

Therapeutic Class Overview Macrolides

INTRODUCTION

- The first agent in the macrolide class, erythromycin, has been used since the 1950s to treat respiratory tract infections and skin and soft tissue infections. Limitations of its use include gastrointestinal intolerance and a short half-life, which makes multiple daily doses necessary.
- Zithromax (azithromycin) and Biaxin (clarithromycin) have broader activity, more favorable pharmacokinetics and pharmacodynamics, and are better tolerated (*Zuckerman et al 2011*). These agents have been used for the treatment of respiratory tract infections, sexually transmitted diseases, and infections caused by *Helicobacter pylori* and *Mycobacterium avium* complex (MAC).
- Dificid (fidaxomicin) is the newest agent in the macrolide category. It exhibits minimal systemic absorption, high fecal concentrations, a long post-antibiotic effect, and restricted activity against normal gut flora, providing active and selective therapy for infection with *Clostridium difficile* (*Louie et al 2009, Tannock et al 2010*).
- Ketek (telithromycin) was the first member of the related ketolide group of antibiotics; however, telithromycin is no longer available in the US market (*Clinical Pharmacology 2019, FDA Web site 2018*).
- This review will focus on the following: Macrolide class containing azithromycin, clarithromycin, erythromycin, and fidaxomicin. Injectable and ophthalmic forms of azithromycin and erythromycin will not be discussed in this review.
- Medispan Class: Macrolides

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Biaxin* (clarithromycin)	✓
Biaxin XL* (clarithromycin extended-release)	✓
Dificid (fidaxomicin)	--
E.E.S., Ery-Tab, EryPed, Erythrocin (erythromycin)	✓
Zithromax (azithromycin)	✓

*The branded product is no longer marketed.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	azithromycin	clarithromycin	clarithromycin XL	erythromycin	Dificid (fidaxomicin)
Pharyngitis/tonsillitis due to <i>Streptococcus pyogenes</i>	✓ ^a	✓ ^a			
<i>Helicobacter pylori</i> infection and duodenal ulcer disease ^b		✓			
Acute maxillary sinusitis due to <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , or <i>Streptococcus pneumoniae</i>	✓	✓ ^a	✓		
Acute bacterial exacerbation of chronic bronchitis due to <i>Haemophilus influenzae</i> , <i>Haemophilus parainfluenzae</i> , <i>Moraxella catarrhalis</i> , or <i>Streptococcus pneumoniae</i>	✓ ^c	✓	✓		
Community-acquired pneumonia (CAP) due to <i>Haemophilus influenzae</i> , <i>Mycoplasma pneumoniae</i> , <i>Streptococcus pneumoniae</i> , or <i>Chlamydia pneumoniae</i>	✓ ^d	✓ ^a	✓ ^e		

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Indication	azithromycin	clarithromycin	clarithromycin XL	erythromycin	Difcid (fidaxomicin)
Uncomplicated skin and skin structure infections due to <i>Staphylococcus aureus</i> or <i>Streptococcus pyogenes</i>	✓ f	✓ a			
Disseminated mycobacterial infections due to <i>Mycobacterium avium</i> or <i>Mycobacterium intracellulare</i>	✓ g	✓ a			
Prevention of disseminated <i>Mycobacterium avium</i> complex (MAC) disease in patients with advanced HIV infection	✓ h	✓ a			
Acute otitis media due to <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , or <i>Streptococcus pneumoniae</i> in children	✓	✓			
Urethritis and cervicitis due to <i>Chlamydia trachomatis</i> or <i>Neisseria gonorrhoeae</i>	✓				
Genital ulcer disease in men due to <i>Haemophilus ducreyi</i> (chancroid)	✓				
<i>Clostridium difficile</i> -associated diarrhea in adults (>18 years of age)					✓
Non-gonococcal urethritis and cervicitis due to <i>Chlamydia trachomatis</i>	✓ i				
Rheumatic fever, prophylaxis of adults and children				✓	
Chlamydial infection				✓	
Diphtheria, adjunct to antitoxin in adults and children				✓	
Erythrasma in adults and children				✓	
Female gonococcal pelvic inflammatory disease in adults and children				✓	
<i>Entamoeba histolytica</i> -intestinal infectious disease in adults and children				✓	
Infection of skin or subcutaneous tissue in adults and children				✓	
Legionnaires disease in adults and children				✓	
Listeriosis in adults and children				✓	
Neonatal chlamydial conjunctivitis in children				✓	
Neonatal chlamydial pneumonia in children				✓	
Nongonococcal urethritis				✓	
Pertussis in adults and children				✓	
Respiratory tract infection in adults and children				✓	
Syphilis in adults and children				✓	

^a Also indicated for children; for clarithromycin, CAP due to *Haemophilus influenzae* is not approved in children.

