

clinical Review

Timely drug trend, pipeline and regulatory information to help you better manage your company's pharmacy benefit.

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Welcome to *Clinical Review*. This publication strives to help you better manage your company's pharmacy benefit. Medco will send you a new issue of *Clinical Review* every two weeks. Please e-mail any comments to: clinical@medco.com

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- On November 8, the FDA announced a new update to the product labels of all ESAs. Medco is reevaluating its coverage criteria based on those updates.

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New Guidelines

Treatment guidelines for erythropoiesis-stimulating agents updated

On October 22, the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) issued joint treatment guidelines on the use of erythropoiesis-stimulating agents (ESA) for the treatment of chemotherapy-induced anemia (red blood cell deficiency). The ESA drugs are darbepoetin alfa (*Aranesp*®) and epoetin alfa (*Epogen*® and *Procrit*®), which stimulate bone marrow to produce red blood cells necessary for carrying oxygen. The guidelines reinforce previous recommendations published in 2002, which recommend ESA use in patients with chemotherapy-induced anemia when their hemoglobin levels fall below 10 g/dL and suggest hemoglobin can be increased to 12 g/dL. Hemoglobin levels represent a rough estimate of the oxygen-carrying capacity of the blood. Normal levels are 14-18 g/dL for men and 12-16 g/dL for women.

Risk of ESAs studied

The reissued guidelines come at a time when the use and safety of ESAs has been under discussion:

- In November, 2006, a *New England Journal of Medicine* study was published on an increased risk of heart problems and death in patients with chronic kidney disease being treated with high-doses of ESAs.
- On March 9, 2007, the Food and Drug Administration (FDA) issued a Public Health Advisory and announced significant new labeling changes, including a new Black Box warning, for all ESAs. The warning advises physicians to monitor hemoglobin and to adjust the ESA dose to maintain the lowest hemoglobin level needed to avoid the need for blood transfusions.
- On May 10, 2007, the Oncologic Drugs Advisory Committee (ODAC) for the FDA met to continue discussion and make recommendations regarding the risks of ESAs.

Following the May meeting, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination (NCD) that restricts reimbursement of ESAs for treatment of cancer patients only for hemoglobin levels less than 10 g/dL. ASCO and other professional organizations have been very critical of CMS' position; however CMS is reluctant to revisit the determination without first being provided with new evidence.

The guidelines are available on the associations' respective websites, www.bloodjournal.org and www.jco.org.^{1,2,3,4,5}

Implications

- After the March 9, 2007 Public Health Advisory and ESA labeling changes, Medco's Pharmacy and Therapeutics (P&T) committee modified coverage criteria for ESAs to exclude cancer-related anemia as a covered use. Also, the use of ESAs for chemotherapy-related anemia was revised to allow coverage for no longer than four months after chemotherapy ends. Coverage is provided when the patient's hemoglobin is less than or equal to 11 g/dL and coverage is renewed provided hemoglobin is less than or equal to 12 g/dL. This is consistent with the ASCO and ASH guidelines and the product labeling.
- Accredo (Medco's specialty pharmacy subsidiary) Therapy Management for anemia includes monitoring hemoglobin and hematocrit levels at appropriate time intervals and recommending dosage adjustments as per national guidelines.
- On November 8, the FDA announced a new update to the product labels of all ESAs. These new statements address the risks that ESAs pose to patients with cancer and patients with chronic kidney failure. Medco's coverage criteria will now be re-evaluated again based on the recently updated ESA product labels.

Study

Younger adults increasingly treated for heart disease-related conditions

Heart disease, high blood pressure and hardening of the arteries--conditions that are usually associated with the senior population--are becoming more prevalent in young adults. According to new research conducted by Medco, prescription drug use by younger adults for heart disease-related conditions is increasing at a rapid rate, far outpacing older adults and offering a glimpse into the forthcoming clinical and financial challenges facing the nation's health care system.

