Pharmaceutical-Approval Update

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Ertapenem Sodium (Invanz)
Manufacturer: Merck and Co. Inc., Whitehouse Station, NJ

Indications: For the treatment of moderate-to-severe infections in adults caused by many common gram-positive and gram-negative aerobic and anaerobic bacteria. Ertapenem is used in the treatment of the following community-acquired infections caused by susceptible strains of the designated bacteria: complicated intra-abdominal infections; complicated skin and skin structure infections; community-acquired pneumonia; complicated urinary tract infections, including pyelonephritis (kidney infection); and acute pelvic infections, including postpartum endomyometritis, septic abortion, and post-surgical gynecologic infections.

Drug Class: Structurally unique 1-(beta) methyl-carbapenem related to the class of antibiotics known as beta-lactam

Uniqueness of Drug: Ertapenem has a spectrum of bacterial activity distinct from other carbapenems in that ertapenem does not cover Pseudomonas and Acinetobacter species—pathogens typically associated with hospital-acquired infections. Like other beta-lactams, ertapenem works by blocking the formation of bacterial cell wall, thereby causing cell death.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity that have experienced severe hypersensitivity reactions when treated with another beta-lactam. Before initiating therapy with ertapenem, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to ertapenem occurs, discontinue the drug immediately.

Ertapenem should not be used in patients with known hypersensitivity to any component of the product, or to other drugs in the same class, or in patients who have demonstrated anaphylactic reactions to beta-lactams. Ertapenem administered intramuscularly should not be used in patients with a known hypersensitivity to local anesthetics of the amide type. Serious and occasionally fatal hypersensitivity (anaphylactic)

Seizures and other central nervous system (CNS) adverse experiences have been reported during treatment with ertapenem. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem, and can range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and might permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of “antibiotic-associated colitis.”

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

Dosage: The dose of ertapenem in adults is 1 gram (g) given once per day. ertapenem may be administered by intravenous infusion for up to 14 days or by intramuscular injection for up to seven days. When administered intravenously, ertapenem should be infused over a period of 30 minutes. Ertapenem will be supplied in single-dose vials for administration either intravenously or intramuscularly following reconstitution or dilution.

Intramuscular administration of ertapenem may be used as an alternative to intravenous administration in the treatment of those infections for which intramuscular therapy is appropriate. In patients with renal insufficiency, ertapenem may be used for the treatment of infections. In preparation of ertapenem for intravenous administration, do not mix or co-infuse ertapenem with other medications. Do not use diluents containing dextrose [(alpha)-D-glucose]. Ertapenem must be reconstituted prior to administration.

P&T Committee Considerations: Imipenem was the first carbapenem approved for use in hospital patients against community-acquired infections produced by virtually all bacterial pathogens with few exceptions. Imipenem often is held

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in reserve as therapy for nosocomial infections because of gram-negative pathogens resistant to third-generation cephalosporins. Limitations to its use are its relatively low blood levels, short serum half-life, and CNS side effects. On the other hand, ertapenem represents an advance in beta-lactam therapy in that it is a structurally unique carbapenem, and is a once-daily, injectable (IM or IV) antibiotic for treating moderate-to-severe adult bacterial infections caused by gram-positive and gram-negative aerobic and anaerobic bacteria. Ertapenem might eventually be used in hospitals as first-line treatment for complicated intra-abdominal, skin, and skin structure infections. The antibiotic’s bacterial coverage and empirical profile combined with its ease of administration should make ertapenem an ideal treatment for common hospital infections. However, one shortcoming of ertapenem is its antibacterial inability against Pseudomonas and Acinetobacter species coverage. Nonetheless, ertapenem should be considered for inclusion on the hospital formulary because of its distinct spectrum of antibacterial activity. The average wholesale price (AWP) of ertapenem is not available at this time.