^b Tablets in combination with amoxicillin and Prevacid (lansoprazole) or Prilosec (omeprazole) as triple therapy.

^c Azithromycin is not indicated for *Haemophilus parainfluenzae*. This was previously termed as acute exacerbations of chronic obstructive pulmonary disease.

^d Also indicated for children. Should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: cystic fibrosis, nosocomially acquired infections, known or suspected bacteremia, requiring hospitalization, elderly or debilitated patients, or significant underlying health problems that may compromise ability to respond to illness (including immunodeficiency or functional asplenia).

^e Also approved for *Haemophilus parainfluenzae* and *Moraxella catarrhalis*.

^f Also approved for *Streptococcus agalactiae*.

^g 600 mg tablet taken in combination with ethambutol.

^h 1200 mg taken alone or in combination with rifabutin.

ⁱ One gram dose.

(Micromedex 2.0 2019, Prescribing information: Clarithromycin 2018, Clarithromycin extended-release 2019, Dificid 2019, E.E.S. 2018, Ery-Tab 2018, EryPed 2019, Erythrocin 2018, Zithromax 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, the macrolide antibiotics have demonstrated efficacy for their respective indications, and available head-to-head studies do not consistently demonstrate the superiority of one macrolide over another.
- Studies evaluating the macrolides in the treatment of acute bacterial sinusitis demonstrate similar clinical and bacteriologic response rates with azithromycin and amoxicillin, amoxicillin/clavulanate, and levofloxacin (*Henry et al 2003, Klapan et al 1999, Murray et al 2005*).
- For the treatment of acute bacterial exacerbations of chronic bronchitis, 1 trial demonstrated no significant difference between clarithromycin and erythromycin in clinical and bacteriologic response rates, and another trial showed no significant difference between 7 days of treatment with immediate-release and 5 days of treatment with extended-release clarithromycin (*Gottfried et al 2005, Swanson et al 2005*). A pooled analysis of studies in the treatment of lower respiratory tract infections, including acute bronchitis and pneumonia did not find a significant difference between azithromycin and amoxicillin or amoxicillin/clavulanate (*Laopaiboon et al 2015*). A network meta-analysis of 48 studies examined the relative efficacy and safety of various antibiotics in the treatment of bronchitis and found no difference in efficacy between macrolides and beta-lactams or quinolones (*Wang et al 2017*).
- There are not enough data to make a conclusion about the efficacy of macrolides compared to non-macrolide antibiotics for the treatment of pediatric community-acquired lower respiratory tract infections caused by *Mycoplasma pneumoniae* (*Gardiner et al 2015*).
- For the treatment of *C. difficile* diarrhea, fidaxomicin was shown in clinical trials to be non-inferior to vancomycin in clinical cure rates, although it was also shown to have significantly lower rates of recurrence and higher rates of global cure (*Cornely et al 2012, Crook et al 2012, Louie et al 2011*). A meta-analysis of antibiotic treatments for *C. difficile*-associated diarrhea found statistical superiority of fidaxomicin over vancomycin in achieving symptomatic cure when pooling results from 2 trials (*Nelson et al 2017*). An additional meta-analysis of treatments for recurrent *C. difficile* infection found that fidaxomicin was superior to vancomycin and metronidazole in achieving a sustained symptomatic cure (*Beinortas et al 2018*).
- Regimens for the treatment of *H. pylori* infection have demonstrated varying results. One study demonstrated significantly better eradication rates with quadruple therapy (omeprazole, bismuth, metronidazole, and tetracycline) compared to triple therapy (clarithromycin, amoxicillin, and omeprazole) (*Malfertheiner et al 2011*). Similarly, another study demonstrated significantly higher eradication rates with quadruple therapy with pantoprazole, bismuth, metronidazole, and tetracycline compared to triple therapy with clarithromycin, amoxicillin, and pantoprazole (*Zheng et al 2010*). A study which compared clarithromycin vs metronidazole-based triple therapy (both combined with esomeprazole and amoxicillin) found significantly higher eradication rates in the group that received metronidazole-based triple therapy (*Adachi et al 2017*). A recent meta-analysis of 44 randomized controlled trials comparing triple therapy (proton pump inhibitor [PPI], clarithromycin, and amoxicillin) and quadruple sequential therapy (amoxicillin plus PPI for 5 days, followed by PPI, clarithromycin and metronidazole for 5 days) showed that eradication rates were statistically significantly better for the quadruple sequential group overall ($p < 0.001$), but equivalent when triple therapy lasted for 10 or 14 days. Neither group achieved optimal efficacy of $\geq 90\%$ eradication rate (*Nyssen et al 2016*).
- A study demonstrated no significant difference between azithromycin and clarithromycin in sterilization rates in patients with human immunodeficiency virus (HIV) and positive blood cultures for MAC disease (*Dunne et al 2001*). However, it is important to note that the study did not enroll the target number of patients, reducing the power of the study to 61%. A meta-analysis of 14 studies examining macrolide-containing regimens for the treatment of MAC found that macrolide-containing regimens have a treatment success rate of 60% (*Kwak et al 2017*). Clarithromycin has shown efficacy compared to placebo in the prevention of the development of disseminated MAC infection in patients with HIV (*Pierce et al 1996*).
- In the treatment of acute otitis media (AOM), azithromycin and clarithromycin have generally shown similar clinical efficacy when compared to other antibiotic agents including amoxicillin, amoxicillin/clavulanate, and cefdinir (*Arguedas et al 2005, Aspin et al 1994, Block et al 2005*).