The analysis shows that between 2001 and 2006, the number of 20-44 year olds taking prescription medications to treat high cholesterol increased 68 percent, and use of antihypertensives (high blood pressure medications) jumped 21 percent.

Based on this new analysis, the estimated number of 20 to 44 year olds nationwide on lipid-lowering

drugs rose from 2.5 million in 2001 to 4.2 million in 2006, while the number of people of that age taking antihypertensives rose from 7 million to 8.5 million in the six-year period.

Increase in usage surpasses older groups

Not only were the increases among 20-44 year olds significant, but so too were the rates of increase when compared to age groups more traditionally associated with those categories of medications. The increase in the number of 20 to 44 year-olds on lipid-lowering medications was 37 percent higher than it was for 45 to 64 year olds; the growth in prevalence of those on antihypertensives was 52 percent greater. When compared with patients 65 years or older, the increase in usage of lipid-lowering medications was 31 percent higher in the 20-44 group, and among those on antihypertensives, it was more than double.

Heart Disease Risks

High cholesterol and high blood pressure are two of the leading risk factors for heart disease, heart attack and stroke. High LDL cholesterol can cause atherosclerosis, a narrowing and hardening of the arteries that feed the heart and brain. High blood pressure, or hypertension, can weaken the arterial walls and make them more prone to atherosclerosis. Both conditions can lead to blood clots that can block blood flow and result in a heart attack or stroke.

For some people with high cholesterol and hypertension, lifestyle changes such as weight loss, dietary changes and exercise can control those conditions. For others, medications may be needed. The most common medications used to treat high cholesterol are statins. To treat hypertension, diuretics, beta-blockers and ACE inhibitors are often prescribed.⁶

Implications

- Medco has developed an approach to help improve and advance pharmacy care through condition-specific resource centers that are staffed with hundreds of pharmacists who receive training and certification in specific chronic conditions and have expertise in the drugs used to treat them. With this training and concentrated practice, Medco's specialist pharmacists can offer deeper, more specific guidance when a medication safety issue arises.
- Medco's specialist pharmacists focus on some of the most common chronic conditions Americans face, including heart disease, high blood pressure and high cholesterol. Aided by advanced, integrated databases that provide real-time prescription medication history, and medical diagnoses (when available), specialist pharmacists can collaborate with doctors and their patients on drug safety issues. Specialist pharmacists may also consult with physicians to help ensure that members receive the most affordable medications.

New Drug

Drug brand/generic name and manufacturer	Date approved, launch date and indication	Dosing and side effects	Implications and pricing
<p><i>Voltaren® Gel</i> 1%^{7,8} diclofenac sodium topical gel</p> <p><i>Voltaren Gel</i> is available in tubes containing 100 gm of the topical gel.</p> <p>Novartis</p>	<p><i>Voltaren Gel</i> was approved October 22, 2007 and is expected to be available by the first quarter of 2008.</p> <p><i>Voltaren Gel</i> is indicated for treating pain associated with osteoarthritis in joints amenable to topical treatment, such as the knees and those of the hands. <i>Voltaren Gel</i> is a topical non-steroidal anti-inflammatory (NSAID) medication. Oral diclofenac is available generically, along with various other generic oral NSAIDs (e.g. ibuprofen, naproxen).</p> <p>Osteoarthritis is a chronic condition characterized by the breakdown of cartilage in the joints such as the knees, hands, elbows and feet. Approximately 21 million people in the U.S. have osteoarthritis. This number is expected to increase due to the aging population. Arthritis and related conditions, such as osteoarthritis, reportedly cost the U.S. economy nearly \$128 billion per year in medical care and lost wages and production.</p>	<p>The proper amount of <i>Voltaren Gel</i> varies with the area being treated. The gel should be applied four times daily. Not more than 16 gm should be applied daily to any single joint of the lower extremities and no more than 8 gm should be applied daily to any single joint of the upper extremities. The total dose should not exceed 32 gm per day, over all affected joints.</p> <p>There were application site reactions in seven percent of treated patients.</p> <p>The systemic absorption of <i>Voltaren Gel</i> is 94 percent less than comparable oral diclofenac treatment which may translate into improved safety.</p> <p>Prescribing information is available at www.voltarengel.com.</p>	<ul style="list-style-type: none"> • <i>Voltaren Gel</i> will be reviewed by Medco's Pharmacy and Therapeutics (P&T) committee. A decision for the Medicare PDP formulary will be made after the review of this drug for the commercial formularies. • All orally administered diclofenac products were deemed "Must Not Add" for Medco's standard formularies by Medco's P&T committee in October 2006 due to safety concerns (such as cardiovascular risk, and liver toxicity). This new topical formulation of diclofenac is thought to have fewer safety issues due to much lower systemic exposure compared to oral diclofenac products. • Coverage criteria limiting use of this product are under consideration. For example, coverage for osteoarthritis could only apply to those who have not responded to acetaminophen. • Quantity limits are under consideration. • Pricing is not available.

