



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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FDA Action

FDA moves against marketing of unapproved hydrocodone products

On September 28, 2007, the Food and Drug Administration (FDA) announced its intention to take enforcement action against companies marketing unapproved prescription drug products containing hydrocodone, a narcotic widely used to treat pain and suppress coughs. The FDA believes that this action could impact approximately 200 cough-suppressant products.

Manufacturers and distributors marketing unapproved hydrocodone products that are currently labeled for use in children younger than six years of age must end further manufacturing and distribution of the products on or before October 31, 2007. Those marketing any other unapproved hydrocodone drug products must stop manufacturing such products on or before December 31, 2007 and must cease further shipment in interstate commerce on or before March 31, 2008.

Action does not affect approved hydrocodone products

Many hydrocodone pain-relief products, such as *Vicodin*[®], are FDA-approved. This action does not affect hydrocodone formulations which have FDA approval. However, most of the hydrocodone formulations now marketed to suppress coughs have not been approved. The agency is particularly concerned about improper pediatric labeling of unapproved hydrocodone cough suppressants, and the risk of medication error involving the unapproved products.

There are a number of alternatives for patients who might be using unapproved hydrocodone cough suppressants. There are seven FDA-approved cough suppressant products containing hydrocodone which are unaffected by this current FDA action:

- *Tussicaps* from Tyco Healthcare
- *Tussionex Pennkinetic* from UCB Inc.
- hydrocodone compound from Acta Vis Med Atlantic
- *Mycodone* from Morton Grove
- homatropine methylbromide/hydrocodone bitartrate from Acta Vis Totowa
- *Hycodan* from Endo Pharms
- *Tussigon* from King Pharma

There also are a variety of approved antitussive products that do not contain hydrocodone. Consumers should consult a health care professional for detailed guidance on treatment options.

The FDA has received reports of medication errors associated with formulation changes in unapproved hydrocodone products and reports of confusion over the similarity of the names of unapproved products to approved drug products. As part of the drug approval process, the agency considers the possibility of medication errors and name confusion, so that potential safety issues associated with these factors can be minimized.

The FDA noted that no hydrocodone cough suppressant has been established as safe and effective for children under six years of age; however some of these unapproved products carry labels with dosing instructions for children as young as two years of age. It is important to note that these products are not being immediately withdrawn from the market. Rather, the manufacturers must cease production and distribution over the next one to six months, depending on the labeling of the product.^{1,2,3}

For additional information on the FDA's action for hydrocodone product visit the FDA's Website at <http://www.fda.gov/medwatch/safety/2007/safety07.htm#Hydrocodone> and http://www.fda.gov/cder/drug/unapproved_drugs/hydrocodone_qa.htm

Implications

- Medco is reviewing its standard formularies and will remove any unapproved hydrocodone products from those formularies. The unapproved products will no longer be Medicare Part D drugs, since the FDA has now made clear that they are "new drugs" that require FDA approval. Consequently, those products will no longer be covered under Medicare Part D, as was the case with the other products recently subjected to a similar FDA decision.
- Effective October 26, Medco By Mail took the fol-

lowing actions regarding unapproved hydrocodone products:

- Medco stopped dispensing unapproved hydrocodone products for any patient less than six years old and first-time therapy patients, even though the FDA is allowing distribution of those products until March 28, 2008.
- All prescriptions for any unapproved hydrocodone product will be sent to Drug Utilization Review (DUR). If the patient is older than six years old and there is no previous prescription for a hydrocodone product, or if the patient is younger than six years old, Medco will contact the patient's physician. If the patient is older than six years old and has a prescription for a hydrocodone product in their drug history within the last six months, Medco will dispense one final hydrocodone prescription and add messaging to the literature package mailed with the prescription directing the patient to see their prescriber for an alternative therapy.
- Since those products are not being withdrawn immediately and pharmacies can continue to dispense these unapproved products, Medco will continue to adjudicate retail prescription claims for those products during the next few months.
- As noted with previous FDA actions to remove unapproved drugs from the market, many other unapproved drug products remain on the market. It will likely be some time before all of those products are subject to a regulatory action. The FDA does not have a listing of those unapproved products, and with numerous possible reasons for their presence in the marketplace, it is not possible to identify them all. In general, if a product is not listed at all in the *Orange Book* (which lists FDA-approved drugs and their associated patents and exclusivity), that is, non-rated, it may likely fall into this broad category of unapproved

