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NEW DRUGS

Ceftazidime pentahydrate/avibactam sodium, Isavuconazonium sulfate, and Daclatasvir dihydrochloride

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Antibacterial agent

Ceftazidime pentahydrate/avibactam sodium (Avycaz—Actavis) is the second combination of a cephalosporin and beta-lactamase inhibitor to be marketed, joining ceftolozane/tazobactam (Zerbaxa). Ceftazidime is a cephalosporin antibacterial agent that has been available as a single agent for many years. Avibactam is the new beta-lactamase inhibitor that protects ceftazidime against inactivation by beta-lactamase enzymes, thereby increasing the activity of the antibacterial agent against gram-negative bacteria. Avibactam is a nonbeta-lactam and may inhibit certain bacteria-produced beta-lactamases that are not inhibited by other beta-lactamase inhibitors (e.g., tazobactam, sulbactam). Of particular importance is the activity of the new combination against gram-negative bacteria that produce *Klebsiella pneumoniae* carbapenemase.

Like ceftolozane/tazobactam, ceftazidime/avibactam is administered by intravenous infusion for the treatment of complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs), although there are some differences in the specific bacteria that have been demonstrated to be susceptible to the two combination formulations. Ceftazidime/avibactam is used in a regimen that also includes metronidazole for the treatment of adults with cIAIs caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*, *Enterobacter cloacae*, *Klebsiella oxytoca*, and *Pseudomonas aeruginosa*. It is also indicated for the treatment of adults with cUTIs, including pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus* species, and *Pseudomonas aeruginosa*. Because the efficacy and safety data for ceftazidime/avibactam are limited, the use of the combination should be reserved for patients who have limited or no alternate treatment options.

The contribution of avibactam to the combination product was based on data from in vitro studies and animal models of infection. The effectiveness of the new combination plus metronidazole was evaluated in a study of patients with cIAIs, in which it was compared with meropenem (Merrem). Both treatments provided a favorable microbiologic response in more than 90% of patients. In patients with cUTIs, ceftazidime/avibactam was compared with imipenem/cilastatin (Primaxin), and both treatments provided a favorable microbiologic response in approximately 70% of patients.

As with the other cephalosporins, as well as the other classes of beta-lactam antibacterial agents (i.e., penicillins, carbapenems), ceftazidime is associated with a risk of hypersensitivity and anaphylactic reactions. The new combination is contraindicated in patients with known serious hypersensitivity to ceftazidime or another cephalosporin, or to avibactam. Because of the potential for cross-sensitivity with other beta-lactam antibacterial agents, caution must be exercised if ceftazidime/avibactam is to be used in a patient known to be allergic to any of the beta-lactam agents.

Almost all systemic antibacterial agents, including ceftazidime, have been reported to cause *Clostridium difficile*–associated diarrhea (CDAD) that ranges in severity from mild diarrhea to fatal colitis. CDAD should be considered in all patients who experience diarrhea after use of an antibacterial agent, including the period of time after completion of treatment, because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

The most commonly experienced adverse events in the clinical studies of ceftazidime/avibactam (and the incidence in patients with cIAIs [who also received metronidazole] and cUTIs, respectively) include vomiting (14%, 0%), nausea (10%, 2%), constipation (4%, 10%), anxiety (5%, 10%), abdominal pain (8%, 7%), upper abdominal pain (1%, 7%), and dizziness (0%, 6%). Most of the adverse events occurred more often in patients treated with ceftazidime/avibactam than in patients treated with meropenem or imipenem/cilastatin. Central nervous system reactions (e.g., neuromuscular excitability, seizures) have been infrequently reported in patients treated with ceftazidime, particularly in the setting of renal impairment. Renal function should be monitored and the dosage adjusted accordingly.

Ceftazidime/avibactam is classified in Pregnancy Category B. Its effectiveness and safety in patients less than 18 years of age have not been established.

Ceftazidime and avibactam undergo little or no metabolism, and both agents are excreted mainly by the kidneys

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in unchanged form. The dosage of the combination formulation should be reduced in patients with moderate and severe renal impairment and end-stage renal disease. Dosage adjustment is not necessary in patients with impaired hepatic function.

The elimination of avibactam may be reduced by probenecid, so concurrent use is not recommended. Ceftazidime may cause a false-positive reaction with some urine glucose tests, so glucose tests based on enzymatic glucose oxidase reactions should be used.

Ceftazidime pentahydrate and avibactam sodium are supplied as a powder in single-use vials in quantities equivalent to 2 grams of ceftazidime and 0.5 gram of avibactam. The recommended dosage is 2 grams/0.5 gram every 8 hours administered by intravenous infusion over 2 hours for 5 to 14 days for the treatment of cIAI and 7 to 14 days for the treatment of cUTI. Metronidazole should also be used in the treatment of cIAI.