New Drug

Drug brand/generic name and manufacturer	Date approved, launch date and indication	Dosing and side effects	Implications and pricing
<p><i>Tasigna</i>^{®9,10,11,12,13} nilotinib 200 mg tablets Supplied in blister packs of 28 capsules. Novartis</p>	<p><i>Tasigna</i> was approved on October 29, 2007 and is expected to be available immediately. It is indicated for treating chronic-phase and accelerated-phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior treatment, including <i>Gleevec</i>[®] (imatinib).</p> <p>CML is one of the four most common types of leukemia, a form of blood cancer, and affects around 4,500 people in the U.S. each year.</p>	<p>The recommended dose of <i>Tasigna</i> is 400 mg orally twice daily. Treatment should continue as long as the patient does not show evidence of progression or unacceptable toxicity.</p> <p>The most frequent adverse events for <i>Tasigna</i> were primarily hematological (associated with blood) in nature and included neutropenia and thrombocytopenia. The most frequent non-hematologic drug-related adverse events were rash, itching, nausea, fatigue, headache, constipation and diarrhea.</p> <p>Prescribing information is available at http://www.fda.gov/cder/foi/label/2007/022068lbl.pdf.</p>	<ul style="list-style-type: none"> • <i>Tasigna</i> will be reviewed by Medco's Pharmacy and Therapeutics (P&T) committee. A decision for the Medicare PDP formulary will be made within 90 days to comply with CMS rules. • Coverage criteria limiting coverage of this product to its approved indication will be presented to the P&T committee chairman for interim approval as soon as possible. • Quantity limits are under consideration. • <i>Tasigna</i> will be added to the Medco/Accredo Specialty program. • Novartis is also studying <i>Tasigna</i> for the treatment of gastrointestinal stromal tumors. • <i>Tasigna</i> faces competition in the imatinib-resistant market from Bristol-Myers Squibb's <i>Sprycel</i>[®] (dasatinib), an inhibitor of multiple tyrosine kinases. • The average wholesale price (AWP) is \$59.38 per 200 mg tablet. With a daily dose of four tablets, the AWP per day is \$237.52.

New Drug

Drug brand/generic name and manufacturer	Date approved, launch date and indication	Dosing and side effects	Implications and pricing
<p><i>Combigan</i>TM 0.2%/0.5%^{14,15}</p> <p>brimonidine tartrate/timolol</p> <p>ophthalmic solution</p> <p>Allergan Inc.</p>	<p><i>Combigan</i> was approved on October 31 to treat elevated intraocular pressure (IOP) in patients with glaucoma or high blood pressure of the eye. <i>Combigan</i> will be launched during the fourth quarter of 2007.</p> <p><i>Combigan</i> is a combination of two medications, which are available generically, approved to treat glaucoma.</p> <p>IOP is a primary risk factor for glaucoma, a disease affecting the optic nerve and a leading cause of preventable blindness. More than 3 million Americans are thought to have glaucoma, although only half know they have it, according to Allergan.</p>	<p>The recommended dose of <i>Combigan</i> is one drop in the affected eye(s) twice daily, approximately 12 hours apart.</p> <p>The most common adverse reactions included allergic conjunctivitis (inflammation of the eye's mucous membrane), itchy eyes, ocular burning and stinging.</p>	<ul style="list-style-type: none"> • <i>Combigan</i> will be reviewed by Medco's Pharmacy and Therapeutics (P&T) committee. A decision for the Medicare PDP formulary will be made after the review of this drug for the commercial formularies. • Pricing is not available.

