <sup>29</sup>	30	NR	0.12
<i>Staphylococcus aureus</i>			
macrolide-susceptible <sup>30,31</sup>	106	0.008-0.03	0.03
macrolide-resistant <sup>30,31</sup>	168	0.03 to >32	0.06 to >32
methicillin-susceptible <sup>32</sup>	180	0.03	0.06
methicillin-resistant <sup>32</sup>	20	0.06	0.06
<i>Streptococcus agalactiae</i> <sup>31</sup>	40	0.015	0.015
<i>Streptococcus pneumoniae</i> <sup>b</sup>			
penicillin-susceptible <sup>30,32-34</sup>	1501	≤0.008-0.06	≤0.01-0.015
penicillin-intermediate <sup>30,33,34</sup>	441	0.004-0.016	0.008-0.03
penicillin-resistant <sup>30,32,33</sup>	362	0.004-0.03	0.03-0.125
macrolide-susceptible <sup>30,31,34</sup>	373	0.001 to ≤0.008	0.002-0.016
macrolide-resistant <sup>30,31,34,35</sup>	684	0.004-0.063	0.015-0.5
<i>Streptococcus pyogenes</i>			
macrolide-susceptible <sup>30-32</sup>	218	≤0.002-0.015	≤0.002-0.015
macrolide-resistant <sup>30,31</sup>	125	0.002-0.12	0.002-0.5
<b>Gram-negative</b>			
<i>Francisella tularensis</i> <sup>36</sup>	30	NR	1
<i>Haemophilus influenzae</i>			
β-lactamase negative <sup>31-33</sup>	1296	2	4
β-lactamase positive <sup>31-33</sup>	695	2	4
<i>Moraxella catarrhalis</i>			
β-lactamase negative <sup>32,33</sup>	79	0.03-0.12	0.06-0.12
β-lactamase positive <sup>31-33</sup>	897	0.03-0.06	0.06-0.12
<i>Neisseria gonorrhoeae</i> <sup>31</sup>	35	0.03	0.06
<i>Yersinia pestis</i> <sup>29</sup>	30	NR	2
<b>Atypical</b>			
<i>Chlamydia pneumoniae</i> <sup>37-39</sup>	53	0.015-0.016	0.015-0.016
<i>Legionella pneumophila</i> <sup>40</sup>	96	0.03	0.03-0.06
<i>Mycoplasma pneumoniae</i> <sup>41</sup>	103	≤0.001	≤0.001
<i>Ureaplasma</i> spp. <sup>41</sup>	24	≤0.008	0.016
<b>Anaerobes</b>			
<i>Bacteroides fragilis</i> <sup>42,43</sup>	120	2-8	4-8
<i>Bacteroides</i> spp. <sup>42</sup>	64	0.25-4	4 to >32
<i>Clostridium difficile</i> <sup>42</sup>	64	0.064-0.125	0.125 to >32
<i>Clostridium perfringens</i> <sup>42,43</sup>	46	0.032 to ≤0.06	0.032 to ≤0.06
<i>Eikenella corrodens</i> <sup>44,45</sup>	28	0.5-1	1
<i>Fusobacterium</i> spp. <sup>42-45</sup>	89	0.25-4	0.5-8
<i>Pasteurella</i> spp. <sup>45</sup>	62	0.25-1	0.5-1
<i>Peptostreptococcus</i> spp. <sup>42-45</sup>	180	≤0.015-0.032	0.03 to ≤0.06
<i>Prevotella</i> spp. <sup>42,44,45</sup>	73	0.03-0.06	0.06-0.5
<i>Propionibacterium</i> spp. <sup>42,43,44</sup>	76	0.016 to ≤0.08	0.015 to ≤0.06
<i>Veillonella</i> spp. <sup>44</sup>	13	1	2

MIC<sub>50</sub> = minimum inhibitory concentration for 50% of tested isolates; MIC<sub>90</sub> = minimum inhibitory concentration for 90% of tested isolates; NR = not reported.

<sup>a</sup>Reported as mean values.

<sup>b</sup>Susceptibility to penicillin was determined using the broth microdilution method as described by the Clinical and Laboratory Standards Institute and the previously accepted breakpoints of MIC <0.1 µg/mL for susceptible, MIC between 0.1 and 1 µg/mL for intermediate, and MIC >1 µg/mL for resistant. The revised breakpoints for infections other than meningitis are MIC ≤2 µg/mL for susceptible, MIC 4 µg/mL for intermediate, and MIC ≥8 µg/mL for resistant. The revised breakpoints for meningitis are ≤0.06 µg/mL for susceptible and ≥0.12 µg/mL for resistant.

cosamides, and streptogramins and is most prevalent in Europe.<sup>46</sup> Both mechanisms of resistance have been associated with clinical failure of treatment in pneumococcal infections.<sup>48,49</sup> The addition of a ketone functional group confers to ketolides additional protection against resistance by adding a second ribosomal target site at domains II and V and by increasing the rate and extent of intracellular accumulation, making it more difficult for bacteria to escape the action of these antibiotics.<sup>46,47</sup> In fact, one study showed that 83% of the penicillin and erythromycin nonsusceptible isolates were inhibited by telithromycin and 97% of these isolates were inhibited by cethromycin.<sup>50</sup> However, rare mutations in 23S rRNA may result in phenotype K and other rare mutations in ribosomal protein L4 may result in phenotype MKS<sub>B</sub>, both of which affect ketolides.<sup>46</sup> For example, strains of phenotype X, a subgroup of the constitutive MLS<sub>B</sub> phenotype, have been shown to be less sensitive to cethromycin compared with other strains of the inducible MLS<sub>B</sub> phenotype.<sup>51</sup> The mechanisms of resistance of *H. influenzae* and *M. catarrhalis* to macrolides have not been clearly defined, but it is believed that gram-negative bacteria usually develop resistance to macrolides by expressing efflux pumps.<sup>52</sup> Since ketolides have a greater affinity to bacterial ribosomes than macrolides, they retain a more potent activity against these organisms.<sup>53</sup>

## Pharmacokinetics

Plasma pharmacokinetic parameters for cethromycin administered orally are listed in Table 2.<sup>54</sup>

### ABSORPTION

Steady-state plasma and intrapulmonary pharmacokinetic parameters of cethromycin were determined in healthy volunteers.<sup>54</sup> Five doses of cethromycin 150 or 300 mg were administered orally once daily to 60 healthy adults. Cethromycin demonstrated nonlinear pharmacokinetic

properties. It is characterized by relatively low serum concentrations, which can be attributed to its large volume of distribution. Plasma concentrations were not impacted by the weight of the subjects, with data available only for patients with a body mass index of 18-29 kg/m<sup>2</sup>. The coadministration of ranitidine reduces the bioavailability of cethromycin. One study demonstrated that the maximum concentration ( $C_{max}$ ) was reduced by 25.7% and the area under the curve (AUC) was reduced by 15.8%.<sup>55</sup> The authors hypothesized that the effect of ranitidine on the bioavailability of cethromycin may be attributed to its decreased solubility at higher gastric pH levels.

