Levofloxacin (Levaquin® Leva-pak)

Manufacturer: Ortho-McNeil, Inc., Raritan, NJ

Indication: The Food and Drug Administration (FDA) has approved a new short-course antibiotic for the treatment of acute bacterial sinusitis. This five-day, 750-mg once-daily dosing regimen of levofloxacin is also indicated for adults with community-acquired pneumonia caused by penicillin-susceptible Streptococcus pneumoniae (excluding multi-drug-resistant strains), Haemophilus influenzae, Haemophilus parainfluenzae, Chlamydia pneumoniae, or Mycoplasma pneumoniae. The overall tolerability of levofloxacin is similar for all doses.

Drug Class: Levofloxacin is an antibiotic in a class of drugs called fluoroquinolones.

Uniqueness of Drug: A clinical study found that the shorter course was as effective as a traditional regimen of levofloxacin 500 mg for 10 days. This product is available in the convenient Leva-pak.

Contraindications: Levofloxacin is contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, and any other components of this product. Serious and occasionally fatal hypersensitivity or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions may occur following the first dose. The drug should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Warnings and Precautions: The safety and efficacy of levofloxacin in pediatric patients, adolescents (under 18 years of age), pregnant women, and nursing mothers have not been established.

Central Nervous System: As with other quinolones, levofloxacin should be used with caution in patients with known or suspected central nervous system (CNS) disorders, peripheral neuropathy, or a predisposition to seizures. Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. These reactions may occur following the first dose. The drug should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Gastrointestinal Tract: Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of Clostridium organisms.

Cardiovascular System: Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving quinolones, including levofloxacin. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.

Drug Interactions: Patients should limit their intake of alcoholic beverages. The following products should be taken at least two hours before or two hours after levofloxacin:

- antacids containing magnesium or aluminum
- sucralfate (Carafate®)
- metal cations such as iron
- multivitamin preparations with zinc
- didanosine (Videx®, Bristol-Myers Squibb Oncology) chewable or buffered tablets or the pediatric powder for oral solution

Sun Exposure: Because this medication may increase sensitivity to the sun, patients should avoid prolonged sun exposure, tanning booths, and sun lamps; they should use a sunscreen and wear protective clothing when outdoors.

Diabetes: Diabetic patients who are taking insulin or oral antidiabetic drugs such as glyburide (DiaBeta®, Aventis) may experience changes in blood glucose levels because of infection or the use of levofloxacin. Blood glucose should be monitored frequently.

Pregnancy: There are no adequate or well-controlled studies of this drug in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adverse Drug Effects: The most common drug-related adverse events in U.S. clinical trials were nausea (1.5%) and diarrhea (1.2%).

Dosage and Administration: The Leva-pak provides a five-day, 750-mg once-daily regimen.

Commentary: The overuse of antibiotics has led to the emergence of antibacterial resistance in the U.S. The greatest advantage of a five-day antibiotic regimen is the use of a limited, effective, and safe dosing schedule that can help prevent potential antibacterial resistance as well cure the infection. The convenience of the Leva-pak can enhance patient com-

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pliance with therapy; however, treatment for more than seven days may double the risk of patient noncompliance. 
Sources: www.pharmacyonesource.com; www.nacdsfoundation.org

Valsartan (Diovan®)
Manufacturer: Novartis, East Hanover, NJ
Indication: Valsartan is approved for patients with left ventricular failure or left ventricular dysfunction who are at high risk for death following a heart attack or myocardial infarction (MI).

Drug Class: Valsartan is an angiotensin II receptor–blocking agent.

Uniqueness of Product: The FDA expanded the drug’s labeling for heart failure and is no longer limited to patients who are intolerant of angiotensin-converting enzyme (ACE)–inhibitors.

The approvals are based on the results of the Valsartan in Acute Myocardial Infarction Trial (VALIANT), one of the largest long-term studies of MI survivors. The drug was reported to improve survival and reduce cardiovascular events, including recurrent MI and hospitalizations for heart failure in these patients.

Warnings and Precautions
Pregnancy: Valsartan should not be used in pregnant women because of the risk of injury and even death to the fetus. The drug should be discontinued as soon as pregnancy is detected.

Drug Interactions: In patients with heart failure, the concomitant use of valsartan and a beta blocker is not recommended.

Hypotension: Because of the risk of hypotension, caution should be observed when therapy is initiated in post-MI or heart failure patients. Although patients with heart failure who take valsartan commonly experience some reduction in blood pressure, discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials, the incidence of hypotension was 5.5% in valsartan-treated patients and 1.8% in placebo-treated patients.

Impaired Hepatic Function: As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment and biliary obstructive disorders showed lower valsartan clearance (i.e., higher area-under-the-curve concentrations). Care should be exercised with these patients.

Impaired Renal Function
Heart Failure: As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACE-inhibitors and angiotensin-receptor antagonists has been associated with oliguria and progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.

Some patients with heart failure have experienced increased levels of blood urea nitrogen (BUN), serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Reducing the dosage or discontinuing the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were receiving concomitant ACE-inhibitors, treatment was discontinued for elevations in creatinine or potassium (a total of 1.0% with valsartan vs. 0.2% with placebo). Evaluation of patients with heart failure should always include assessment of renal function.

Hypertension: In studies of ACE-inhibitors in hypertensive patients with renal artery stenosis, increases in serum creatinine or BUN have been reported. In a four-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or BUN were observed. The long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis has not been studied, but an effect similar to that seen with ACE-inhibitors should be anticipated.

