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NEW DRUGS

Delafloxacin meglumine, Meropenem trihydrate/vaborbactam, Secnidazole, and Benznidazole

Daniel A. Hussar, Molly A. Walter

Antibacterial agents

Approximately 3 million patients are hospitalized each year because of acute bacterial skin and skin structure infections (ABSSSIs) such as cellulitis, wound infection, major cutaneous abscess, and burn infection. Empirical treatment is often initiated before the availability of the results of cultures and commonly includes an antibiotic, such as vancomycin, with a high level of activity against gram-positive bacteria and an antibiotic, such as aztreonam, with a high level of activity against gram-negative bacteria.

Delafloxacin meglumine

Delafloxacin meglumine (Baxdela–Melinta) is a fluoroquinolone antibacterial agent with properties that are most similar to other members of this class such as levofloxacin, moxifloxacin, and ciprofloxacin. It is supplied in formulations for oral and intravenous administration, and is indicated for the treatment of adults with ABSSSIs caused by susceptible isolates of the gram-positive bacteria *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible isolates), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis*, and the gram-negative bacteria *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. It is the first fluoroquinolone to be demonstrated to be effective in the treatment of infections caused by MRSA, and its spectrum of antibacterial action, which also includes problem pathogens such as *Pseudomonas aeruginosa*, is broader than that of other antimicrobial agents that are indicated for the treatment of ABSSSIs.

The effectiveness of delafloxacin was demonstrated in 2 noninferiority studies in ~1500 patients in which it was compared with the intravenous use of vancomycin and aztreonam. Aztreonam was discontinued if no gram-negative bacteria were identified in the baseline cultures. An objective clinical response 48 to 72 hours after initiation of treatment was defined as a ≥20% decrease in lesion size. This response was achieved in ~80% of the patients with both of the treatment regimens in both studies. The success of treatment, defined as cured plus improved in clinically evaluable patients as assessed by the investigators on follow-up at ~14 days, exceeded 95% for both treatment regimens.

In addition to the treatment of ABSSSIs, levofloxacin, moxifloxacin, and ciprofloxacin have been approved for the treatment of numerous other types of infections (e.g., urinary tract, respiratory tract). However, these are not labeled indications for delafloxacin at the present time.

Delafloxacin was well tolerated in the clinical studies, and the most commonly experienced adverse events include nausea (8%), diarrhea (8%), headache (3%), transaminase elevations (3%), and vomiting (2%). Treatment was discontinued because of adverse events in <1% of patients, compared with discontinuation in ~3% of patients treated with vancomycin and aztreonam. Because *Clostridium difficile*–associated diarrhea has been reported with the use of almost all systemic antibacterial agents, this possibility should be considered in any patient who experiences diarrhea while being treated with delafloxacin. Phototoxicity and QT-interval prolongation have been reported with the use of other fluoroquinolones, but these were not experienced in the clinical studies with delafloxacin.

As with the other fluoroquinolones, the labeling for delafloxacin includes boxed warnings about the risks of tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects (e.g., dizziness, confusion, tremors), and exacerbation of myasthenia gravis. These risks are associated with serious and potentially irreversible complications, and fluoroquinolones should be avoided in patients with a history of tendon disorders, peripheral neuropathy, or myasthenia gravis. Treatment with a fluoroquinolone should be immediately discontinued in patients in whom such adverse events occur. Patients should be

The **New Drugs** column informs readers about new chemical and biologic entities approved for marketing by the U.S. Food and Drug Administration. The column is written by Contributing Editor Daniel A. Hussar, PhD, Remington Professor of Pharmacy, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, PA.

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advised to not drive or engage in other activities that require mental alertness and coordination until they know how the drug affects them.

Data regarding the use of delafloxacin during pregnancy and in nursing mothers is very limited, but studies in animals have not suggested a risk of significant problems. Because fluoroquinolones have been reported to cause arthropathies in juvenile animals, the use of delafloxacin in children is not recommended. The use of any of the systemic fluoroquinolones in children is limited to the treatment of serious infections (e.g., inhalational anthrax, plague) for which there are very few antimicrobial treatment options.