- For the treatment of pertussis, azithromycin has shown efficacy in an open-label study, with up to 100% eradication rates (*Pichichero et al 2003*). A study directly comparing azithromycin, clarithromycin, and erythromycin demonstrated 100% eradication rates for all agents after 2 weeks (*Aoyama et al 1996*). Other studies comparing the macrolides for the treatment of pertussis show similar results (*Langley et al 2004, Lebel et al 2001*).
- Head-to-head studies evaluating the treatment of pharyngitis and pneumonia generally show no significant difference between agents in clinical and bacteriologic response (*Drehobl et al 2005, O'Doherty et al 1998, Schonwald et al 1990, Venuta et al 1998*). For the treatment of multiple diseases including pharyngitis, pneumonia and skin and skin structure infections, a study demonstrated no significant difference in clinical response between immediate- and extended-release clarithromycin (*Block et al 2006*).
- For the treatment of pelvic inflammatory disease, a Cochrane review found no clear difference between azithromycin and doxycycline. A sensitivity analysis that included a single study with low risk of bias found that azithromycin was superior to doxycycline for mild to moderate pelvic inflammatory disease (*Savaris et al, 2017*).
- A Cochrane review of 14 RCTs evaluated the safety and efficacy of antibiotic treatments for genital infections with *C. trachomatis*, and found a higher rate of microbiological failure in men treated with azithromycin single-dose vs doxycycline once or twice daily for 7 days (RR, 2.45; 95% CI, 1.36 to 4.41); the effect of both treatments on clinical failure was uncertain (RR, 0.94; 95% CI, 0.43 to 2.05). Results for microbiological failure with azithromycin vs doxycycline in women were uncertain (RR, 1.71; 95% CI, 0.48 to 6.16), and no studies assessed clinical failure. Azithromycin is likely associated with fewer adverse events compared to doxycycline in both men and women (RR, 0.83; 95% CI, 0.71 to 0.98) (*Páez-Canro et al 2019*).