### DISTRIBUTION

Cethromycin achieves high intrapulmonary concentrations. For the 24-hour dosing interval in one study, the mean (SD) epithelial lining fluid concentrations ranged from 0.9 (1.0) µg/mL at 2 hours ( $C_{max}$ , time to  $C_{max}$  [ $t_{max}$ ]) to 0.1 (0.1) µg/mL at 24 hours (minimum concentration [ $C_{min}$ ], time to  $C_{min}$  [ $t_{min}$ ]) for the 150-mg dose group and from 2.7 (2.0) µg/mL at 4 hours ( $C_{max}$ ,  $t_{max}$ ) to 0.1 (0.1) µg/mL at 24 hours ( $C_{min}$ ,  $t_{min}$ ) for the 300-mg dose group.<sup>54</sup> Cethromycin alveolar concentrations achieved in this study ranged from 12.7 (6.4) µg/mL at 8 hours ( $C_{max}$ ,  $t_{max}$ ) to 2.9 (2.4) µg/mL at 24 hours ( $C_{min}$ ,  $t_{min}$ ) for the 150-mg dose group and from 55.4 (38.7) µg/mL at 6 hours ( $C_{max}$ ,  $t_{max}$ ) to 6.7 (3.4) µg/mL at 24 hours ( $C_{min}$ ,  $t_{min}$ ) for the 300-mg dose group.<sup>54</sup> In vitro studies, cethromycin demonstrated high penetration into human polymorphonuclear leukocytes, reaching intracellular concentrations several fold higher than extracellular concentrations.<sup>56</sup>

### METABOLISM

Cethromycin is metabolized by the liver and a total of 7 metabolites were identified. The major metabolite (M1) was

**Table 2.** Cethromycin Pharmacokinetic Parameters for Oral 150- and 300-mg Daily Doses<sup>54</sup>

Daily Dose <sup>a</sup>	$C_{max}$ , µg/mL	$t_{max}$ , h	AUC <sub>0-24</sub> , µg/h/mL	$t_{1/2}$ , h	Vd <sub>ss</sub> , mL/kg
<b>150 mg</b>					
Plasma, mean (SD)	0.181 (0.084)	2.01 (1.30)	0.902 (0.469)	4.85 (1.10)	1453 (997)
Epithelial lining fluid	0.94	2.0	11.4	6.43	
Alveolar concentration	12.7	8.0	160.8	10.0	
<b>300 mg</b>					
Plasma, mean (SD)	0.500 (0.168)	2.09 (0.03)	3.067 (1.205)	4.94 (0.66)	769 (272)
Epithelial lining fluid	2.75	4.0	24.15	5.26	
Alveolar concentration	55.4	6.0	636.2	11.6	

AUC<sub>0-24</sub> = area under the concentration-time curve from 0 to 24 hours;  $C_{max}$  = maximum concentration;  $t_{1/2}$  = elimination half-life;  $t_{max}$  = time to  $C_{max}$ ; Vd<sub>ss</sub> = volume of distribution at steady-state.  
<sup>a</sup>Administered as a daily oral dose for 5 days.

*N*-desmethyl cethromycin, which accounted for 34.7% of the administered dose. Other metabolites included a 10-hydroxy compound and an *N*-desmethyl-10-hydroxy compound, which accounted for less than 10% of the administered dose.<sup>57</sup>

## ELIMINATION

The primary route of elimination for oral cethromycin is fecal (average of 87.2%), with 31% of the administered dose (150 mg) excreted unchanged in the feces. Seven percent of the administered dose is eliminated in the urine, of which cethromycin accounted for 90% and the remaining 10% was the *N*-desmethyl metabolite.<sup>57</sup> The plasma elimination half-life ( $t_{1/2}$ ) of cethromycin 150 mg and 300 mg after daily administration for 5 days in healthy volunteers, was 4.85 hours and 4.94 hours, respectively.<sup>54</sup>

## SPECIAL POPULATIONS

### Renal Impairment

The pharmacokinetics of cethromycin in patients with severe renal impairment were recently studied.<sup>29,58</sup> A study enrolled 10 subjects with normal renal function (creatinine clearance >80 mL/min) and with stable severe chronic renal impairment (creatinine clearance 10–29 mL/min). Subjects received cethromycin 300 mg once daily for 5 days. Cethromycin's AUC at 24 hours (AUC<sub>24</sub>) and the C<sub>min</sub> were approximately 2.5 times greater in subjects with severe renal impairment. Similar increases were seen with exposure to unbound cethromycin. Elevated drug exposure was observed for subjects with severe renal impairment, which was somewhat unexpected, considering that only approximately 10% of an oral dose of cethromycin is excreted in urine. No dosage adjustment recommendations in patients with severe renal impairment were made in this study.<sup>58</sup> Also, cethromycin was evaluated in individuals with estimated creatinine clearance >80 mL/min and between 10 and 29 mL/min after the administration of 300-mg dose daily for 5 days. The investigators recommended a dose adjustment of 150 mg daily in subjects with estimated creatinine clearance between 10 and 29 mL/min; however, those with mild to moderate renal impairment and undergoing dialysis were not studied.<sup>29</sup>

### Hepatic Impairment

The pharmacokinetic properties of cethromycin were assessed following oral administration to subjects with mild and moderate chronic hepatic impairment.<sup>59</sup> This study included 12 participants with normal hepatic function, 6 patients with mild chronic hepatic impairment (Child-Pugh class A), and 6 patients with moderate chronic hepatic impairment (Child-Pugh class B). Each subject received a single 300-mg dose of cethromycin on study day

1 and 300 mg once daily for 5 days on study days 3–7. No apparent difference in steady-state exposure was observed between subjects with mild hepatic impairment or those with normal hepatic function. However, after 5-day dosing, the AUC<sub>24</sub> and C<sub>min</sub> of the total and unbound drug were greater for participants with moderate hepatic impairment than for those with normal hepatic function. The  $t_{1/2}$  was more prolonged in patients with moderate hepatic impairment compared to those with normal hepatic function (13.7 vs 9.9 hours,  $p < 0.05$ ). In each group, 95% of cethromycin was bound to plasma proteins. The authors concluded that no dosage adjustment was necessary in patients with mild or moderate hepatic impairment.<sup>59</sup> Data are limited in patients with severe hepatic impairment; cethromycin should be avoided in this population.