products. However, due to many reasons--for example, a drug is still subject to an ongoing Drug Efficacy Study Implementation (DESI) proceeding--non-listing in the *Orange Book* does not absolutely mean that the product is being marketed illegally.

- Medco is carefully watching for any new hints of FDA regulatory actions regarding this category of unapproved products, and will proactively take actions with respect to formulary status and mail dispensing of those products.
- An FDA Advisory Committee recently recommended that multi-symptom over-the-counter (OTC) pediatric cough and cold medicines should be banned for chil-

dren under six years old. The FDA has not made a final ruling yet. This recommendation came a week after major manufacturers agreed to withdraw more than a dozen OTC cough and cold products (e.g. *Robitussin Infant Cough DM drops, Tylenol Plus Cold, Triaminic Infant & Toddler Thin Strips Decongestant*) labeled for use in children under two years of age over concerns that some caregivers are misusing the drugs, resulting in accidental overdose. Warnings will be placed on other cold medicines advising that they should not be used in children under two years of age.^{4,5}

A look behind recent FDA actions regarding unapproved active ingredients

The Food and Drug Administration (FDA) has estimated that there are several hundred different unapproved active ingredients in perhaps a few thousand unapproved prescription drug products on the market today. The agency has estimated that less than two percent of prescribed drugs on the market today are unapproved. Furthermore, since the FDA has been actively removing those products from the market over the past year or more, the number of marketed unapproved drug products has decreased substantially during this time.

Many of the unapproved drugs affected by the FDA's final guidance, including the hydrocodone cough and cold products, are older medicines that were developed and marketed before successive changes to the drug approval process that is established in the Federal Food, Drug and Cosmetic Act.

Health care providers are often unaware of the unapproved status of some prescription drugs and have continued to unknowingly prescribe unapproved drugs because the drugs' labels do not disclose that they lack FDA approval. Often those drugs may be advertised in medical journals or are included in widely used pharmaceutical references such as the *Physicians' Desk Reference* (PDR).

FDA action started in 2006

On June 8, 2006, the FDA announced the strengthening of its efforts against unapproved drug products. As part of its ongoing drug safety initiative, the FDA took an important action to ensure the safety and quality of prescription and over-the-counter (OTC) drugs in the United States by issuing a final guidance entitled "*Marketed Unapproved Drugs--Compliance Policy Guide*."

The guidance is designed to make sure that all drugs marketed in the U.S., prescription and OTC, have been shown to be safe and effective. The finalization of this guidance, which was initially issued in 2003, demonstrates the agency's commitment to taking action against unapproved drug products. The *Marketed Unapproved Drugs--Compliance Policy Guide* is available on the FDA website at:

<http://www.fda.gov/cder/guidance/6911fnl.pdf>.

When it issued the initial guidance, the FDA began taking enforcement action to stop the manufacturing of unapproved prescription products beginning with the antihistamine carbinoxamine (see June 26, 2006 *Clinical Review*). This was similar to previous enforcement action against levothyroxine. Because those drugs are unapproved, the FDA has not reviewed their labeling, including the dosing information, warnings and precautions and indications.

FDA focusing on products that may be associated with safety concerns

Since June, 2006, the FDA has taken regulatory action on more than a half dozen categories of drug products that were marketed illegally, including guaifenesin timed-release products, ergotamine containing products, trimethobenzamide suppositories, quinine products and others. The process of eliminating those illegally marketed prescription drug products continues with the FDA focusing first on those products that may be associated with safety concerns and categories of product where at least one FDA-approved product is already on the market. However, with time, the agency intends to have all those products either removed from the market or have their manufacturers submit the required applications.