In patients with changing renal function, creatinine clearance should be monitored at least daily and the dosage appropriately adjusted. The dosage should be reduced to 1 gram/0.25 gram every 8 hours in patients with a creatinine clearance of 31 to 50 mL/min, to 0.75 gram/0.19 gram every 12 hours in patients with a creatinine clearance of 16 to 30 mL/min, to 0.75 gram/0.19 gram every 24 hours in patients with a creatinine clearance of 6 to 15 mL/min, and to 0.75 gram/0.19 gram every 48 hours in patients with a creatinine clearance of $\leq$5 mL/min.

When preparing ceftazidime/avibactam for administration, the contents of a vial should be constituted with 10 mL of Sterile Water for Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Lactated Ringer's Injection, or all combinations of Dextrose Injection and Sodium Chloride Injection containing up to 2.5% dextrose and 0.45% sodium chloride. With the same diluents used for the constitution of the powder (except Sterile Water for Injection), the constituted solution should be diluted to achieve a total volume of 50 mL to 250 mL. The diluted solution in the infusion bag should be administered within 12 hours when stored at room temperature. The diluted solution may be stored under refrigeration for up to 24 hours after dilution and should be administered within 12 hours of subsequent storage at room temperature.

Antifungal agent

Isavuconazonium sulfate (Cresemba—Astellas) is a prodrug that is converted to isavuconazole after administration. Isavuconazole is an azole antifungal drug with an antifungal spectrum that is generally similar to those of posaconazole (Noxafil) and voriconazole (e.g., Vfend). It acts by inhibiting the synthesis of ergosterol, a key component of the fungal cell membrane.

Isavuconazonium is administered orally or intravenously. It is indicated for the treatment of patients 18 years of age and older with invasive aspergillosis or invasive mucormycosis (caused by Mucorales fungi), both of which are rare fungal infections for which patients with compromised immune function are at greatest risk. The new drug has been granted orphan drug status, and is the sixth antibacterial or antifungal drug to be designated as a Qualified Infectious Disease Product, a designation that is given to a product used in the treatment of serious or life-threatening infections under the provisions of the FDA Safety and Innovation Act.

The effectiveness of isavuconazonium in the treatment of invasive aspergillosis was demonstrated in a clinical trial that involved 516 patients who received either isavuconazonium or voriconazole. Overall success at the end of treatment was seen in 35% of the patients treated with the new drug and 39% of the patients treated with voriconazole. The approval of isavuconazonium for the treatment of invasive mucormycosis was based on the results of a clinical trial in which 37 patients were treated with the new drug and compared with the natural disease progression associated with untreated mucormycosis. The overall response success rate at the end of treatment was 31%.

The type and incidence of adverse events with isavuconazonium are generally similar to those reported with voriconazole. The adverse events most commonly experienced with the use of isavuconazonium include nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%). Elevated liver function tests were reported in 16% of patients. Serious hepatic adverse events have occurred, so liver function tests should be conducted at the start and during the course of therapy.

Isavuconazonium shortens the QT interval in a dose-related manner, so it is contraindicated in patients with familial short QT syndrome. Serious hypersensitivity (e.g., anaphylaxis) and severe skin reactions (e.g., Stevens-Johnson syndrome) have been reported with other azole antifungal agents. Treatment should be discontinued if a patient develops a severe cutaneous adverse event. It is not known whether cross-sensitivity exists between isavuconazonium and other azole antifungal agents, and caution should be exercised if the new agent is used in patients with hypersensitivity to other azoles. Infusion-related reactions (e.g., hypotension, dyspnea, chills, dizziness, paresthesia) have been experienced during intravenous administration of isavuconazonium, and the infusion should be discontinued if these reactions occur.

If isavuconazonium is administered during pregnancy, it may cause harm to the unborn child. It is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit outweighs the risks. Mothers should not breast feed while being treated with the drug. The effectiveness and safety of isavuconazonium in patients less than 18 years of age have not been established.

After administration of isavuconazonium, it is rapidly hydrolyzed by esterases to isavuconazole which generally reaches maximum plasma concentrations in 2 to 3 hours. The absolute bioavailability of isavuconazole after oral administration is 98%, and it may be administered without regard to food. The prodrug is not identified in significant concentrations in plasma after oral administration. Isavuconazole is a substrate of the CYP3A4 and CYP3A5 metabolic pathways. Approximately equal amounts of a dose are recovered in the feces and urine. Dosage adjustment is not necessary in patients with impaired renal function or in patients with mild or moderate hepatic impairment. Isavuconazonium has not been studied in patients with severe hepatic impairment, so if it is used in these patients, treatment must be closely monitored for the occurrence of adverse events.

Strong CYP3A4 inhibitors (e.g., ketoconazole) may significantly increase the