## Pharmacodynamics

Pharmacodynamic parameters, including C<sub>max</sub>/90% minimum inhibitory concentration (MIC<sub>90</sub>), AUC/MIC<sub>90</sub>, and percentage of time above MIC<sub>90</sub> (%T>MIC<sub>90</sub>), were determined for *M. pneumoniae*, *S. pneumoniae*, *C. pneumoniae*, *M. catarrhalis*, and *H. influenzae*. High intrapulmonary C<sub>max</sub>/MIC and AUC/MIC<sub>90</sub> ratios, high intrapulmonary drug exposure values, and prolonged %T>MIC<sub>90</sub> were found for all organisms except *H. influenzae*. The authors suggested that a higher daily dose would be necessary to exceed the MIC<sub>90</sub> for *H. influenzae* in the lungs.<sup>54</sup> A murine pneumonia model that investigated pharmacodynamic parameters demonstrated that cethromycin achieved rapid concentration-dependent bactericidal activity against *S. pneumoniae* isolates, with variable susceptibilities to macrolides. As with other macrolides and ketolides, the pharmacodynamic parameters that most closely predict outcomes are AUC<sub>unbound</sub>/MIC and C<sub>max unbound</sub>/MIC.<sup>60</sup> One study determined the post-antibiotic effect (PAE) of cethromycin compared to that of amoxicillin/clavulanate against clinical isolates of *S. pneumoniae* and *H. influenzae*. The PAEs of cethromycin and amoxicillin/clavulanate ranged from 2.3 to 6.0 hours and 0 to 2.2 hours against *S. pneumoniae* and from 2.7 to 9.1 hours and 0 to 0.8 hours against *H. influenzae*, respectively.<sup>61</sup>

## Animal Studies

### INHALATION ANTHRAX

In February 2007, the FDA designated cethromycin as an orphan drug for the prophylactic treatment of patients exposed to inhalation anthrax due to *B. anthracis*.<sup>62</sup> In May 2007, Advanced Life Sciences announced positive data from a study that showed a 30-day course of cethromycin to be effective in preventing inhalation anthrax infection in primates. Oral cethromycin 16 mg/kg was 100% protective against a lethal dose of inhaled anthrax as compared to the

current standard of care, oral ciprofloxacin, which demonstrated 90% protection.<sup>63</sup> Newer studies involving animals exposed to a lethal dose of inhaled anthrax showed that a 14-day course of oral cethromycin achieved between 60% and 100% survival rates after the animals demonstrated symptoms of anthrax infection.<sup>64</sup>

### TULAREMIA

In September 2009, the FDA designated cethromycin as an orphan drug for the prophylactic treatment of tularemia due to *F. tularensis*.<sup>62</sup> In December 2009, Advanced Life Sciences announced positive data from a pivotal study that showed a 14-day course of once-daily oral cethromycin to be effective in preventing tularemia infection in primates. Oral cethromycin 16 mg/kg, when initiated within 24 hours after exposure to a lethal dose of inhaled tularemia, was 100% protective as compared to placebo.<sup>14</sup>

### PLAGUE

In September 2009, the FDA designated cethromycin as an orphan drug for the prophylactic treatment of plague due to *Y. pestis*.<sup>62</sup> Advanced Life Sciences announced positive data from a pivotal study that showed a 14-day course of once-daily oral cethromycin to be effective in preventing plague infection in primates. Oral cethromycin, at doses up to 64 mg/kg initiated 24 hours after exposure to a lethal dose of inhaled plague, had a 90% survival rate as compared to placebo.<sup>15</sup> Recently, another study was done on *Y. pestis*-infected rats to evaluate the dose-related response to cethromycin. Rats were given 140 mg/kg/day orally in 2 divided doses every 24 hours after infection with *Y. pestis* for 7 days. Levofloxacin 20 mg/kg/dose was used as a positive control. Complete protection against mortality without any toxic effects was noted in the cethromycin group. Furthermore, blood and spleen cultures performed after treatment detected no plague bacilli. All survivors were rechallenged with 2 lethal doses of *Y. pestis* and did not require additional antibiotic treatment due to the development of specific antibodies against the V antigens of *Y. pestis*. These data demonstrate that cethromycin is potent treatment for pneumonic plague.<sup>65</sup> In November 2010, Advanced Life Sciences submitted a full proposal to the National Institute of Allergy and Infectious Diseases for the development of an intravenous formulation of cethromycin as a biodefense countermeasure.<sup>66</sup>

## Clinical Efficacy: Phase 2 and 3 Trials

### COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA

A randomized, parallel-group, double-blind, multicenter Phase 2 study (N = 182) compared the safety and efficacy of a 7-day course of orally administered cethromycin 300

