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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

New labeling regarding possible increased risk for heart attacks

- People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack may want to discuss this new warning with their health care provider.
- Medco clinical programs, such as RationalMed® and concurrent drug utilization review, already provide alerts for patients on *Avandia*.

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Safety/Labeling Revisions

Revised Black Box warning for *Avandia*® (rosiglitazone), but drug to remain on the market

On November 14, 2007, GlaxoSmithKline announced changes to the existing Black Box warning in the *Avandia*® (rosiglitazone) labeling regarding possible increased risk for heart attacks. While the labeling indicates that the evidence is inconclusive, people with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack may want to discuss this new warning with their health care provider as they evaluate treatment options.

The Food and Drug Administration (FDA) advises health care providers to closely monitor patients who take *Avandia* for cardiovascular risks. The product's indication section also includes recommendations against the coadministration of *Avandia* and insulin or nitrates due to a possible increased risk of heart attack. However, those combinations are not contraindicated in the product labeling. *Avandia* is a thiazolidinedione drug (TZD or glitazone) and is used in conjunction with diet and exercise to improve blood sugar control in adults with type 2 diabetes.

New warning follows previous warning for entire glitazone class

This decision follows an August 14, 2007 Black Box warning for the entire glitazone class of antidiabetic drugs: *Avandia*, *Actos*® (pioglitazone), *ACTOplus met*™ (pioglitazone and metformin), *Avandaryl*® (rosiglitazone and glimepiride), *Avandamet*® (rosiglitazone and metformin), and *Duetact*® (pioglitazone and glimepiride). The August labeling update warned of the increased risks of heart failure in patients taking those drugs.

At this time, the FDA has concluded that there isn't enough evidence to indicate that the risks of heart attacks or death are different between *Avandia* and some other oral type 2 diabetes treatments. Therefore, the FDA has requested that GSK conduct a new long-term study to evaluate the potential cardiovascular risk of *Avandia*, compared to an active control agent. GSK has agreed to conduct the study and FDA will ensure it is initiated promptly.

Avandia sales were estimated at approximately \$1.8 billion in 2006, according to IMS. *Avandamet* and *Avandaryl* had sales of \$167 million and \$62 million, respectively, in 2006. The oral hypoglycemic category as a whole had sales of \$8.8 billion in 2006. According to a *Wall Street Journal* article, sales of *Avandia*, *Avandamet* and *Avandaryl* have fallen by almost 50 percent in the U.S. since May 2007 when Cleveland Clinic cardiologist Steven Nissen published an analysis of 42 studies suggesting *Avandia* increased risk of heart attacks by 43 percent.

Revised prescribing information for *Avandia* is available at: http://us.gsk.com/products/assets/us_avandia.pdf.^{1,2,3}

Implications

- Medco clinical programs, such as RationalMed[®], Medco's patient safety system, and concurrent drug utilization review (DUR) already provide alerts for patients on *Avandia* and insulin or nitrates concomitantly. Those programs also already include clinical alerts for patients with congestive heart failure (CHF) or edema who receive glitazones. Patients with CHF who receive *Avandia* are known to be among the high risk population who may experience an increased rate of cardiovascular ischemic events. Medco implemented those alerts in August, 2007 based on the briefing documents for the July 2007 FDA advisory committee meetings.
- Medco will share this new label information with its Pharmacy and Therapeutics (P&T) committee to determine how it may influence formulary and other clinical programs, such as step therapy rules for the glitazone class of drugs. RationalMed and concurrent DUR alerts will also be reviewed for any need to update information on cardiovascular risk with *Avandia*.

New Non Prescription Drug

Zyrtec-D[®] 12-hour[®] and Zyrtec[®] approved for nonprescription use

The FDA recently approved all strengths of McNeil Consumer Healthcare's *Zyrtec-D[®] 12-hour[®]* (cetirizine 5 mg/pseudoephedrine 120 mg) and *Zyrtec[®]* (cetirizine 5 mg and 10 mg tablet, 5 mg and 10 mg chewable tablet and 1 mg/mL syrup) to be used without a prescription for adults and children. *Zyrtec* and *Zyrtec-D* have been available as prescription products. *Zyrtec* syrup and a 5 mg chewable tablet will be available as both prescription and nonprescription products to treat pediatric patients.

Zyrtec is a once-a-day nonsedating antihistamine. *Zyrtec* tablets and chewable tablets are approved for adults and children six years of age and older for treating hay fever symptoms and other respiratory allergies, and to relieve itching due to hives.

The *Zyrtec* syrup is approved for adults and chil-

dren two years of age and older for treating hay fever symptoms and other respiratory allergies, and adults and children six years of age and older to relieve itching due to hives.