Following oral administration of delafloxacin, the absolute bioavailability is ~60%. Glucuronidation is the primary pathway of metabolism, and ~65% of a dose of the drug is excreted in the urine as unchanged drug and glucuronide metabolites, with most of the remaining part of the dose excreted in the feces as unchanged drug. Adjustment of dosage is not necessary in patients with hepatic impairment or in patients with mild or moderate renal impairment. In patients with severe renal impairment (estimated glomerular filtration rate [eGFR], 15–29 mL/min/1.73 m^2) in whom delafloxacin is to be administered intravenously, the dosage should be reduced because of potential accumulation of the intravenous vehicle, sulfobutylether-beta-cyclodextrin. Serum creatinine concentrations should be closely monitored in patients with severe renal impairment receiving delafloxacin intravenously. If serum creatinine concentrations increase, consideration should be given to changing to oral administration of the drug. If eGFR decreases to <15 mL/min/1.73 m^2, delafloxacin should be discontinued. Use of the drug is not recommended in patients with end-stage renal disease.

Delafloxacin is less likely than ciprofloxacin and certain other fluoroquinolones to interact with other medications. However, all of the fluoroquinolones may form chelates with multivalent metal cations (e.g., in antacids and vitamin/mineral formulations) which may reduce absorption of the antibacterial agent following oral administration. Accordingly, delafloxacin should be administered at least 2 hours before or 6 hours after products containing metal cations. When administered intravenously, delafloxacin should not be coadministered with any solution containing multivalent cations (e.g., magnesium) through the same intravenous line.

The bioavailability of a single oral dose of 450 mg delafloxacin is similar to that of a single intravenous dose of 300 mg. The tablets may be administered with or without food. The recommended dosage of delafloxacin is 300 mg every 12 hours over 60 minutes by intravenous infusion, or 450 mg every 12 hours orally. Treatment may be initiated intravenously and then switched to oral administration as appropriate. The duration of treatment is 5 to 14 days. In patients with severe renal impairment, the dosage for intravenous administration should be reduced to 200 mg every 12 hours.

Delafloxacin meglumine is supplied in tablets and as a lyophilized powder for injection in quantities equivalent to 450 mg delafloxacin (tablets) and 300 mg for injection. The contents of a vial for intravenous use must be reconstituted with 10.5 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection. The vial should be shaken vigorously until the contents are dissolved, and the reconstituted solution should then be diluted with the same vehicle to a total volume of 250 mL to achieve a concentration of 1.2 mg/mL.

Meropenem trihydrate/vaborbactam

Beta-lactam antibacterial agents (e.g., penicillins, cephalosporins, carbapenems) are highly effective in the treatment of many bacterial infections. However, an increasing number of bacteria are able to produce beta-lactamase enzymes (penicillinases, cephalosporinases, carbapenemases) that break the beta-lactam ring and inactivate the antibacterial agent. To address this common mechanism of resistance, pharmaceutical companies have developed beta-lactamase inhibitors that preserve and extend the activity of the beta-lactam antibacterial agents with which they are used in combination. Early examples of these combination formulations include amoxicillin with clavulanate potassium (e.g., Augmentin) and piperacillin with tazobactam (e.g., Zosyn). More recently, combinations of a beta-lactamase inhibitor with a cephalosporin have been developed and include ceftolozane with tazobactam (Zerbaxa) and ceftazidime with avibactam (Avycaz). The latter combination was the first to have activity against some carbapenem-resistant Enterobacteriaceae, including those that produce *Klebsiella pneumoniae* carbapenemase (KPC). It was approved in 2015 for the treatment of complicated urinary tract infections, including pyelonephritis, caused by susceptible gram-negative bacteria and, in combination with metronidazole, for the treatment of complicated intra-abdominal infections caused by susceptible gram-negative bacteria.

The carbapenem antibacterial agents marketed in the United States include imipenem (used in combination with cilastatin [e.g., Primaxin]), meropenem (e.g., Merrem IV), ertapenem (Invanz), and doripenem (Doribax). The indications for meropenem include complicated skin and skin structure infections, complicated intra-abdominal infections, and bacterial meningitis. Meropenem trihydrate/vaborbactam (Vabomere—The Medicines Company) represents a combination of meropenem with the new beta-lactamase inhibitor, vaborbactam. Vaborbactam does not have antibacterial activity but protects meropenem from degradation by certain beta-lactamases, such as KPC. The new product is administered intravenously and is indicated for the treatment of adult patients with complicated urinary tract infections, including pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* species complex.

The effectiveness of meropenem/vaborbactam was demonstrated in a multicenter trial in which it was compared with piperacillin/tazobactam. At the end of intravenous treatment with meropenem/vaborbactam, 98% of patients, compared with 94% of patients treated with piperacillin/tazobactam, had cure or improvement of symptoms and a negative urine culture. Approximately 7 days after completing treatment, 77% of patients treated with meropenem/vaborbactam, compared with 73% of patients treated with piperacillin/tazobactam, had resolved symptoms and a negative urine culture.

Hypersensitivity reactions were experienced by 2% of the patients who received meropenem/vaborbactam in