mg to that of cethromycin 600 mg for the treatment of CAP.<sup>67</sup> Both doses were effective in achieving clinical cure (84% vs 73%, respectively) and microbiologic cure (85% vs 75%, respectively); however, p values were not provided.<sup>27</sup> The study supported the selection of once-daily cethromycin 300 mg for the treatment of CAP, as fewer gastrointestinal adverse events were observed.<sup>67</sup> A randomized, parallel-group, multicenter Phase 2-3 study (N = 583) compared the efficacy and safety of a 10-day course of therapy with that of cethromycin 150 mg once daily versus cethromycin 150 mg twice daily in ambulatory subjects with CAP.<sup>27,68</sup> Both doses were safe and well tolerated. Equivalence in the clinical cure rates (83% vs 81%), overall bacteriologic cure rates (83% vs 82%) (p values not provided), and pathogen eradication rates were demonstrated in the intent-to-treat population. Higher clinical cure rates in the clinically evaluable and clinically and bacteriologically evaluable populations were observed in the 150-mg once-daily treatment arm. A randomized, parallel-group, multicenter study (N = 582) compared a 7-day course of therapy of cethromycin 300 mg once daily versus cethromycin 250 mg twice daily in subjects with CAP.<sup>69</sup> Clinical cure rates were 83% versus 81%, respectively, and bacteriologic cure rates were 90% versus 86%, respectively (p values not provided). Results from these studies, combined with the pharmacokinetics/pharmacodynamics results from other studies, support a clinical dose selection for CAP treatment of 300 mg daily of cethromycin for 7 days. Two Phase 3 prospective, double-blind, randomized, parallel-group, multicenter, multinational, noninferiority studies (CL05-001 and CL06-001) evaluated the safety and efficacy of a 7-day course of oral cethromycin 300 mg daily versus oral clarithromycin 250 mg twice daily in patients with mild to moderate CAP.<sup>17</sup> CL05-001 and CL06-001 demonstrated noninferior cure rates at the visit 4 test-of-cure in the cethromycin group compared to the clarithromycin group in both the intent-to-treat analysis (CL05-001: 83.1% vs 81.1% [95% CI -4.8% to 8.9%], CL06-001: 82.9% vs 88.5% [95% CI -11.9% to 0.6%]) and the per protocol clinical population (CL05-001: 94% vs 93.8% [95% CI -4.5% to 5.1%], CL06-001: 91.5% vs 95.9% [95% CI -9.1% to 0.3%]). No clinically significant adverse events were observed during the studies. Cethromycin may be potential oral therapy for the outpatient treatment of CAP.

### ACUTE BACTERIAL SINUSITIS

A Phase 2 double-blind, randomized, parallel-group, multicenter study compared the safety and efficacy of 10-day oral courses of cethromycin 150 mg daily, cethromycin 300 mg daily, and cethromycin 600 mg daily for the treatment of acute bacterial sinusitis (ABS).<sup>70</sup> The clinical and bacteriologic cure rates were generally greater in the 300-mg daily group. Approximately 300 subjects were enrolled, and the study found that clinical and radiographic

response rates were generally lower for patients taking 600 mg of cethromycin daily, possibly because they exhibited a statistically significant increase in the number of gastrointestinal adverse events, making them somewhat less adherent to their treatment regimen. As a result, the overall pathogen cure rate was significantly higher ( $p < 0.05$ ) in the 300-mg group than in the 600-mg group.

A Phase 2-3 study compared the safety and efficacy of a 10-day course of oral cethromycin 150 mg once daily to that of oral cethromycin 150 mg twice daily for the treatment of ABS.<sup>70</sup> The study enrolled more than 600 patients and demonstrated that both treatment regimens were effective in resolving or improving clinical signs and symptoms of ABS and eradicating the target pathogens in the adults.<sup>70</sup> This study, combined with previous clinical trials for CAP and acute bacterial exacerbation of chronic bronchitis, supports the selection of a 300-mg daily dosing regimen in further studies of cethromycin in treating ABS.

#### ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS

A randomized, double-blind, multicenter, parallel-group Phase 2 study compared the efficacy and safety of once-daily cethromycin 150 mg, 300 mg, and 600 mg given orally for 5 days in patients with acute bacterial exacerbation of chronic bronchitis (ABECB).<sup>71</sup> Clinical cure rates with cethromycin in the clinically evaluable patients were 87% (150 mg), 90% (300 mg), and 90% (600 mg). The bacteriologic cure rates in the clinically evaluable patients were 86% (150 mg), 88% (300 mg), and 92% (600 mg) ( $p$  values not provided). Lower efficacy was observed with the 150-mg dose and an increased incidence of gastrointestinal adverse effects was observed with the 600-mg dose. A randomized, double-blind, multicenter, parallel-group Phase 3 study showed the efficacy of both a 5-day once-daily course of oral cethromycin 150 mg and a 7-day once-daily course of oral levofloxacin 500 mg, in ambulatory males and females older than 40 years with ABECB.<sup>72</sup> The study did not establish noninferiority of cethromycin, suggesting a dose of 300 mg may be more appropriate in comparator clinical studies of cethromycin versus standard-of-care therapy in ABECB.

#### Safety/Adverse Effects

Data on adverse effects are limited, but suggest that cethromycin is safe and well tolerated. Adverse effects appear to be dose-related, with gastrointestinal (diarrhea, nausea, vomiting, and abdominal pain) and nervous system (headaches) disorders as the most prominent. The overall incidence of treatment-emergent adverse effects is proportional to the frequency of drug administration and notably higher with the once-daily regimen compared to the twice-daily or 3-times-daily regimens.<sup>8</sup> In Phase 2 CAP trials, the

rate of serious adverse events and drug discontinuation due to these events was very low, ranging from 0 to 6.2%.<sup>67,68</sup> The most common adverse effects were gastrointestinal, affecting 18% of patients receiving 150 mg once daily, 27% receiving 300 mg once daily, and 49% receiving 600 mg once daily. Similar safety results were observed in Phase 2 and Phase 3 ABECB trials.<sup>71,72</sup> Unlike with telithromycin, no cases of severe hepatotoxicity were detected. In a recent Phase 3 CAP trial, dysgeusia was significantly reported in patients receiving cethromycin 300 mg daily compared to clarithromycin 250 mg twice daily (4.0% vs 9.3%,  $p = 0.001$ ), but it did not impact adherence or withdrawal from the study.<sup>17</sup>

A double-blind, randomized, parallel design study demonstrated that cethromycin therapeutic (300 mg once daily for 5 days) and supratherapeutic (900 mg once daily for 5 days) doses showed a nonsignificant prolongation of the QTc interval compared to placebo or moxifloxacin in healthy volunteers.<sup>73</sup> There had been no reports of serious hepatotoxicity, exacerbation of myasthenia gravis, or elevated bilirubin at the time of this writing. However, as with any investigational agent, continued diligence is warranted.