Two distinct *Zyrtec* products will be marketed for each dosage form. One will provide directions for treating the symptoms of hay fever and other respiratory allergies. The other will contain directions for use to relieve the itching due to hives.

Zyrtec-D combines *Zyrtec* with a nasal decongestant. Nonprescription *Zyrtec-D* was approved for the relief of symptoms due to hay fever or other upper respiratory allergies such as runny nose, sneezing, itchy, watery eyes, itching of the nose or throat and nasal congestion.

Zyrtec-D is also approved for reducing swelling of nasal

passages, for relief of sinus congestion and pressure, and for restoring freer breathing through the nose due to hay fever and other upper respiratory allergies. *Zyrtec-D* is not approved for the relief of itching due to hives.

Zyrtec-D is subject to the same restrictions as other nonprescription products containing pseudoephedrine, including being sold without a prescription "behind-the-pharmacy counter." Customers must ask the pharmacist for it, show a drivers license or other government-issued identification, sign a log book and be limited on the amount that can be purchased. Pseudoephedrine is an ingredient that can be used for making methamphetamine, a highly addictive illegal stimulant.

Nonprescription *Zyrtec* and *Zyrtec D* are expected to be available in pharmacies in late January 2008 in their original prescription strength. Nonprescription *Zyrtec* and *Zyrtec D* will have short exclusivity periods, allowing for generic nonprescription alternatives in 2008.^{4,5}

Implications

- McNeil has stated that for many allergy sufferers, nonprescription *Zyrtec* will cost up to one-third less than prescription *Zyrtec*.
- Once *Zyrtec* and *Zyrtec-D* become available without a prescription in early 2008, they will no longer be on the Medicare D formulary.
- As additional nonprescription non-sedating antihistamines become available, plans may need to re-evaluate coverage of the entire category. Several options are available to Medco plans for managing this class of drugs, such as excluding coverage of non-sedating antihistamines or increasing copayments. Medco formularies and coverage programs may also need to be re-evaluated.
- More information on Medco's plans for the pending introduction of non prescription *Zyrtec* and *Zyrtec-D* will be forthcoming.

Study

Study: *Crestor*[™] (rosuvastatin) does not improve treatment for advanced heart failure

On November 5, new data from the CORONA (CONtrolled ROsuvastatin MultiNAtional Study in Heart Failure) study presented at the American Heart Association Scientific Sessions showed that patients with advanced heart failure treated with the statin, *Crestor*[™], did not have a significant improvement in their outcomes. This may be because it could not reverse or prevent the deterioration of the failing heart.

Patients with advanced heart failure who added *Crestor* 10 mg to their optimized therapy experienced an eight percent reduction in the combined primary endpoint of cardiovascular death, myocardial infarction or stroke, which is not statistically significant.

The reduction was primarily due to a decrease in atherosclerotic events, such as stroke and myocardial infarctions, which is where statins have a proven benefit. In the study, most of the deaths did not appear to be impacted by the *Crestor* therapy. In addition, significantly fewer hospitalizations occurred in the patients who were taking *Crestor* as compared to placebo, whether due to any cause, cardiovascular causes or for worsening of heart failure.

The CORONA study was a long-term, randomized, placebo-controlled study of more than 5,000 patients with chronic, symptomatic, systolic heart failure of ischemic origin. The study was designed to evaluate the effect of adding *Crestor* 10 mg to optimized treatment on cardiovascular mortality and morbidity and overall survival in patients whom investigators felt did not need cholesterol-lowering therapy.⁶

Implications

- This is new scientific information as no other statins have been studied in patients with advanced heart failure. These patients are clearly different than patients without heart failure in their response to statins. The study findings suggest that the major cause of death in the heart failure patients was likely not related to atherosclerotic events, where statins have shown a benefit in non-heart failure patients, but instead may have been caused by the deterioration of the failing heart muscle damaged beyond repair.
- This study underscores the importance of early intervention in treating patients with advanced heart failure.