The FDA has not and cannot provide a list of all the drug products that are marketed illegally. Until the FDA places

a new notice in the *Federal Register* and announces their next regulatory action against a new category of products, it is unclear which products are marketed illegally. This makes it difficult, if not impossible, to proactively notify clients and members with respect to the currently marketed prescription drug products that are non-approved and marketed illegally.

Legislative history of drug approval

The original Federal Food and Drugs Act of June 30, 1906, first brought drug regulation under federal law. That law prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by the FDA. In 1938, Congress passed the Federal Food Drug, and Cosmetic Act (the Act), which required that "new drugs" be approved for safety by the FDA before they could legally be sold in interstate commerce. To this end, the Act made it the drug sponsor's burden to show the FDA that its drug was safe through the submission of a new drug application (NDA).

Between 1938 and 1962, if a drug obtained approval, the FDA considered drugs that were identical, related or similar (IRS) to the approved drug to be covered by that original approval, and allowed those IRS drugs to be marketed without independent review and approval.

In 1962, Congress amended the Act to require that new drugs also be proven effective for their labeled indications, as well as safe. This amendment also required the FDA to conduct a retrospective evaluation of the effectiveness of the drug products that the agency had approved as safe between 1938 and 1962. The FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety.

The NAS/NRC reports for those drug products were submitted to the FDA in the late 1960s and early 1970s. The agency reviewed and re-evaluated the reports and published its findings in Federal Register notices. The FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the 3,400 products specifically reviewed by the NAS/NRCs, as well as the even larger number of IRS products that entered the market without FDA approval.

When "old drugs" are considered "new drugs"

All drugs covered by the DESI review are "new drugs" under the Act. If the FDA's final DESI determination classified a drug product as ineffective, that drug product and those IRS to it could no longer be marketed, and could be subject to enforcement action as unapproved new drugs. If the FDA's final DESI determination classifies the drug product as effective for its labeled indications, the drug can be marketed, provided it is the subject of an application approved for safety and effectiveness.

Those drug products with NDAs approved before 1962 for safety therefore require approved supplements to their original applications; IRS drug products require an approved new drug application (NDA) or abbreviated new drug application (ANDA), as appropriate. Furthermore, labeling for drug products classified as effective may contain only those indications for which the review found the product effective, unless the firm marketing the product has received an approval for the additional indication(s).

This requirement of an approved application for drugs that were DESI effective has apparently been a point of contention with many manufacturers. Manufacturers have apparently argued for years that these DESI effective products are not, "new drugs", but rather they are recog-

nized as generally safe and effective given their long history of use and availability. Therefore, an NDA or ANDA was not needed. However, the FDA has now made it clear that approved applications are needed for those drugs to stay on the market.

Some marketed products still undergoing DESI reviews

Today, a small number of unapproved marketed products are still undergoing DESI reviews in which a final determination regarding efficacy has not yet been made. In addition to the products specifically reviewed by the NAS/NRC (that is, those products approved for safety only between 1938 and 1962), this group includes unapproved products identical, related or similar to those products specifically reviewed. In virtually all these proceedings, the FDA has made an initial determination that the products lack substantial evidence of effectiveness, and the manufacturers have requested a hearing on that finding.

It is the agency's longstanding policy that products subject to an ongoing DESI proceeding may remain on the market while the proceeding is pending. There is no published listing of those drugs that are still undergoing DESI review.

Some unapproved marketed products are subject to already-completed DESI proceedings and lack required approved applications. This includes a number of products IRS to DESI products for which approval was withdrawn due to a lack of substantial evidence of effectiveness. That group also includes a number of products IRS to those DESI products for which the FDA made a final determination that the product is effective, but applications for the IRS products have not been both submitted and approved as required under the statute and longstanding enforcement policy. The FDA now considers all of those products to be marketed illegally.