CLINICAL GUIDELINES

- Per treatment guidelines, azithromycin and clarithromycin are recommended as first-line treatment for CAP, prevention of MAC in children, and treatment of MAC in children and adults (*Bradley et al 2011, Mandell et al 2007, Panel 2019[b], Uthman et al 2013*). Both azithromycin and clarithromycin were also previously recommended for the prevention of MAC in adults; however, a recent update to the guidelines no longer recommends primary prophylaxis against disseminated MAC disease in patients with HIV who initiate ART therapy immediately. In patients whom prophylaxis is being considered, azithromycin and clarithromycin are still the preferred agents (*Panel 2019[a]*). Clarithromycin is also recommended as part of a multi-drug regimen for *H. pylori* infections (*Chey et al 2017, Jones et al 2017*).
- Macrolides are recommended as first-line treatment for pertussis, some sexually transmitted infections such as chancroid, urethritis, cervicitis, chlamydia, some skin and soft tissue infections such as impetigo (although some strains of *Staphylococcus aureus* and *Streptococcus pyogenes* may be resistant), cat scratch disease, and bacillary angiomatosis (*CDC 2005, Stevens et al 2014, Workowski 2015*). Azithromycin should not be used in patients with cardiovascular disease due to the risk of abnormal electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm; an alternative macrolide should be selected (*CDC 2017*).
- Per treatment guidelines, azithromycin in combination with ceftriaxone is recommended as first-line treatment for gonorrhea (*Workowski 2015*).
- The macrolides are recommended as an alternative treatment for Group A streptococcal pharyngitis (*Shulman et al 2012, Short et al 2017, van Driel et al 2016*). In general, children that require treatment of AOM should receive high-dose amoxicillin 90 mg/kg/day if amoxicillin has not been given in the last 30 days or the child does not have purulent conjunctivitis (*Lieberthal et al 2013*). For children with recent amoxicillin use, concurrent purulent conjunctivitis, or penicillin allergy, an antibiotic with additional beta-lactamase coverage for AOM should be prescribed. Macrolides such as erythromycin and azithromycin have limited efficacy against *Haemophilus influenzae* and *S. pneumoniae*.
- Azithromycin is recommended to be used to improve lung function and reduce exacerbations in individuals aged 6 years and older who have cystic fibrosis with *Pseudomonas aeruginosa* persistently present in cultures of the airways. In individuals without *P. aeruginosa* persistently present in cultures of the airways, the chronic use of azithromycin should be considered to reduce exacerbations (*Mogayzel et al 2013*). Treatment appears safe over a 6-month period (*Southern et al 2012*).
- For exacerbations of chronic obstructive pulmonary disease (COPD) that are due to bacterial infections, it is recommended to use amoxicillin with clavulanate, a macrolide, or tetracycline (*GOLD 2019*).
- First-line treatment for acute sinusitis is amoxicillin-clavulanate. Macrolides are no longer recommended due to increasing resistance (*Short et al 2017*).

- Fidaxomicin is a unique agent for the treatment of *C. difficile* diarrhea. Preliminary data suggest it may have efficacy in treating more resistant strains than metronidazole or vancomycin. It may also decrease the number of recurrent infections. Older guidelines mention this agent as a treatment option for severe cases of *C. difficile* diarrhea but do not explicitly recommend its use due to a lack of data (Surawicz et al 2013, Steele et al 2015). More recent guidelines recommend the use of either fidaxomicin or vancomycin as initial therapy for *C. difficile* diarrhea, as well as in recurrent episodes (McDonald 2018).