#### Drug Interactions

Preliminary in vitro data suggest that cethromycin is a substrate and inhibitor of CYP3A and a substrate and an inhibitor of P-glycoprotein.<sup>8</sup> Coadministration of rifampin, a potent CYP3A4 inducer, reduced the cethromycin  $C_{max}$  by 92% and the AUC by 95%, suggesting that cethromycin should not be used with potent CYP3A inducers. Coadministration of ketoconazole, a potent CYP3A4 inhibitor, increased the mean cethromycin  $C_{max}$  2.6-fold and its AUC 4.9-fold, suggesting a need for cethromycin dose adjustment when administered with potent CYP3A inhibitors. Coadministration with midazolam, a CYP3A substrate, increased the mean midazolam  $C_{max}$  1.5-fold and its AUC 2.3-fold, suggesting a need for midazolam dose adjustment.<sup>8</sup> One study showed that the administration of ranitidine in healthy volunteers 1 hour prior to cethromycin significantly prolonged the  $t_{1/2}$  of cethromycin by approximately 10%, extended the  $t_{max}$  by 14%, reduced the  $C_{max}$  by 25.7%, and reduced the AUC by 15.8%. The effect of ranitidine might result from the decreased solubility of cethromycin at higher gastric pH levels.<sup>55</sup> However, the 1-hour prior administration of sucralfate did not significantly affect the bioavailability of cethromycin. Another double-blind crossover study showed that concomitant oral administration of cethromycin and theophylline was well tolerated in healthy volunteers and cethromycin did not significantly increase the theophylline  $C_{max}$ ,  $C_{min}$ , or AUC.<sup>74</sup> Continued plasma concentration monitoring is recommended when theophylline, warfarin, and digoxin are coadministered with cethromycin. Awaiting further evidence, electrocardiogram monitoring may also be warranted with concomitant use of drugs that prolong the QT interval.



## Dosage/Administration

Several cethromycin doses have been studied for the treatment of CAP, ranging from 150 mg to 600 mg once daily.<sup>71</sup> Clinical cure and safety profile, in addition to pharmacokinetic data, favored 300-mg once-daily dosing.<sup>67-70</sup> An Advanced Life Sciences pivotal study showed that cethromycin doses up to 64 mg/kg achieved 90% cure rates for plague in primates<sup>15</sup>; however, a more recent study showed that doses up to 140 mg/kg/day are needed to be effective.<sup>65</sup> Doses of 16 mg/kg, which are equivalent to 300 mg/day in humans, are recommended for anthrax and tularemia prophylactic treatment.<sup>14,15,64</sup>

Dosage adjustments for patients with mild to moderate renal impairment or those undergoing dialysis have not been recommended for cethromycin.<sup>8,29</sup> However, Heine et al. recommend dose adjustment of 150 mg daily for individuals with estimated creatinine clearance between 10 and 29 mL/min.<sup>29</sup> Based on pharmacokinetic studies, no dose adjustments are needed in patients with any degree of hepatic impairment.<sup>29</sup>

## Summary

Cethromycin, a novel ketolide, was shown to be safe and effective in the treatment of mild to moderate CAP. It possesses reliable activity against the bacteria most commonly associated with CAP including *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. Unlike fluoroquinolones, cethromycin has a narrower spectrum of activity against gram-negative bacteria, which may reduce the risk of collateral damage and the incidence of *Clostridium difficile* infection. It offers an advantage over telithromycin in that hepatotoxicity does not seem to be a concern. The FDA denied approval of cethromycin for the treatment of CAP in 2009, requesting more efficacy data. However, a recent trial showed cethromycin to be noninferior to clarithromycin for the treatment of mild to moderate pneumonia. Thus, if further evaluated and approved by the FDA, cethromycin may represent an attractive therapeutic option for the treatment of mild to moderate CABP. In addition, cethromycin has been designated by the FDA as an orphan drug for prophylactic treatment of anthrax inhalation, tularemia, and plague and may represent a valuable addition to the armamentarium of antibiotics directed against bioterrorism.

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**Reprints/Online Access:** www.theannals.com/cgi/reprint/aph.1R435

**Conflict of interest:** Dr. Chahine serves on the speakers' bureaus for Forest Pharmaceuticals, Inc. and Optimer Pharmaceuticals, Inc.

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## References

- Nugent R, Back E, Beith A. The race against drug resistance. Washington, DC: Center for Global Development's Drug Resistance Working Group, 2010.
- Xu J, Kochanek KD, Murphy SL, Tejada-Vera B. 2010. Deaths: final data for 2007. *Natl Vital Stat Rep* 2010;58:1-136.
- Centers for Disease Control and Prevention. Fastats: pneumonia, September 2008. www.cdc.gov/nchs/fastats/pneumonia.htm (accessed 2012 May 5).
- Pal-Leung H, Cheng V, Chu C. Antibiotic resistance in community-acquired pneumonia caused by *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*, and *Acinetobacter baumannii*. *Chest* 2009; 136:1119-27.
- Farrell DJ, File TM, Jenkins SG. Prevalence and antibacterial susceptibility of mef( $\Delta$ )-positive macrolide-resistant *Streptococcus pneumoniae* over 4 years (200 to 2004) of the PROTEKT US study. *J Clin Microbiol* 2007;45:290-3.
- Felmingham D, Canton R, Jenkins SG. Regional trends in beta-lactam, macrolide, fluoroquinolone and telithromycin resistance among *Streptococcus pneumoniae* isolates 2001-2004. *J Infect* 2007;55:111-8.
- Bertrand D, Bertrand S, Neveu E, Fernandes P. Molecular characterization of off-target activities of telithromycin: a potential role for nicotinic acetylcholine receptors. *Antimicrob Agents Chemother* 2010;54:5399-402.
- Cethromycin for the treatment of community-acquired bacterial pneumonia. FDA Briefing Document for Anti-Infective Drugs Advisory Committee Meeting June 2, 2009. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-Infective-DrugsAdvisoryCommittee/UCM161847.pdf> (accessed 2012 Apr 30).
- Greene D. "Dear healthcare professional" letter. Sanofi-Aventis, March 2007. <http://www.ketek.com/pdf/dhcpletter.pdf> (accessed 2012 May 13).
- Package insert. Ketek (telithromycin). Bridgewater, NJ: Sanofi-Aventis, February 2007.
- Food and Drug Administration. News: FDA announces label and indication changes for the antibiotic Ketek. February 2007. <http://www.fda.gov/bbs/topics/news/2007/new01561.html> (accessed 2012 May 13).
- Food and Drug Administration. Patient safety news: narrower indications and new warnings for Ketek. April 2007. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=62> (accessed 2012 May 13).
- Cethromycin: A-195773, A-195773-0, A-1957730, Abbott-195773, ABT 773. *Drugs R D* 2007;8:95-102.
- Advanced Life Sciences' Restanza shows 100% survival in tularemia pivotal animal study. Press release: December 16, 2009. <http://www.advancedlifesciences.com> (accessed 2012 Apr 29).
- Advanced Life Sciences' Restanza demonstrates efficacy in plague pivotal animal study. Press release: September 29, 2009. <http://www.advancedlifesciences.com> (accessed 2012 Apr 29).
- Advanced Life Sciences' Annual report. <https://materials.proxyvote.com/00765H> (accessed 2012 May 9).
- English ML, Fredericks CE, Milanese NA et al. Cethromycin versus clarithromycin for community-acquired pneumonia: comparative efficacy