### Tenofovir disoproxil fumarate (Viread)

**Manufacturer:** Gilead Sciences, Inc., Foster City, CA

**Indications:** An antiviral drug used for the treatment of HIV-1 infection.

**Drug Class:** Nucleotide reverse transcriptase inhibitor

**Uniqueness of Drug:** This is the first acyclic nucleotide analog approved for HIV-1 treatment. It helps block an enzyme crucial for the production and replication of HIV. Its active ingredient, tenofovir disoproxil fumarate, is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. In the body, this analog is first converted to tenofovir, then to tenofovir diphosphate, by cellular enzymes that result in activity against HIV reverse transcriptase. Lowering the amount of HIV in the blood might increase the number of T cells. This would improve the immune system’s ability to defend the body against HIV infection.

**Warnings:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. The most common adverse events that occurred in patients receiving tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials were mild-to-moderate gastrointestinal events such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of patients discontinued participation in the clinical trials because of gastrointestinal adverse events.

**Dosage:** The dose of tenofovir disoproxil fumarate is 300 mg once daily, taken orally with a meal. When administered concomitantly with didanosine (Videx, Bristol-Myers Squibb), tenofovir disoproxil fumarate should be taken two hours before or one hour after administration of didanosine.

**P&T Committee Considerations:** Tenofovir disoproxil fumarate is the first nucleotide analog approved for HIV-1 treatment and should be included in the formulary as part of the arsenal of drugs against HIV infection. The drug should be used in conjunction with other antiviral medications. The approval of another potent anti-HIV-1 medication for patient use is always good news because these drugs cause markedly reduced replication of HIV in many patients, which results in improved survival rates. Because HIV mutates rapidly, resistance to one or more of these potent drugs may develop over time, necessitating the development of new drugs to eliminate resistant virus strains. Studies of tenofovir disoproxil fumarate still need to be conducted in untreated patients to determine its benefit-to-risk ratio in such patients as were determined in subjects treated previously with antiretroviral drugs. There are no study results to show long-term inhibition of the clinical progression of HIV by tenofovir disoproxil fumarate. The cost of the drug is high: the AWP of tenofovir disoproxil fumarate is $408.00 for a bottle of 30 tablets.

### Anakinra (Kineret)

**Manufacturer:** Amgen Inc., Thousand Oaks, CA.

**Indications:** For the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis (RA) in patients 18 years of age or older who have failed one or more disease-modifying antirheumatic drugs (DMARDs). Anakinra can be used alone or in combination with DMARDs other than Tumor Necrosis Factor (TNF)-blocking agents. Anakinra should be used in adult patients who have failed one or more DMARDs.

**Drug Class:** Anakinra is a recombinant, nonglycosylated form of the human Interleukin-1 receptor antagonist (IL-1Ra). Anakinra differs from native human IL-1Ra in that it has the addition of a single methionine residue at its amino terminus. It is produced by recombinant DNA technology using an Escherichia coli bacterial expression system.

**Uniqueness of Drug:** It is the first direct and selective blocker of interleukin-1 (IL-1), a protein present in excessive quantities in RA patients. By blocking IL-1, anakinra inhibits the signs and symptoms of inflammation and pain in these RA patients.

**Warnings:** Anakinra has been associated with an increased incidence of serious infections (2%) versus placebo (<1%). Administration of anakinra should be discontinued if a person develops a serious infection. Treatment with anakinra should not be initiated in patients with active infections. The safety and efficacy of anakinra in immunosuppressed patients or in patients with chronic infections have not been evaluated. The safety of anakinra used in combination with TNF-blocking agents has not been established. Preliminary data suggest a higher rate of serious infections (7%, 4/58) when anakinra and etanercept are used in combination, compared to anakinra alone. In this combination study, neutropenia (neutrophil count ≤1000/mm³) was observed in 3% of patients (2/58). The use of anakinra with the blocking agents should be permitted only with extreme caution, and when no satisfactory alternatives exist.

The most common side effect was a reaction at the site of injection; this was usually mild and characterized by redness,
swelling, and pain. Although anakinra should be discontinued if a patient develops an infection, most patients can continue taking anakinra after their infections resolve. Anakinra should not be used with the DMARDs etanercept (Enbrel, Wyeth-Ayerst) and infliximab (Avakine, Schering-Plough or Remicade, Centecor).