Adverse Drug Effects: The most common adverse effects in patients with heart failure with valsartan were dizziness, hypotension, and diarrhea. The most common effects in post-MI patients that caused them to stop taking the drug were hypotension, cough, rash, and elevated serum creatinine levels.

Dosage and Administration: Valsartan may be initiated as early as 12 hours after an MI. The recommended starting dose is 20 mg twice daily. The dose may be titrated upward within seven days to 40 mg twice daily, with subsequent titrations targeted to a maintenance dose of 160 mg twice daily, as tolerated. If symptomatic hypotension or renal dysfunction occurs, a lower dose should be considered.

Valsartan may be given with other standard post-MI treatment, including thrombolytic agents, aspirin, beta blockers, and statins.

Commentary: When examined in the setting of acute MI and left ventricular dysfunction, valsartan was found to reduce the mortality rate of post-MI patients at high risk. The approval of valsartan for this indication provides an alternative for patients who cannot tolerate ACE-inhibitors. Consequently, a selective angiotensin-receptor blocker can be considered a clinically effective alternative to an ACE-inhibitor in the early phase of MI and even the first-line choice in subgroups such as patients with hypertension or diabetes in whom endothelial dysfunction has been clearly demonstrated.

Sources: www.pharmacyonesource.com; www.pharma.us.novartis.com

Dapsone Gel (Aczone™)
Manufacturer: QLT, Inc., Vancouver, BC
Indication: Dapsone gel, 5%, has been approved for the topical treatment of acne vulgaris.

Drug Class: Dapsone was initially found to be an antibacterial drug belonging to the sulfonamide class. It also has anti-inflammatory activity and interferes with the activation of the G-protein that initiates the signal transduction cascade common to chemotactic stimuli.

Uniqueness of Drug: The combination of dapsone and a solvent microparticulate gel enables the product to be applied topicaly, safely, and conveniently. In two randomized, double-blind, vehicle-controlled clinical studies of 3,000 acne patients, dapsone gel achieved a statistically significant ($P = <.05$)
reduction in the number of acne lesions. Patients achieved better scores on the global acne assessment scale.

**Warnings and Precautions:** The safety and efficacy of dapsone have not been established in patients younger than 12 years of age.

**G6PD Deficiency:** Glucose 6-phosphate dehydrogenase (G6PD) concentrations should be assessed for all patients before treatment is begun. Baseline blood counts, including reticulocytes, in G6PD-deficient patients or in those with a history of anemia should also be obtained. Patients should be screened to detect whether they are predisposed to hemolytic anemia because of a G6PD deficiency. Patients with this enzyme deficiency need to be monitored with regular blood counts.

Dose-related hemolysis is the most common adverse event seen in patients taking oral dapsone (with or without G6PD deficiency). Hemolysis may be exaggerated in individuals with G6PD deficiency, methemoglobin reductase deficiency, or hemoglobin M.

Although clinical studies have not demonstrated evidence of clinically significant anemia, an increased reticulocyte count and a decreased hemoglobin concentration have been associated in a G6PD-deficient patient receiving dapsone gel for acne vulgaris after undergoing a complete blood count. Only 25 patients with low plasma G6PD activity who were treated with dapsone gel were included in the clinical study program. The safety of dapsone gel has not been fully evaluated in patients with G6PD deficiency.

**Breast-Feeding:** Because dapsone is excreted in breast milk, either breast-feeding or dapsone therapy should be discontinued.

**Adverse Reactions:** Although adverse reactions were not observed in the clinical trials of topical dapsone, serious reactions have been reported with the oral use of dapsone, including agranulocytosis, hemolytic anemia, and peripheral neuropathy. Skin reactions have included toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria.

Serious adverse events reported in patients treated with dapsone gel, 5%, during clinical trials included CNS and psychiatric symptoms (suicide attempts, tonic–clonic movements), gastrointestinal symptoms (abdominal pain, severe vomiting, pancreatitis), and others (severe pharyngitis).

The most common adverse events reported from controlled clinical trials included erythema and oiliness, peeling, and dryness of the skin.

**Dosage and Administration:** After the skin is gently washed and patted dry, the patient applies a pea-sized amount of the gel in a thin layer to the acne-affected areas twice daily. The gel, which is gritty with visible drug substance particles present, should be rubbed into the skin gently and completely. Patients should wash their hands after applying the gel. If there is no improvement after 12 weeks, the appropriateness of treatment should be reassessed.

**Commentary:** Dapsone gel, 5%, which uses a solvent microparticulate technology to make its active ingredient dapsone (which is extremely insoluble) effective topically, has been tested in more than 3,000 patients with acne of varying severity. Twelve-week trial results document its efficacy in reducing the number of inflammatory lesions by 46% to 48% and the number of non-inflammatory lesions by 30% to 31%. The systemic absorption of dapsone from the topical formulation into the blood is quite low, at least 100-fold less than a dose of oral dapsone.

There are three driving factors in the pathogenesis of acne: increased sebum production, bacterial infection, and inflammation; it is thought that dapsone gel might affect bacterial infection and inflammation. Existing anti-acne products typically combine a drying agent with an antibacterial agent. A possible way of enhancing the efficacy of the gel might be to add a drying agent to the preparation.

Serious toxicity is associated with dapsone after absorption. Despite very clear data, the FDA is requiring labeling for dapsone gel that mandates screening of patients for G6PD deficiency. A study should be conducted in G6PD-deficient patients to justify the addition of the warnings and precautions on the product’s label. If there is no adverse reaction, the FDA would then remove the warning.

**Sources:** http://biz.yahoo.com; www.qltinc.com