- cy and safety outcomes from two double-blinded, randomized, parallel-group, multicenter, multinational non-inferiority studies. *Antimicrob Agents Chemother* 2012;56:2037-47.
18. Hammerschlag MR, Sharma R. Use of cethromycin, a new ketolide, for treatment of community-acquired respiratory infections. *Expert Opin Investig Drugs* 2008;17:387-400.
  19. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881-90.
  20. Champney WS, Pelt J. The ketolide antibiotic ABT 773 is a specific inhibitor of translation and 50S ribosomal subunit formation in *Streptococcus pneumoniae* cells. *Curr Microbiol* 2002;45:155-60.
  21. Nilius AM, Ma Z. Ketolides: the future of the macrolides? *Curr Opin Pharmacol* 2002;2:493-500.
  22. Jenni S, Ban N. The chemistry of protein synthesis and voyage through the ribosomal subunit. *Curr Opin Struct Biol* 2003;13:212-9.
  23. Vimberg V, Xiong L, Bailey M, Tenson T, Mankin A. Peptide mediated macrolide resistance reveals possible specific interactions in the nascent peptide exit tunnel. *Mol Microbiol* 2004;54:376-85.
  24. Tipathi S, Kloss PS, Mankin AS. Ketolide resistance conferred by short peptides. *J Biol Chem* 1998;273:20073-7.
  25. Tenson T, Lovmar M, Ehrenberg M. The mechanism of action of macrolides, lincosamides and streptogramin B reveals the nascent peptide exit path in the ribosome. *J Mol Biol* 2003;330:1005-14.
  26. Kouvela E, Kalpaxis D, Wilson D, Dinos G. Distinct mode of interaction of a novel ketolide antibiotic that displays enhanced antibiotic activity. *Antimicrob Agents Chemother* 2009;53:1411.
  27. Rafie S, MacDougall C, James C. Cethromycin: a promising new ketolide antibiotic for respiratory infections. *Pharmacotherapy* 2010;30:290-303.
  28. Carbon CJ, Rubinstein E. Macrolides, ketolides, lincosamides and streptogramins. In: Cohen J, Powderly WG, eds. *Infectious diseases*. 2nd. Edinburgh, Scotland: Mosby Elsevier, 2004:1791-803.
  29. Heine HS, Miller L, Bassett J, et al. Antimicrobial activity of cethromycin, a novel ketolide, tested against diverse collections of *Bacillus anthracis* (BA) and *Yersinia pestis* (YP). Presented at: 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006.
  30. Shortridge VD, Zhong P, Cao Z, et al. Comparison of in vitro activities of ABT-773 and telithromycin against macrolide-susceptible and -resistant streptococci and staphylococci. *Antimicrob Agents Chemother* 2002;46:783-6.
  31. Barry AL, Fuchs PC, Brown SD. In vitro activity of the ketolide ABT-773. *Antimicrob Agents Chemother* 2001;45:2922-4.
  32. Dubois J, St-Pierre C. In vitro activity of ABT-773 versus macrolides and quinolones against resistant respiratory tract pathogens. *Diagn Microbiol Infect Dis* 2001;40:35-40.
  33. Brueggemann AB, Doern GV, Huynh HK. In vitro activity of ABT-773, a new ketolide, against recent clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. *Antimicrob Agents Chemother* 2000;44:447-9.
  34. Davies TA, Ednie LM, Hoellman DM, et al. Antipneumococcal activity of ABT-773 compared to those of 10 other agents. *Antimicrob Agents Chemother* 2000;44:1894-9.
  35. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus *Streptococcus pneumoniae*: coping with antimicrobial susceptibility in an era of resistance. *Clin Infect Dis* 2009;48:1596-600.
  36. Heine HS, Miller L, Bassett J, et al. Antimicrobial activity of cethromycin, a novel ketolide, tested against diverse collection of *Francisella tularensis* (FT). Presented at: 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007.
  37. Strigl S, Roblin PM, Reznik T, et al. In vitro activity of ABT 773, a new ketolide antibiotic, against *Chlamydia pneumoniae*. *Antimicrob Agents Chemother* 2000;44:1112-3.
  38. Hammerschlag MR, Reznik T, Roblin PM, et al. Microbiological efficacy of ABT-773 (cethromycin) for the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae*. *J Antimicrob Chemother* 2003;51:1025-8.
  39. Miyashita N, Fukano H, Yoshida K, et al. In vitro activity of cethromycin, a novel antibacterial ketolide, against *Chlamydia pneumoniae*. *J Antimicrob Chemother* 2003;52:497-9.
  40. Stout JE, Sens K, Mietzner S, et al. Comparative activity of quinolones, macrolides and ketolides against *Legionella* species using in vitro broth dilution and intracellular susceptibility testing. *Int J Antimicrob Agents* 2005;25:302-7.
  41. Waites KB, Crabb DM, Duffy LB. In vitro activities of ABT-773 and other antimicrobials against human mycoplasmas. *Antimicrob Agents Chemother* 2003;47:39-42.
  42. Citron DM, Appleman MD. Comparative in vitro activities of ABT-773 against 362 clinical isolates of anaerobic bacteria. *Antimicrob Agents Chemother* 2001;45:345-8.
  43. Sillerström E, Wahlund E, Nord CE. In vitro activity of ABT-773 against anaerobic bacteria. *Eur J Clin Microbiol Infect Dis* 2000;19:635-7.
  44. Goldstein EJ, Conrads G, Citron DM, et al. In vitro activities of ABT-773, a new ketolide, against aerobic and anaerobic pathogens isolated from antral sinus puncture specimens from patients with sinusitis. *Antimicrob Agents Chemother* 2001;45:2363-7.
  45. Goldstein EJ, Citron DM, Merriam CV, et al. Comparative in vitro activities of ABT-773 against aerobic and anaerobic pathogens isolated from skin and soft-tissue animal and human bite wound infections. *Antimicrob Agents Chemother* 2000;44:2525-9.
  46. Edelstein PH. Pneumococcal resistance to macrolides, lincosamides, ketolides, and streptogramin B agents: molecular mechanisms and resistance phenotypes. *Clin Infect Dis* 2004;38:S322-7.
  47. Jorgensen JH, Crawford SA, McElmeel ML, et al. Activities of cethromycin and telithromycin against recent North American isolates of *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2004;48:605-7.
  48. Kelley MA, Weber DJ, Gilligan P, et al. Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. *Clin Infect Dis* 2000;31:1008-11.
  49. Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 2002;35:556-64.
  50. Mason EO Jr, Lamberth LB, Wald ER, et al. In vitro activities of cethromycin (ABT-773), a new ketolide, against *Streptococcus pneumoniae* strains that are not susceptible to penicillin or macrolides. *Antimicrob Agents Chemother* 2003;47:166-9.
  51. Hamilton-Miller JM, Shah S. Activity of ketolide ABT-773 (cethromycin) against erythromycin-resistant *Streptococcus pneumoniae*: correlation with extended MLSK phenotypes. *J Antimicrob Chemother* 2002;50:907-13.
  52. Credito KL, Lin G, Pankuch GA, et al. Susceptibilities of *Haemophilus influenzae* and *Moraxella catarrhalis* to ABT-773 compared to their susceptibilities to 11 other agents. *Antimicrob Agents Chemother* 2001;45:67-72.
  53. Cao Z, Zhong P, Ruan X, et al. Ribosome affinity and the prolonged molecular postantibiotic effect of cethromycin (ABT-773) in *Haemophilus influenzae*. *Int J Antimicrob Agents* 2004;24:362-8.
  54. Conte JE Jr, Golden JA, Kipps J, Zurlinden E. Steady-state plasma and intrapulmonary pharmacokinetics and pharmacodynamics of cethromycin. *Antimicrob Agents Chemother* 2004;48:3508-15.
  55. Pletz MW, Preechachatchaval V, Bulitta J. ABT-773: pharmacokinetics and interactions with ranitidine and sucralfate. *Antimicrob Agents Chemother* 2003;47:1129-31.
  56. García I, Pascual A, Ballesta S. Accumulation and activity of cethromycin (ABT-773) within human polymorphonuclear leucocytes. *J Antimicrob Chemother* 2003;52:24-8.
  57. Guan Z, Fukumoto S, Fan L, et al. Human disposition and metabolism of orally administered [<sup>14</sup>C] ABT773 (abstract 942). Presented at: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, December 16-19, 2001.
  58. Bukofzer S, Gustavson L, Eizhamer DA, et al. Safety and pharmacokinetics of cethromycin following administration of multiple doses to subjects with severe renal impairment (abstract A-797). Presented at: 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007.
  59. Bukofzer S, Gustavson L, Eizhamer DA. Safety and pharmacokinetics of cethromycin following administration of single and multiple doses to

