



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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More children taking prescription medications for gastrointestinal disorders

- Infants and preschoolers (4 and under) taking medications to treat gastrointestinal conditions rose almost 56 percent from 2002 to 2006.
- Medco uses a number of drug utilization review (DUR) rules to assess if a drug is appropriate given the age of the patient and if the prescribed dosage is correct.

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Study

Medco study finds increasing use among children of medications for gastrointestinal ailments

The number of children taking prescription medications to treat gastrointestinal disorders has increased significantly in the past five years, according to a new analysis conducted by Medco.

The research reviewed prescription drug claims of more than 575,000 insured children and found that the number of infants and preschoolers (4 and under) taking medications to treat gastrointestinal conditions rose almost 56 percent from 2002 to 2006, and the prevalence of elementary school-age children (5 to 11 year olds) using these drugs increased by 31 percent during that time frame. While the actual prevalence rate was highest among adolescents, 12 to 18 year olds showed the smallest increase in use of gastrointestinal medications--rising only about six percent over the five-year period. Based on the analysis, it's estimated that more than 2 million children in the U.S. used these drugs in 2006.

Drug spend for this group up 50 percent

The amount spent on gastrointestinal medications also rose substantially for the pediatric group, up 50 percent from 2002 to 2006. The jump in drug spend was likely due to a combination of higher utilization and the introduction of more expensive pediatric formulations of some of these drugs. The most commonly prescribed gastrointestinal medications, proton pump inhibitors (PPIs), are now the second leading class of drugs sold in the U.S., trailing only cholesterol-lowering medications in sales.

In addition to PPIs, Histamine-2 (H2) blockers are also widely prescribed for children. Both these classes of medications are used to treat heartburn and gastroesophageal reflux disease (GERD)--a condition in which harsh stomach acid backs up into the esophagus--as well as other gastrointestinal ailments.

While reflux is common in babies during the first three months of life, symptoms usually cease between 12 to 24 months and only a very small number of children have symptoms severe enough to warrant drug treatment. In extreme cases, gastrointestinal medications including PPIs and H2 blockers may be recommended.

Recent studies have shown a link between obesity and GERD in adults, a connection that may also be affecting children and could explain why these medications are growing in use among the pediatric population. More than

10 percent of preschoolers and 30 percent of children are now considered overweight in the U.S.

To avoid overuse, non-drug approaches for treating reflux and digestive problems should be tried. Such treatments include eating smaller, more frequent meals; avoiding food two to three hours before bed; using an elevated sleep position with the head at a 30 degree angle and avoiding carbonated drinks, chocolate, caffeine, and foods that are high in fat or are very acidic or spicy. Infants may benefit from having their feedings

thickened with cereal; smaller, more frequent meals and being kept upright after being fed.¹

Implications

- To help ensure that gastrointestinal medications are being utilized properly in the pediatric population, Medco uses a number of drug utilization review (DUR) rules to assess if the drug is appropriate given the age of the patient and if the prescribed dosage is correct.

New Drug

Drug brand/generic name and manufacturer	Date approved, launch date and indication	Dosing and side effects	Implications and pricing
<p><i>Azor</i>^{TM2,3}</p> <p>amlodipine and olmesartan</p> <p>5/20 mg; 10/20 mg; 5/40 mg and 10/40 mg</p> <p>tablet</p> <p>Daiichi Sankyo, Inc</p>	<p><i>Azor</i> was approved on September 26, 2007 and is indicated for the treatment of hypertension, also known as high blood pressure; alone or with other antihypertensive agents. <i>Azor</i> is not indicated for the initial therapy of hypertension. A launch date has not been announced.</p> <p>This is a combination product containing the dihydropyridine calcium channel blocker amlodipine (<i>Norvasc</i>[®] and various generics) and the angiotensin receptor blocker olmesartan (<i>Benicar</i>[®]).</p> <p><i>Exforge</i>[®] (amlodipine and valsartan) was the first combination product containing a calcium channel blocker and an angiotensin receptor blocker.</p> <p>Hypertension affects approximately 72 million people in the United States and approximately one billion people worldwide.</p>	<p><i>Azor</i> tablets are taken once daily. Dosage may be increased after two weeks. The maximum recommended dose is 10/40 mg (amlodipine/olmesartan).</p> <p>The adverse events seen with <i>Azor</i> are similar to those seen with the individual components. The most common adverse event was edema (swelling) which is attributed to the amlodipine component. There was some data to suggest that the addition of olmesartan actually reduced the incidence of amlodipine-induced edema. Other adverse events included hypotension (low blood pressure), orthostatic hypotension, rash, itching, palpitation, urinary frequency and excessive urination at night.</p> <p>Prescribing information is available at: http://www.azor.com/AZOR_PI.pdf.</p>	<ul style="list-style-type: none"> • <i>Azor</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. • Quantity limits are under consideration. • The average wholesale price (AWP) for <i>Azor</i> ranges from \$2.66 to \$3.82 for the various strengths.