New Drug

Drug brand/generic name and manufacturer	Date approved, launch date and indication	Dosing and side effects	Implications and pricing
<p><i>Isentress</i>^{TM 6,7,8}</p> <p>raltegravir</p> <p>400 mg tablet</p> <p>Merck</p>	<p><i>Isentress</i> was approved on October 12 and is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. The product is expected to be available in pharmacies within two weeks of approval.</p> <p><i>Isentress</i> received a priority review.</p> <p><i>Isentress</i> is the first agent to be approved in a new class of antiretroviral drugs called integrase inhibitors.</p> <p>In 2006, over one million Americans were living with HIV/AIDS, and it is estimated that approximately 40,000 new cases of HIV/AIDS are diagnosed each year in the U.S.</p>	<p><i>Isentress</i> is taken as a single 400 mg tablet twice daily without regard to food.</p> <p>The most commonly reported adverse experiences of any severity were diarrhea, nausea, headache and fever.</p> <p>Prescribing information is available at: www.isentress.com.</p>	<ul style="list-style-type: none"> • <i>Isentress</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 maintain compliance with CMS rules. • Quantity limits for <i>Isentress</i> will be available. • Merck has stated that the wholesale acquisition cost (WAC) of <i>Isentress</i> will be \$27 per day (two 400 mg tablets). • Merck has initiated the SUPPORTTM program for patients in the U.S. who cannot afford treatment with <i>Isentress</i>.

New Drug

Drug brand/generic name and manufacturer	Date approved, launch date and indication	Dosing and side effects	Implications and pricing
<p><i>Ixempra</i>^{TM9,10,11}</p> <p>ixabepilone injection</p> <p>Bristol-Myers Squibb</p> <p><i>Ixempra</i> is supplied as two different injection kits: one containing one vial of <i>Ixempra</i> 15 mg and one vial of diluent 8 mL and the other containing one vial of <i>Ixempra</i> 45 mg and one vial of diluent 23.5 mL.</p>	<p><i>Ixempra</i> was approved October 16, 2007 and is expected to be available within 30 days of approval. <i>Ixempra</i> is indicated as monotherapy and in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer in patients who have failed previous chemotherapy.</p> <p><i>Ixempra</i> is a microtubule inhibitor belonging to a new class of antineoplastic agents, the epothilones and their analogs.</p> <p>The American Cancer Society estimates that more than 180,000 new cases of breast cancer will be diagnosed in the U.S. in 2007, and almost 41,000 people will die from the disease. Metastatic breast cancer is the most advanced form of the disease in which the cancer has spread to other organs in the body.</p>	<p>The recommended dosage of <i>Ixempra</i> is 40 mg/m² administered intravenously over three hours every three weeks.</p> <p><i>Ixempra Kit</i> must be refrigerated.</p> <p>The most common adverse reactions were peripheral sensory neuropathy (nerve damage), fatigue/asthenia, myalgia/arthralgia (muscle pain), alopecia (hair loss), nausea, vomiting, stomatitis/mucositis, diarrhea and musculoskeletal pain. Additional reactions can include: hand-foot syndrome, anorexia, abdominal pain, nail disorder and constipation. The most common blood abnormalities include neutropenia, leukopenia, anemia and thrombocytopenia.</p> <p>Prescribing information is available at http://www.bms.com/cgi-bin/anybin.pl?sql=PI_SEQ=118.</p>	<ul style="list-style-type: none"> • <i>Ixempra</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. • Traditional prior authorization limiting coverage of <i>Ixempra</i> to the FDA-approved indication is being considered. • <i>Ixempra</i> is being considered for inclusion in the Medco/Accredo specialty pharmacy program. The drug will likely be administered in a physician's office or clinic setting. • Pricing is not available.