Drug Labeling Revisions/Safety

Drug brand/generic name and manufacturer	Indication	Product labeling update	Implications
<p><i>Provigil</i>^{®16,17}</p> <p>modafinil</p> <p>100 mg and 200 mg tablets</p> <p>Cephalon</p>	<p><i>Provigil</i> is indicated to improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS), narcolepsy and shift work sleep disorder (SWSD). In OSAHS, <i>Provigil</i> is indicated as an adjunct to standard treatment(s) for the underlying obstruction. <i>Provigil</i> is a Schedule IV controlled substance.</p>	<p>The labeling for <i>Provigil</i> has been updated with a bolded warning on the risk of life-threatening skin and hypersensitivity reactions, including Stevens-Johnson Syndrome (a serious disorder of the skin and mucous membranes) and the possibility of suicidal thoughts, hallucinations, mania and anxiety, based on rare postmarketing reports.</p>	<ul style="list-style-type: none"> • Medco added a drug utilization review (DUR) rule to alert health care professionals about the risk of Stevens-Johnson Syndrome and the risk of suicidal ideation and bipolar disorder. • Medco will educate health care professionals about this warning when reviewing prior authorization criteria for <i>Provigil</i>. • Medco will update the patient package inserts included with Medco By Mail prescriptions.

New generic

Generic drug name strength/dosage form, reference brand and manufacturer	Approval and launch dates	Indication	Comments
<p>norethindrone acetate and ethinyl estradiol tablet, and ferrous fumarate tablet^{18,19}</p> <p><i>TriLegest™Fe</i></p> <p>Barr Pharmaceuticals</p> <p><i>Estrostep® Fe</i></p> <p>Warner Chilcott Company, Inc.</p>	<p>Barr's generic was approved on October 26 and an immediate launch is planned. The generic product will have the brand name <i>TriLegest™Fe</i>.</p>	<p><i>Estrostep Fe</i> is an oral contraceptive product, indicated to prevent pregnancy in women who elect to use oral contraceptives as a method of contraception. It is also indicated for treating moderate acne vulgaris in females 15 years of age and older, who desire an oral contraceptive for birth control and plan to stay on it for at least six months.</p>	<ul style="list-style-type: none"> • <i>Estrostep Fe</i> had annual sales of \$110 million for the twelve months ending August 2007, according to IMS data.
<p>paroxetine extended-release^{20,21}</p> <p>12.5 mg and 25 mg tablets</p> <p>Mylan</p> <p><i>Paxil CR®</i></p> <p>GlaxoSmithKline (GSK)</p>	<p>Mylan's generic version of 12.5 mg and 25 mg <i>Paxil CR</i> was approved June 29, 2007. Launch was pending patent litigation. In a settlement agreement announced October 23, Mylan gains patent licenses and the right to market all three strengths (12.5 mg, 25 mg and 37.5 mg) of the generic versions of <i>Paxil CR</i> beginning no later than October 1, 2008. All litigation between GSK and Mylan has been dropped.</p>	<p><i>Paxil CR</i> is indicated for treating major depressive disorder, social anxiety disorder and premenstrual dysphoric disorder.</p>	<ul style="list-style-type: none"> • Once the generic is launched, Mylan will have 180-day market exclusivity for paroxetine extended-release 12.5 mg and 25 mg tablets. • <i>Paxil CR</i> had U.S. sales of \$342 million for the 12 months ending June 30, 2007, including all three strengths (12.5 mg, 25 mg and 37.5 mg), according to Mylan.

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