New Indication

Drug brand/generic name and manufacturer	Indication	Implications
<p><i>Norditropin</i>^{® 4,5}</p> <p>somatropin</p> <p>Individually cartoned in 5 mg/1.5 mL or 15 mg/1.5 mL cartridges which must be administered using corresponding NordiPen delivery system.</p> <p>NovoNordisk</p>	<p>On September 21, <i>Norditropin</i> was approved to treat short stature in children with Turner syndrome.</p> <p>Turner syndrome results from a rare chromosomal abnormality in which a female is born with only one X chromosome (instead of the usual two) or is missing part of one X chromosome. Short stature is the most common feature associated with Turner syndrome. Affected females may also have a variety of other associated features and medical problems. This syndrome occurs in 1 in 2,500 live female births.</p> <p><i>Norditropin</i> was previously approved to treat children with growth failure due to growth hormone deficiency (GHD), short stature in children with Noonan syndrome and for adults with either adult onset or childhood onset GHD.</p> <p><i>Norditropin</i> is an injection that is administered under the skin.</p> <p>Prescribing information is available at http://www.novonordisk.com/images/growth_hormone/pdf/norditropin_prescribing_information_Feb04.pdf.</p>	<ul style="list-style-type: none"> • <i>Genotropin</i>[®] (somatropin), <i>Humatrope</i>[®] (somatropin), and <i>Nutropin</i>[®] (somatropin) are also indicated for Turner syndrome. • <i>Norditropin</i> is a preferred agent on Medco's standard formularies and the Medicare PDP formulary. • Coverage criteria are available to reduce exposure to costs associated with use of growth hormone for conditions for which its effectiveness is not known.

FDA Action

Drug brand/generic name and manufacturer	Indication	Implications
<p><i>Evista</i>^{6,7,8}</p> <p>raloxifene</p> <p>60 mg tablet</p> <p>Eli Lilly and Company</p>	<p><i>Evista</i> was recently approved for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.</p> <p>The FDA debated about whether the benefits of <i>Evista</i> as a preventive treatment are worth the risks, which include deep vein thrombosis (blood clots in a deep vein, such as in the leg), pulmonary embolism (obstruction of a blood vessel in the lung by an abnormal particle) and death from stroke. Therefore, along with the approved indication, a Black Box warning was added to the labeling to address these increased risks. Both risks were previously included in the warnings section of the labeling. The indications section of the labeling states, "After an assessment of the risk of developing breast cancer, the decision regarding therapy with <i>Evista</i> should be based upon an individual assessment of the benefits and risks."</p> <p><i>Evista</i> was previously approved for treating and preventing osteoporosis in postmenopausal women.</p> <p>Breast cancer is the second leading cause of cancer death in U.S. women. An estimated 178,480 new cases of invasive breast cancer are expected to occur among women in the U.S. during 2007.</p> <p>Prescribing information is available at http://pi.lilly.com/us/evista-pi.pdf.</p>	<ul style="list-style-type: none"> • <i>Evista</i> is only the second drug approved to reduce the risk of breast cancer. <i>Nolvadex</i>[®] (tamoxifen) was the first. • <i>Evista</i> is a preferred agent on Medco's standard formularies.

