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New Drug Approvals

FDA Grants Official Approval For Synthroid Tablets

On July 24, the U.S. Food and Drug Administration (FDA) approved Abbott

Laboratories' Synthroid (levothyroxine sodium) tablets for thyroid disease management. Synthroid is prescribed as replacement or supplemental therapy for hypothyroidism and pituitary thyroid-stimulating hormone suppression.

Comments: Although never formally approved by the FDA, Synthroid has been marketed and treated as an established medical product for 40 years. The recent formal approval removes the possibility that Abbott would have to pull the product, a threat that surfaced five years ago when the FDA noted potency problems with oral levothyroxine products and decided that all manufacturers needed to submit new drug applications (NDAs) to demonstrate their safety and effectiveness. An approved NDA on file with the FDA also paves the way for generic competition to Synthroid, which Abbott expects in 12-18 months.

Zelnorm Approved For IBS Treatment

On July 24, the FDA approved Novartis' Zelnorm (tegaserod maleate) tablets for short-term treatment of women with irritable bowel syndrome (IBS) whose primary symptom is constipation. Zelnorm is the first drug approved for this indication.

Comments: Zelnorm is likely to impact the outpatient pharmacy benefit because it is approved without restrictions for short-term treatment of women with IBS. The drug is available in mid-August. Another recently approved IBS drug, Lotronex™, will be re-introduced to the U.S. market later this year.

Clarinex Reditabs Approved

On June 28, the FDA approved Schering-Plough's Clarinex Reditabs, a rapidly disintegrating tablet formulation of desloratadine, for the treatment of seasonal and year-round allergies. Clarinex Reditabs also are approved for treating hives (chronic idiopathic urticaria) in adults and children aged 12 and older. These indications mirror those for regular Clarinex (desloratadine) tablets, and like Clarinex tablets, Clarinex Reditabs will be available in a 5mg dosage strength.

Comments: Clarinex was originally approved in December 2001 for the treatment of seasonal allergic rhinitis. The introduction of Clarinex Reditabs will have minimal impact on plan sponsors because most of its use is expected to come from an existing product, such as Clarinex or Claritin. If, as expected, Claritin products are approved for OTC use, Clarinex Reditabs may have a slightly higher impact on the prescription benefit. Pricing information on Clarinex Reditabs is not yet available.

New Indications

FDA Approves Aranesp For Cancer Anemia

On July 22, the FDA approved Amgen's biological drug Aranesp (darbepoetin alfa) for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies. Aranesp is a long-acting version of epoetin alfa, which is marketed by Amgen as Epogen® and Ortho Biotech as Procrit®. It is administered once weekly, rather than up to three times weekly for Epogen and Procrit.



Comments: Aranesp was originally approved in September 2001 for the treatment of anemia associated with chronic renal failure, and Epogen was its major competitor in the marketplace. Now that it has received the chemotherapy-induced anemia indication, Aranesp will compete with Procrit as well. In 2001, combined sales of Epogen, Procrit and Aranesp totaled \$4.5 billion. The addition of Aranesp to the marketplace may not significantly increase the overall market for anemia therapy but will likely result in some utilization shifts among products.

Remicade Approved For Crohn's Maintenance

The FDA recently approved Centocor's Remicade (infliximab) for maintaining remission of Crohn's disease in patients with moderately to severely active disease. Previously, the drug was indicated for reducing symptoms in patients with an inadequate response to conventional therapy.

Comments: Remicade, a tumor necrosis factor alpha blocker, is also indicated in combination with methotrexate for the treatment of rheumatoid arthritis. Remicade is also being studied for other conditions, including ulcerative colitis, psoriasis, ankylosing spondylitis and psoriatic arthritis. Remicade is administered intravenously in a doctor's office. This new indication for long-term use may result in increased overall utilization for Remicade; however, it is possible that some physicians were already using it for some Crohn's disease patients.

Updates on New Generic Products

The FDA Has Recently Approved Generic Versions of:

Axid® (nizatidine - Lilly): Several manufacturers have received approval for

generic Axid 150mg and 300mg tablets. Generic versions of Axid are available in the market.

Comments: Axid, an H2 blocker, was originally approved in 1986 for the treatment of peptic ulcer disease and acid reflux. In 2001, annual sales for Axid reached \$180 million. Other H2 blockers available as generics include cimetidine, famotidine and ranitidine.

Cytotec® (misoprostol - Pharmacia): Currently, only IVAX has announced approval for generic Cytotec 100mcg and 200mcg tablets. The generic version of Cytotec is available in pharmacies.

Comments: Cytotec was approved in 1988 to prevent stomach ulcers caused by aspirin, ibuprofen and other nonsteroidal anti-inflammatory drugs. In 2001, annual sales for Cytotec reached approximately \$95 million. Annual sales for this product have been declining in recent years, which may be partially due to the use of COX-2 inhibitors.

Prinivil® and Zestril®: On July 1, the FDA began approving generic versions of Prinivil (Merck) and Zestril (AstraZeneca), which both contain the blood pressure medication lisinopril, an angiotensin converting enzyme (ACE) inhibitor. In addition, approval was granted to combination products containing lisinopril and the diuretic hydrochlorothiazide, generic equivalents to Prinizide® and Zestoretic®. These generics are available in the market from multiple manufacturers.

Comments: The FDA rates Prinivil and Zestril as equivalent products, as are Prinizide and Zestoretic. In 2001, Prinivil and Zestril combined sales reached \$1.8 billion. There is not a single company that will have

six months' exclusivity for the lisinopril products. Immediate generic competition will have a significant positive impact on plan-sponsor costs for the ACE inhibitor category.