- subjects with mild and moderate chronic hepatic insufficiency (abstract A-796). Presented at: 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007.
60. Kim MK, Zhou W, Tessier PR, et al. Bactericidal effect and pharmacodynamics of cethromycin (ABT-773) in a murine pneumococcal pneumonia model. *Antimicrob Agents Chemother* 2002;46:3185-92.
  61. Neuhauser MM, Prause JL, Danziger LH, et al. Postantibiotic effects of ABT-773 and amoxicillin-clavulanate against *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Antimicrob Agents Chemother* 2001;45:3613-5.
  62. Food and Drug Administration. Searchable database for orphan designated and or approved products. <http://www.accessdata.fda.gov/scripts/opdlisting/ocpd/> (accessed 2012 Apr 29).
  63. Advanced Life Sciences. Advanced Life Sciences' Restanza shows 100% survival in confirmatory anthrax study. Press release: June 23, 2009. <http://www.advancedlifesciences.com> (accessed 2012 Apr 29).
  64. Advanced Life Sciences. Advanced Life Sciences' Restanza demonstrates efficacy in treating anthrax infection: study shows Restanza's significant efficacy after symptoms of anthrax infection are present. Press release: August 31, 2009. <http://www.advancedlifesciences.com> (accessed 2012 Apr 29).
  65. Rosenzweig JA, Brackman SM, Kirtley ML. Cethromycin-mediated protection against the plague pathogen *Yersinia pestis* in a rat model of infection and comparison with levofloxacin. *Antimicrob Agents Chemother* 2011;55:5034-5042.
  66. Advanced Life Sciences. Advanced Life Sciences submits full proposal to NIAD for development of intravenous formulation of Restanza as a biodefense countermeasure. Press release: November 9, 2010. <http://www.advancedlifesciences.com> (accessed 2012 Apr 29).
  67. Bukofzer S, Valdes J, Eiznhamer DA, et al. A phase 2 comparative study of the safety and efficacy of two oral doses of cethromycin for the treatment of community-acquired pneumonia (abstract: L-1442). In: Abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006.
  68. Bukofzer S, Gu Y, Eiznhamer DA, et al. A phase 2/3 comparative study of the safety and efficacy of two oral doses of cethromycin for the treatment of community-acquired pneumonia (CAP) (abstract L-1445). In: Abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006.
  69. Milanesio NA, English ML, Fredericks CE, et al. A comparative study of the safety and efficacy of cethromycin (CER) to clarithromycin (CLR) for the treatment of community-acquired pneumonia (CAP) in adults (CL05-001) (abstract L-683). In: Abstracts of the joint 48th Interscience Conference on Antimicrobial Agents and Chemotherapy/45th Annual Meeting of the Infectious Diseases Society of America, Washington, DC, October 25-28, 2008.
  70. Advanced Life Sciences. Advanced Life Sciences presents clinical data on selected cethromycin trials at the Infectious Diseases Society of America 44th Annual Meeting. Press release: October 13, 2006. <http://www.advancedlifesciences.com> (accessed 2012 May 2).
  71. Valdes J, Bukofzer S, Eiznhamer DA, et al. A phase 2 comparative study of the safety and efficacy of three oral doses of cethromycin for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) (abstract L-1443). In: Abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006.
  72. Bukofzer S, Gu Y, Eiznhamer DA, et al. A phase 3 comparative study of cethromycin 150 mg QD and levofloxacin 500 mg QD for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) (abstract L-1444). In: Abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006.
  73. Fredericks CE, Morganroth J, English ML, et al. A thorough QT study to define the ECG effects of cethromycin using a clinical and supratherapeutic dose compared to placebo and moxifloxacin in healthy subjects (CL07-001) (abstract). In: Abstracts of the Joint 48th Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Annual Meeting of the Infectious Diseases Society of America, Washington, DC, October 25-28, 2008.
  74. Gustavson LE, Ye X, Beason J, et al. ABT-773 has no clinically-important effect on the pharmacokinetics and safety of theophylline (abstract