New Drug

Drug brand/generic name and manufacturer	Date approved, launch date and indication	Dosing and side effects	Implications and pricing
<p><i>Mircera</i>^{®7,8,9}</p> <p>methoxy polyethylene glycol-epoetin beta injection</p> <p>Roche</p>	<p>On November 14, the FDA approved <i>Mircera</i> for the treatment of anemia associated with chronic kidney disease (CKD) in patients on dialysis and patients not on dialysis. <i>Mircera</i> is not indicated for the treatment of anemia due to cancer chemotherapy.</p> <p>The outcome of an ongoing patent case will determine when patients can gain access to <i>Mircera</i> in the U.S. The launch may be delayed by up to six years.</p> <p>Anemia is a complication associated with CKD from its early stages up to kidney failure requiring dialysis.</p>	<p><i>Mircera</i> is given once-every-two-weeks to provide correction of anemia in CKD patients. <i>Mircera</i> is given once-monthly or once-every-two-weeks to maintain stable hemoglobin levels in CKD patients.</p> <p>The most common adverse reactions are hypertension (high blood pressure), diarrhea, nasopharyngitis, headache and upper respiratory tract infection.</p> <p>Approval of <i>Mircera</i> follows labeling changes made to other erythropoietin stimulating agents (ESAs), <i>Aranesp</i>[®] (darbepoetin alfa) and <i>Epogen</i>[®]/<i>Procrit</i>[®] (epoetin alfa). The changes to the labeling reflect the safety and benefit/risk profile of ESAs. Labeling for <i>Mircera</i> includes warnings on the risk of death and serious cardiovascular events consistent with the class. Dosage and administration instructions for ESA use in chronic renal failure patients were recently modified to individualize dosing to achieve and maintain hemoglobin levels between 10 to 12 g/dL, using the lowest dose possible.</p> <p>Prescribing information is not available.</p>	<ul style="list-style-type: none"> • The timing of a Medco Pharmacy and Therapeutics (P&T) committee review of <i>Mircera</i> will depend on the outcome of ongoing patent litigation. The product will not be reviewed until issues involving availability and marketing are resolved. A decision for the Medicare PDP formulary will be made after the review of this drug for the commercial formularies. • Once available, <i>Mircera</i> will roll into existing coverage criteria for the erythropoietin agents. • The drug will be added to the Medco/Accredo specialty offering when it becomes available. • The cost of <i>Mircera</i> is not available.

New Dosage Formulation

Drug brand/generic name and manufacturer	Indication	New dosage formulation	Implications
<p><i>Protonix</i>^{®10} pantoprazole delayed-release oral suspension Wyeth</p>	<p><i>Protonix For Delayed-Release Oral Suspension</i> is a proton-pump inhibitor (PPI) that is indicated for the treatment and maintenance of healing of erosive esophagitis with associated gastroesophageal reflux disease (GERD) symptoms.</p>	<p><i>Protonix For Delayed-Release Oral Suspension</i> was approved on November 15.</p> <p><i>Protonix For Delayed-Release Oral Suspension</i> can be administered orally in applesauce or apple juice, or through a nasogastric (NG) tube.</p>	<ul style="list-style-type: none"> • <i>Protonix</i> is a non-preferred drug on Medco's standard formularies. <i>Protonix</i> is targeted in the PPI preferred-drug step-therapy program. • <i>Protonix</i> is also available as delayed-release tablets and intravenous injection.
<p><i>Kaletra</i>^{®11,12} 100 mg of lopinavir and 25 mg of ritonavir tablet Abbott</p>	<p><i>Kaletra</i> is used in combination with other anti-HIV medicines to treat people with HIV infection.</p>	<p>The FDA approved this low-dose version of <i>Kaletra</i> on November 12 and the drug was launched a few days later. The new dose is indicated for treating pediatric patients with HIV.</p> <p>The new tablet is half the dose of the original tablet commonly used by adults, which contains 200 mg of lopinavir and 50 mg of ritonavir.</p>	<ul style="list-style-type: none"> • Pricing for the new dosage form is not available. • <i>Kaletra</i> oral solution (80 mg lopinavir/ 20 mg ritonavir) has also been available for pediatric use since it was approved in 2000.

New Indication

Drug brand/generic name and manufacturer	Indication	Implications
<p><i>Seroquel XR</i>^{TM13}</p> <p>quetiapine</p> <p>200 mg, 300 mg, 400 mg extended-release tablet</p> <p>AstraZeneca</p>	<p>On November 16, <i>Seroquel XR</i>, an atypical antipsychotic, was approved for the maintenance treatment of schizophrenia in adult patients.</p> <p><i>Seroquel XR</i> was approved on May 18, 2007 for the once-daily acute treatment of schizophrenia in adult patients.</p> <p><i>Seroquel</i>[®] (immediate-release) is approved to treat schizophrenia and bipolar disorder.</p> <p>Schizophrenia is a serious brain disorder with symptoms including distorted perceptions of reality, hallucinations and delusions, illogical thinking and flat or blunted emotions. This condition affects more than two million American adults – about one per cent of the population age 18 and older.</p>	<ul style="list-style-type: none"> • <i>Seroquel XR</i> will be added to the dispensing quantity rules for the atypical antipsychotic therapeutic class. • <i>Seroquel</i> and <i>Seroquel XR</i> are preferred drugs on Medco's standard formularies.