SAFETY SUMMARY

- The most frequently reported adverse events for macrolides are gastrointestinal in nature and include nausea/vomiting, abdominal pain, abnormal taste, dyspepsia, and diarrhea/loose stools. In clinical trials, patients also reported headache, and pediatric patients reported rashes.
- The macrolides should not be used in patients reporting a sensitivity or hepatic dysfunction with previous use.
- The macrolides act on the cytochrome (CYP) P450 system; therefore, many drug interactions can occur. Some interactions include the statins, pimozide, colchicine, protease inhibitors, and calcium channel blockers.
- Prolongation of the QTc interval has been reported with use of these agents. They should not be used in patients with congenital QTc interval prolongation or in patients with proarrhythmic conditions.
- With the exception of fidaxomicin, all agents in the class can cause hepatic injury. If signs and symptoms occur, the drug should be discontinued immediately.
- A large, multicenter, randomized controlled trial that studied the effects of a 2-week course of clarithromycin on patients with stable coronary heart disease who were followed for up to 3 years found a significant increase in cardiovascular mortality associated with the use of clarithromycin (Jespersen 2006). A 10-year follow-up to the initial study found that clarithromycin was associated with an increased risk of all-cause mortality and cerebrovascular disease (Winkel 2015). Risks and benefits of clarithromycin treatment should be weighed in patients with suspected or confirmed coronary artery disease.
- Azithromycin and clarithromycin have been associated with serious allergic and skin reactions, including angioedema, anaphylaxis, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS). These may recur even after discontinuation of therapy. Fatalities have been reported.
- In August 2018, the FDA issued a warning that azithromycin should not be used as a long-term prophylaxis therapy against bronchiolitis obliterans syndrome in patients after a stem cell transplant (FDA MedWatch 2018). Results of a clinical trial indicated that use of azithromycin in this setting may increase the risk of cancer relapse and death.
- Azithromycin and erythromycin are Pregnancy Category B (no evidence of risk in humans, but there remains a remote possibility; animal reproductive studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women). Clarithromycin is not recommended for use in pregnant women based on animal reproduction studies that have shown an adverse effect on the fetus; current data in humans are insufficient to inform drug-associated risks. The labeling for fidaxomicin has also been updated to follow the FDA's Pregnancy and Lactation Labeling Rule Conversion, and states that there are limited data in humans to inform any drug-associated risk; however, reproduction studies in animals have not shown evidence of harm to the fetus. Safety labeling changes for erythromycin products include a precaution that observational studies have described cardiovascular malformations that have occurred in early pregnancy after exposure to erythromycin products.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Biaxin (clarithromycin)	Granules for suspension, tablet	Oral	Twice daily	The dose of clarithromycin should be reduced by 50% in patients with creatinine clearance (CrCL) < 30 mL/min; for patients with CrCL 30 to 60 mL/min taking atazanavir or ritonavir, the clarithromycin dose
Biaxin XL (clarithromycin extended release)	Extended release tablet	Oral	Once daily	

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				should be reduced by 50%; for CrCL < 30 mL/min and on atazanavir or ritonavir, the clarithromycin dose should be reduced by 75%.
Dificid (fidaxomicin)	Tablet	Oral	Twice daily	
E.E.S., Ery-Tab, EryPed, Erythrocin	Delayed release capsule, suspension, delayed release tablet, film-coated tablet, tablet	Oral	Two to 4 times daily	Use caution in patients with impaired hepatic function.
Zithromax (azithromycin)	Dose packet, suspension, tablet	Oral	Once daily	

See the current prescribing information for full details

CONCLUSION

- The macrolides have been proven effective by clinical trials for many different infections; however, antibiotics are overused, and thus, many bacteria have become resistant to the macrolides as well as other antibiotics. Selection of agents for treatment of different infections is based on local susceptibility patterns.
- Per treatment guidelines (*Bradley et al 2011, Chey et al 2017, Mandell et al 2007, Panel 2019[a], Panel 2019[b]*), azithromycin and clarithromycin are recommended as first line treatment for CAP, prevention and treatment of MAC in children and treatment of MAC in adults, and clarithromycin as part of a multi-drug regimen for *H. pylori* infections.
- Macrolides are recommended as first line treatment for pertussis, some sexually transmitted infections, and some skin and soft tissue infections (*CDC 2005, Stevens et al 2014, Workowski 2015*).
- The macrolides are recommended as an alternative treatment for Group A streptococcal pharyngitis (*Shulman et al 2012, Short et al 2017, van Driel et al 2016*).
- The macrolides are often used when patients are allergic to penicillins (*Stevens et al 2014, Workowski 2015*).
- Dificid (fidaxomicin) is recommended in recent *C. difficile* treatment guidelines as an initial therapy alternative to vancomycin for *C. difficile* diarrhea, as well as in recurrent infections (*McDonald 2018*). Earlier guidelines suggest that it may have a place in therapy for severe, recurrent cases due to limited data (*Cohen et al 2010, Surawicz et al, 2013, Steele et al 2015*).
- The most common side effects seen with the macrolides are gastrointestinal including nausea/vomiting, diarrhea, and abdominal pain.
- Many drug interactions can occur with agents in this category due to their action on the CYP 450 system; caution should be used when adding a macrolide to a patient's drug regimen.

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