New Drug Dosage Formulation

Drug Brand/Generic Name and Manufacturer	Indication	New Dosage Formulation	Implications
<p><i>Hycamtin</i>^{®12,13,14} topotecan</p> <p>0.25 mg, 1 mg capsules</p> <p>GlaxoSmithKline (GSK)</p>	<p><i>Hycamtin</i> is indicated for treating relapsed small cell lung cancer in patients who had a complete or partial response to first-line chemotherapy and who are at least 45 days from the end of that treatment.</p> <p><i>Hycamtin</i> intravenous is also approved to treat cervical and ovarian cancers.</p>	<p>The first oral version of <i>Hycamtin</i> was approved on October 12. GSK plans to launch this dosage form in 2008.</p> <p><i>Hycamtin</i> capsules are dosed once daily for five consecutive days of therapy every three weeks.</p> <p><i>Hycamtin</i> is currently available as an intravenous formulation, requiring five consecutive days of therapy every three weeks.</p>	<ul style="list-style-type: none"> • <i>Hycamtin</i> capsule is being considered for inclusion in the Medco/Accredo specialty pharmacy program.

New Indication

Drug Brand/Generic Name and Manufacturer	Indication and other labeling changes	Implications
<p><i>Januvia</i>^{TM15,16}</p> <p>sitagliptin</p> <p>25 mg, 50 mg and 100 mg tablets</p> <p>Merck</p>	<p><i>Januvia</i> is indicated as an adjunct to diet and exercise to improve glycemic (blood sugar) control in adults with type 2 diabetes.</p> <p><i>Januvia</i> was originally approved as monotherapy or combination therapy with either metformin or thiazolidinediones (TZDs) [<i>Actos</i>[®] (pioglitazone), <i>Avandia</i>[®] (rosiglitazone)] when a single agent does not provide adequate blood sugar control.</p> <p>On October 17, <i>Januvia</i> was approved for additional treatment regimens:</p> <ul style="list-style-type: none"> • as initial therapy in combination with metformin (<i>Glucophage</i>[®] and generics) • as an add-on therapy to a sulfonylurea when the single agent alone does not provide adequate glycemic control • as an add-on therapy to the combination of a sulfonylurea and metformin when dual therapy does not provide adequate glycemic control. <p>The warnings and precautions section of the <i>Januvia</i> label were updated based on postmarketing reports of serious hypersensitivity reactions in patients treated with the drug. Those reactions include anaphylaxis (severe or life-threatening allergic reaction) angioedema (skin swelling, similar to hives) and exfoliative skin conditions (scaly skin) including Stevens-Johnson syndrome.</p> <p><i>Januvia</i> should not be used in patients with type 1 diabetes.</p>	<ul style="list-style-type: none"> • This expanded labeling allows for <i>Januvia</i> to be used as initial therapy to control blood sugar.

Drug Discontinued

Drug brand/generic name and manufacturer	Date approved/withdrawn and indication	Implications
<p><i>Exubera</i>^{®17}</p> <p>insulin human, rDNA origin</p> <p>inhalation powder</p> <p>Pfizer</p>	<p>Pfizer has announced that they will stop selling <i>Exubera</i> due to low sales. <i>Exubera</i> was approved and launched in 2006.</p> <p><i>Exubera</i> is an inhaled insulin that is indicated for the treatment of adult patients with diabetes type 1 and 2 for the control of hyperglycemia (high blood sugar).</p> <p><i>Exubera</i> had less than 0.3 percent of the insulin market-share, according to A.G. Edwards brokerage firm.</p>	<ul style="list-style-type: none"> • Pfizer plans to work with physicians to transition the therapy of patients who are taking <i>Exubera</i> to other products within three months. • Medco By Mail will send letters to all patients (about 900) who have received any <i>Exubera</i> product within the last four months to notify them of the discontinued supply of <i>Exubera</i>. • All prescriptions for <i>Exubera</i> received at Medco By Mail will be routed to Drug Utilization Review (DUR) and the following will occur: <ul style="list-style-type: none"> • Medco will call physicians of patients that are new to <i>Exubera</i> therapy to request a change in therapy. • For continuing therapy prescriptions, a fax will be sent to the patient's physician and the prescription will be held to allow the physician to change the prescription order. • For any prescriptions for <i>Exubera</i> that are not changed after the physician is contacted, Medco will include a patient letter with their <i>Exubera</i> prescription to notify them of the discontinued supply of <i>Exubera</i>. • Medco By Mail will allow its <i>Exubera</i> inventory to be exhausted. • Retail claims will continue to be processed until the supply has been exhausted. • Other manufacturers (Eli Lilly, Novo Nordisk, Mannkind) are developing inhaled insulin in their pipelines.