A-941). In: Abstracts of the 41st Interscience Conference of Antimicrobial Agents and Chemotherapy, Chicago, IL, December 16-19, 2001.

## EXTRACTO

## Cetromicina: Un Nuevo Antibiótico Quetólido

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*Ann Pharmacother* 2013;47:368-79.

**OBJETIVO:** Revisar la farmacología, química, microbiología, susceptibilidad in vitro, mecanismo de resistencia, farmacocinética, farmacodinámica, eficacia clínica, seguridad, interacciones con otros fármacos, dosificación y administración de cetromicina, un nuevo antibiótico quetólido.

**FUENTES DE INFORMACIÓN:** Se obtuvo la literatura a través de una búsqueda de PubMed (1950-octubre 2012), International Pharmaceutical Abstracts (1970-octubre 2012), y una revisión bibliográfica de los artículos publicados. Los términos de búsqueda incluyeron cetromicina, ABT-773, antibiótico quetólido, y pulmonía adquirida en comunidad.

**SELECCIÓN Y EXTRACCIÓN DE FUENTES DE INFORMACIÓN:** Todos los estudios in vitro y preclínicos disponibles, así como estudios clínicos Fase I, II y III publicados en inglés fueron evaluados para resumir la farmacología, química, microbiología, eficacia, y seguridad de cetromicina en el tratamiento de infecciones del trayecto respiratorio.

**SÍNTESIS:** Cetromicina, un nuevo quetólido, tiene un mecanismo de acción similar a telitromicina con un perfil de seguridad aparentemente mejor. Presenta una actividad in vitro contra bacterias selectas gram-positivas, gram-negativas y atípicas. La indicación propuesta para cetromicina es el tratamiento de pulmonía bacteriana leve a moderada adquirida en la comunidad en pacientes de 18 años o más. Según los estudios clínicos, la dosis recomendada es 300 mg por vía oral una vez al día con o sin comidas. Cetromicina ha sido designada como fármaco huérfano para la prevención de tularemia, plaga y ántrax. Aunque la Administración de Alimentos y Drogas de los Estados Unidos (FDA) en 2009 no aprobó su uso en el tratamiento de pulmonía adquirida en comunidad, un estudio reciente de no-inferioridad demostró una eficacia comparable a claritromicina. Información preliminar sobre sus efectos adversos sugieren que cetromicina es segura y que sus efectos adversos gastrointestinales aparentan ser relacionado a la dosis.

**CONCLUSIONES:** Cetromicina aparenta ser un quetólido prometedor para el tratamiento de pulmonía leve a moderada adquirida en comunidad. La FDA denegó su aprobación en 2009 pendiente a más evidencia que demuestre su eficacia. Estudios más recientes demuestran que no es inferior a otros antibióticos para la misma indicación.

Traducido por Giselle Rivera-Miranda

## RÉSUMÉ

## Céthromycine: Un Nouvel Antibiotique de la Classe des Kétolides

H Mansour, EB Chahine, LR Karaoui, R El-Lababidi

*Ann Pharmacother* 2013;47:368-79.

**OBJECTIF:** Revoir la pharmacologie, la chimie, la microbiologie, l'activité in vitro, les mécanismes de résistance, la pharmacocinétique, la pharmacodynamique, l'efficacité clinique, l'innocuité, les interactions médicamenteuses, et la posologie de la céthromycine, un nouvel antibiotique de la classe des kétolides.

**PROVENANCE DES DONNÉES:** Les publications ont été identifiées à l'aide d'une recherche informatisée des banques de données PubMed (1950-octobre 2012) et International Pharmaceutical Abstracts (1970-octobre 2012), de même que de la revue de la bibliographie des publications identifiées. Les termes utilisés pour la recherche incluaient céthromycine, ABT-773, antibiotique kétolide, et pneumonie extra-hospitalière.

**SÉLECTION DES DONNÉES:** Toutes les études disponibles qu'elles soient précliniques, in vitro, de phase I, II ou III publiées en langue anglaise ont été évaluées et résumées.

**RÉSUMÉ:** La céthromycine, un nouvel antibiotique de la classe des kétolides, possède un mécanisme d'action similaire à la téliithromycine, avec apparemment, un profil d'innocuité plus favorable. Elle est active in vitro contre les bactéries gram-positif, les bactéries gram-négatif et les bactéries atypiques. La céthromycine est proposée pour le traitement des pneumonies extra-hospitalières d'intensité légère à modérée chez les adultes de 18 ans et plus. Pour cette indication, la dose recommandée serait de 300 mg une fois par jour sans égard à la prise d'aliments. En 2009, la FDA des États-Unis d'Amérique a rejeté la soumission du fabricant et demandé des évidences supplémentaires. La céthromycine a cependant obtenu le statut de médicament orphelin pour le traitement de la tularémie, de la peste et en prophylaxie lors d'exposition à

l'anthrax. Depuis lors, une étude contrôlée et à répartition aléatoire a démontré une efficacité non-inférieure à celle de la clarithromycine et des données préliminaires suggèrent un profil d'innocuité acceptable et des effets gastro-intestinaux associés à la dose.

**CONCLUSIONS:** La céthromycine apparaît prometteuse comme antibiotique de la classe des kétolides pour traiter les pneumonies extra-hospitalières d'intensité légère à modérée. Après un premier rejet en 2009 de la part de la FDA des États-Unis d'Amérique, des données plus récentes soutiennent une efficacité non-inférieure de la céthromycine à celles des autres antibiotiques de cette classe.

Traduit par Suzanne Laplante