New Indication

Drug brand/generic name and manufacturer	Indication	Implications
<p><i>Abilify</i>^{®14,15,16}</p> <p>aripiprazole</p> <p>tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablets</p> <p><i>Abilify Discmelt</i>[™] orally disintegrating tablets: 10 mg and 15 mg</p> <p>oral solution: 1 mg/mL</p> <p>single-dose, ready-to-use solution for intramuscular injection: 7.5 mg/mL</p> <p>Otsuka Pharmaceutical and Bristol-Myers Squibb</p>	<p>On November 7, the atypical antipsychotic <i>Abilify</i> was approved for treating schizophrenia in adolescents aged 13 to 17 years.</p> <p>On November 16, <i>Abilify</i> was approved as an add-on therapy for the treatment of major depressive disorder in adults.</p> <p><i>Abilify</i> is also indicated for treating acute manic or mixed episodes associated with Bipolar I Disorder in adults. <i>Abilify</i> injection is indicated for treating adults with agitation associated with schizophrenia or Bipolar I Disorder, manic or mixed.</p>	<ul style="list-style-type: none"> • Dispensing quantity rules are available for the atypical antipsychotic therapeutic class, which includes <i>Abilify</i> tablets and <i>Discmelt</i>. • <i>Risperdal</i>[®] was also recently approved for treating schizophrenia in adolescents, ages 13 to 17. • <i>Zyprexa</i>[®] has also been submitted for supplemental New Drug Applications (sNDAs) for treatment of adolescents. <i>Zyprexa</i> is being studied for schizophrenia in patients aged 13 to 17 and for acute manic/mixed episodes of bipolar I disorder in children aged 13 to 17. • <i>Abilify</i> is a non-preferred drug while <i>Risperdal</i> and <i>Zyprexa</i> are preferred drugs on Medco's standard formularies.
<p><i>Crestor</i>^{™17,18,19}</p> <p>rosuvastatin</p> <p>5 mg, 10 mg, 20 mg and 40 mg tablets</p> <p>Astra-Zeneca</p>	<p>On November 9, <i>Crestor</i> was approved as an adjunct to diet to slow the progression of atherosclerosis (hardening of the arteries) in adult patients with elevated cholesterol.</p> <p><i>Crestor</i> is already indicated as adjunctive therapy to diet to reduce elevated total LDL-C cholesterol ("bad cholesterol") and triglycerides and to increase HDL-C ("good cholesterol") in adult patients with hyperlipidemia or mixed dyslipidemia. <i>Crestor</i> belongs to the statins class of drugs that are used to lower cholesterol levels.</p>	<ul style="list-style-type: none"> • <i>Crestor</i> is a preferred drug on Medco's standard formularies.

Safety/Labeling Revisions

Drug brand/generic name and manufacturer	Indication	Product labeling update	Implications
<p><i>Sprycel</i>^{®20,21}</p> <p>dasatinib</p> <p>20 mg, 50 mg and 70 mg tablets</p> <p>Bristol-Myers Squibb (BMS)</p>	<p><i>Sprycel</i>, an inhibitor of tyrosine kinase, is indicated for treating adults with chronic, accelerated or myeloid or lymphoid blast phase chronic myelogenous leukemia (CML) with resistance or intolerance to prior treatment, including <i>Gleevec</i>[®] (imatinib). It is also indicated for treating adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia with resistance or intolerance to prior therapy.</p> <p>CML is one of the four most common types of leukemia, a form of blood cancer, and affects about 4,500 people in the U.S. each year.</p>	<p>On November 8, the FDA approved a lowered starting dose for <i>Sprycel</i>. The label now recommends a 100 mg daily starting dose, as opposed to 70 mg twice daily, for patients with chronic-phase CML. The starting dose for the remaining indications is unchanged. BMS states that the lower dose will improve the drug's side effect profile, such as less fluid retention.</p>	<ul style="list-style-type: none"> • In October, <i>Tasigna</i>[®], another inhibitor of tyrosine kinase, was approved as the only other drug indicated for treating adults with CML who fail treatment with <i>Gleevec</i>.

New Generic

Generic drug name strength/dosage form, reference brand and manufacturer	Approval and launch dates	Indication	Comments
<p>rivastigmine tartrate^{22,23}</p> <p>1.5 mg, 3 mg, 4.5 mg and 6 mg capsules</p> <p>Sun Pharmaceuticals, Dr. Reddy's Labs</p> <p><i>Exelon</i>® capsules</p> <p>Novartis</p>	<p>Sun Pharmaceutical's generic was approved October 23. However, the launch is pending patent litigation.</p> <p>Dr. Reddy's Labs also received approval on October 31.</p>	<p><i>Exelon</i> is indicated for treating mild to moderate dementia "of the Alzheimer's type" and associated with Parkinson's disease.</p>	<p>Once the generic is launched, Sun Pharmaceuticals shares 180-day market exclusivity for rivastigmine tartrate capsules.</p>

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