New Dosage Form

Drug Brand/Generic Name and Manufacturer	Indication	Latest FDA action	Comments
<p><i>Lamisil</i>®^{9,10} terbinafine oral granules 125 mg and 187.5 mg One carton contains 14 pack- ets. Also available as a pack of three cartons. Novartis</p>	<p><i>Lamisil</i> oral granules are indicated for treating <i>tinea capitis</i>, a fungal infection of the scalp, in children ages four years and older.</p> <p><i>Tinea capitis</i> is a persistent and contagious fungal infection that most commonly affects children. Symptoms include severe itching, dandruff and bald patches.</p>	<p><i>Lamisil</i> oral granules were approved as a new dosage form.</p> <p>The granules are administered once a day for six weeks. The dose (125 mg, 187.5 mg or 250 mg per day) is based on the weight of the child. The entire contents of each packet of granules should be sprinkled on a spoonful of non-acidic food and swallowed in its entirety.</p> <p><i>Lamisil</i> is also available as an oral tablet and topical cream, gel and solution. The oral tablet is available generically while the topical cream is available over the counter.</p> <p>Prescribing information for <i>Lamisil</i> oral granules is available at: http://www.fda.gov/cder/foi/label/2007/022071lbl.pdf.</p>	<ul style="list-style-type: none"> • <i>Lamisil</i> oral granules will be reviewed by Medco's P&T committee. • Other antifungal medications, such as ketoconazole, itraconazole and fluconazole, have been reported to be effective alternative therapeutic agents for <i>tinea capitis</i>. Of those agents, itraconazole and terbinafine are used most commonly.

Drug Labeling Revisions/Safety

Drug brand/generic name and manufacturer	Indication	Product labeling update	Implications
<p><i>Zyprexa</i>^{®11,12,13,14} olanzapine 2.5 mg, 5 mg, 7.5 mg and 10 mg tablet</p> <p><i>Zyprexa</i>[®] <i>Zydis</i>[®] olanzapine orally disintegrating tablet 5 mg, 10 mg, 15 mg and 20 mg</p> <p><i>Zyprexa</i>[®] IntraMuscular 10 mg vial</p> <p><i>Symbyax</i>[®] olanzapine and fluoxetine 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50mg Eli Lilly and Company</p>	<p><i>Zyprexa</i> and <i>Symbyax</i> are both atypical antipsychotic drugs.</p> <p><i>Zyprexa</i> is indicated for treating schizophrenia, acute mixed or manic episodes associated with Bipolar I Disorder, agitation associated with schizophrenia and bipolar I mania and maintaining bipolar patients on monotherapy.</p> <p><i>Symbyax</i> is indicated for treating depressive episodes associated with bipolar disorder.</p>	<p>Eli Lilly updated the labeling of both products with new warnings regarding weight gain and hyperlipidemia (high blood cholesterol) and new information to the existing warning for hyperglycemia (high blood sugar).</p> <p>Information on these risks is already on the product labels. The updates reflect recently completed pooled analyses of Lilly's clinical trial data in adults and adolescents.</p> <p>Lilly sent letters to health care professionals that stressed the importance of monitoring glucose, weight and lipids in patients treated with <i>Zyprexa</i> or <i>Symbyax</i>.</p> <p>Prescribing information for <i>Zyprexa</i> is available at http://pi.lilly.com/us/zyprexa-pi.pdf, and for <i>Symbyax</i> at: http://pi.lilly.com/us/symbyax-pi.pdf.</p>	<ul style="list-style-type: none"> • RationalMed[®], Medco's patient safety system, has alerts in place to warn of the increased risk of high blood cholesterol and high blood sugar that may be due to weight gain when taking <i>Zyprexa</i>. <i>Symbyax</i> will be added to the rule and the rule itself will be modified based on the new information. • <i>Zyprexa</i> is a preferred agent on Medco's formularies while <i>Symbyax</i> is not a preferred agent.

New Generic

Generic drug name strength/dosage form, reference brand and manufacturer	Approval and launch dates	Indication	Comments
<p>albuterol sulfate inhalation solution^{15,16}</p> <p>0.021% (base)</p> <p>Watson Pharmaceuticals, Inc.</p> <p><i>AccuNeb</i>[®]</p> <p>Dey, L.P.</p>	<p>Approved September 26 and available immediately.</p>	<p>Albuterol sulfate inhalation solution is indicated for the relief of bronchospasm in patients with asthma ages 2 to 12.</p>	<ul style="list-style-type: none"> • Watson has been awarded 180 days of marketing exclusivity for the 0.021% base. • Nephron Pharmaceuticals Corporation received approval in June 2004 for a generic of the albuterol sulfate inhalation solution 0.042% base. • For the 12-months ending June 2007, <i>AccuNeb</i> had total U.S. sales of approximately \$20 million, according to IMS.

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