**Dosage and Administration:** The recommended dose of anakinra for the treatment of patients with rheumatoid arthritis is 100 mg daily, to be administered by subcutaneous injection. One dose, provided in single use 1-mL prefilled glass syringes, should be administered at approximately the same time every day.

**P&T Committee Considerations:** Anakinra is a genetically engineered biological product that alleviates the acute symptoms of inflammation and pain in RA patients by inhibiting the action of the molecule interleukin-1 (IL-1). IL-1 has a broad range of activities, including cartilage degradation, through its induction of the rapid loss of proteoglycans, as well as stimulation of bone resorption. Anakinra is a man-made protein that is similar to a naturally occurring protein called IL-1 receptor antagonist that is found in the bodies of people with RA. In people with RA, the body produces too much IL-1, leading to joint damage, pain, swelling, and stiffness. Anakinra blocks the action of IL-1 and contributes to a beneficial therapeutic effect in patients requiring DMARDs to alleviate their symptoms of RA. The inclusion of anakinra in the formulary is highly recommended as a serious therapeutic modality to treat active RA. The AWP of anakinra is $41.25 for a 100-mg vial or $288.75 for a package of seven 100-mg prefilled glass syringes for a seven-day period.

**Frovatriptan Succinate (Frova)**

**Manufacturer:** Elan Pharma International, Inc.

**Indications:** The acute treatment of migraine attacks, with or without aura, in adults.

**Drug Class:** Frovatriptan succinate is derived from the triptan class of anti-migraine drugs. It is a serotonin receptor agonist, which binds with a high affinity for the serotonin 1B and 1D receptors.

**Uniqueness of Drug:** In contrast to currently marketed triptans having a half-life of six hours or less, frovatriptan succinate, 2.5-mg tablet, has a 26-hour half-life, thereby offering a greater benefit to the patient. Migraine attacks generally last four to 72 hours. Frovatriptan succinate binds to and stimulates serotonin receptors that cause constriction of extracerebral intracranial arteries. Frovatriptan succinate is believed to inhibit excessive dilation of these vessels during migraine attacks. Frovatriptan succinate has no significant effects on GABA-mediated channel activity and has no significant affinity for benzodiazepine binding sites.

**Warnings:** The side effects that occurred most frequently following administration of frovatriptan succinate 2.5-mg tablets (in at least 2% of patients, and at an incidence of greater than or equal to 1% compared to placebo) were dizziness, paresthesia, headache, dry mouth, fatigue, flushing, hot or cold sensation, and chest pain. Patients with the following conditions should not use frovatriptan succinate: uncontrolled high blood pressure, heart disease, hemiplegic or basilar migraine, and history of stroke or circulation problems. Side effects associated with frovatriptan include the following: dizziness, fatigue, tingling, dry mouth, hot flashes, feeling hot or cold, chest pain, indigestion, and skeletal pain.

**Dosage:** A 2.5-mg frovatriptan succinate tablet is effective in treating acute migraine.

**P&T Committee Considerations:** Triptans are considered as first-line therapy in people with moderate-to-severe migraine who do not have risk factors such as history of cardiovascular disease, stroke, or hypertension. There are more than a half-dozen triptans on the market, all of which have slightly different characteristics, reflecting the ongoing search for a better triptan (i.e., one with high selectivity and low toxicity). It is too early to know whether the longer half-life of frovatriptan succinate offers a distinct advantage over the other marketed triptans. Only time and head-to-head clinical studies with the other triptans will allow us to make definitive statements regarding the advantages of frovatriptan succinate, in terms of safety and efficacy, compared to the others. In a market in which only 29% of patients report that they are very satisfied with their migraine therapy, the benefits of frovatriptan succinate make it an important alternative therapy in the treatment of migraine for many patients. Frovatriptan succinate might represent an important advance in the treatment of migraine headache, as no other currently marketed triptans have a half-life of more than six hours. The AWP of frovatriptan succinate tablets is not yet available.