Drug Labeling Revisions/Safety

Drug brand/generic name and manufacturer	Indication	Product labeling update
<p><i>Cialis</i>^{®18,19} tadalafil tablet GlaxoSmithKline</p> <p><i>Levitra</i>[®] vardenafil tablet GSK/Schering-Plough</p> <p><i>Viagra</i>[®] sildenafil tablet Pfizer</p> <p><i>Revatio</i>[®] sildenafil tablet Pfizer</p>	<p><i>Cialis</i>, <i>Levitra</i> and <i>Viagra</i> are indicated for treating erectile dysfunction.</p> <p><i>Revatio</i>, also a member of the same drug class (PDE5 inhibitors), is indicated for treating pulmonary arterial hypertension (PAH). PAH is a rare lung disorder in which the high blood pressure in the arteries leading to the lungs rises to an unusually high level. That condition can lead to heart failure.</p>	<p>The product labeling for all four products has been updated to display more prominently the potential risk of sudden hearing loss, and to guide consumers on what to do if they experience sudden hearing problems.</p> <p>Patients taking <i>Cialis</i>, <i>Levitra</i> or <i>Viagra</i> who experience sudden hearing loss should immediately stop taking the drug and contact their physician.</p> <p>Patients taking <i>Revatio</i> should continue taking their medication, but should contact their physician for further evaluation.</p> <p>For more information, refer to http://www.fda.gov/cder/drug/infopage/ed_drugs/QA.htm.</p>

New generic

Generic drug name strength/dosage form, reference brand and manufacturer	Approval and launch dates	Indication	Comments
<p>risedronate^{20,21}</p> <p>5 mg, 30 mg, 35 mg tablets</p> <p>Teva</p> <p><i>Actonel</i>®</p> <p>Proctor and Gamble</p>	<p>Generic approved on October 8. Launch is pending patent litigation.</p>	<p><i>Actonel</i> is indicated for treating and preventing postmenopausal and glucocorticoid-induced osteoporosis. It is also indicated for treating Paget's disease (a bone disorder).</p>	<ul style="list-style-type: none"> • Teva is currently in patent litigation over this product. A trial was held in November 2006 but a decision has not been reached. Teva agreed to provide 30 days advance notice to Proctor and Gamble of any launch activities and has not yet provided such notice. • Teva has been awarded 180 days of marketing exclusivity, which will begin the first date of commercial marketing. • <i>Actonel</i> had annual sales of \$1 billion in the U.S. for the 12 months ending June 30, 2007, based on IMS sales data.

New Generic

Generic drug name strength/dosage form, reference brand and manufacturer	Approval and launch dates	Indication
<p>oxcarbazepine²²</p> <p>150 mg, 300 mg and 600 mg tablet</p> <p>Three generic manufacturers (Sun Pharmaceutical Industries, Ltd, Roxane Laboratories Inc., Glenmark Pharmaceuticals Ltd.)</p> <p><i>Trileptal</i>[®]</p>	<p>Generic approved October 9. On October 17, Caraco Pharmaceutical Laboratories, Ltd., on behalf of Sun Pharma, announced their generic launch, although it is expected to be in low supply for two to three weeks.</p>	<p><i>Trileptal</i> is indicated for use alone or in combination with other medications in the treatment of partial seizures in adults and children aged four years and above with epilepsy, and as combination therapy in children aged four years and above with epilepsy.</p>

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