Drug Safety Issues

Zonegran Gets Warning Label

On July 15, Elan Pharmaceuticals and the FDA announced a new bolded WARNING to prescribing information for Zonegran (zonisamide). The warning was added to reflect reports of oligohidrosis (reduced sweating) and hyperthermia (increased body temperature) in pediatric patients who received zonisamide therapy. In many of the cases, the patients were also exposed to higher environmental temperatures. Pediatric patients appear to be at increased risk. The new labeling recommends that patients, especially children, who are treated with zonisamide receive close monitoring for evidence of decreased sweating and increased body temperature, especially in warm or hot weather.

Comments: Zonegran was approved in the United States on March 31, 2000. The safety and effectiveness of zonisamide in pediatric patients have not been established, and the drug is not approved for pediatric use. Express Scripts communicated the Zonegran labeling changes to physicians on behalf of clients enrolled in the Emerging Therapeutic Issues program.

No Resumption of Norplant Kit Distribution

On July 26, Wyeth Pharmaceuticals announced that it does not plan to resume distribution or marketing of the six-capsule Norplant System (levonorgestrel implants), which provides contraception for five years.



Norplant distribution was halted in September 2000 due to concerns about lower-than-expected release of the hormone levonorgestrel from the implants. Recent studies have proven contraceptive efficacy of the product; however, those who wish to continue using contraceptives after their Norplant System expires will need to consider other contraceptive options. Wyeth is advising patients who want to have their Norplant capsules removed that the company will pay for removal until Dec. 31.

Literature Updates

[AHA Announces New Prevention Guidelines](#)

The American Heart Association (AHA) recently published updates to its 1997 Guidelines for Primary Prevention of Cardiovascular Disease and Stroke. According to the guidelines, risk-factor assessment should begin at age 20. Additional recommendations include control of blood pressure and blood lipid management; weight loss for those with a body mass index over 25, or a waist measurement over 40 inches for males and 35 inches for women; moderate-intensity physical exercise of 30 minutes per day; and low-dose aspirin for patients with a 10% risk of developing heart disease within 10 years. The update was published in the July 16 issue of *Circulation*: circ.ahajournals.org/cgi/content/full/106/3/388.

[Treatment for Adult HIV Infection Revised](#)

New guidelines indicate that symptom-free HIV patients can wait longer than previously recommended before taking drugs for AIDS treatment. For these patients, the panel recommends beginning drug treatment when CD4 white blood cells drop between 200 and

350 per cubic millimeter. The previous recommendations were to begin treatment when CD4 levels reached about 350. The new guidelines appear in the July 10 issue of the *Journal of the American Medical Association*: jama.ama-assn.org/issues/v288n2/toc.html.

[New Colorectal Cancer Screening Recommendations](#)

The United States Preventive Services Task Force recently released new guidelines for colorectal cancer screening. According to the guidelines, men and women at average risk for colorectal cancer should begin screening at the age of 50. In persons at a higher risk (for example, those with a first-degree relative diagnosed with colorectal cancer before the age of 60), the guidelines indicate that initial screening at an earlier age is reasonable. The new guidelines appear in the July 16 issue of the *Annals of Internal Medicine*: www.annals.org.

[JAMA Reports on HRT and Ovarian Cancer Risks](#)

A recent article published in the July 17 *Journal of the American Medical Association (JAMA)* reports that women who receive long-term estrogen-only replacement therapy for treatment for the symptoms of menopause may be at increased risk for ovarian cancer. Short-term estrogen/progestin hormone replacement therapy was not shown to increase risk but may warrant further investigation. In this retrospective study, more than 44,241 postmenopausal women were followed for about 20 years. Women who used estrogen-only replacement therapy for 10 or more years were at a significantly greater risk of developing ovarian cancer than those who never used hormone replacement therapy. This risk also increased with the length of estrogen use. However,

researchers noted that although increased risk was identified, the development of ovarian cancer was rare, occurring in 329 women during the 20-year study. View the article at jama.ama-assn.org/issues/v288n3/toc/html.

[NIH Drops HRT Portion Of Women's Study](#)

The National Institutes of Health (NIH) announced its discontinuation of the combination hormone replacement therapy (HRT) arm of the Women's Health Initiative Study. The HRT portion of the study will be stopped due to the increased risk of breast cancer and the NIH's determination of an overall lack of evidence for long-term benefits. The study was set up to provide more information about risks and benefits associated with the long-term use of estrogen-plus-progestin therapy. It was not set up to evaluate the use of combination HRT for the treatment of menopausal symptoms. The combination of HRT increased the risk of cardiovascular disease and, over time, increased the risk of breast cancer. Combination HRT reduced the risk of hip and other fractures, and reduced the risk of colon cancer.

The article, "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women," is available on the *Journal of American Medical Association's* Web site, jama.ama-assn.org/issues/v288n3/ffull/joc21036.html.

There was no evidence of increased risk of breast cancer in women taking estrogen alone in this trial. Therefore, the NIH is recommending that women in the estrogen-only arm of the study continue taking estrogen and continue participating in the study.

Clinical News and Notes

Clinical Advisory On Statin Safety

The American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute recently released a clinical advisory on the use and safety of the cholesterol-lowering class of drugs called HMG CoA reductase inhibitors, more commonly known as "statins." The voluntary withdrawal of cerivastatin (Baycol®) from the U.S. market on Aug. 8, 2001, prompted concern from physicians and patients regarding the safety of statins. This advisory is intended to summarize for professionals the current understanding of statin use and to provide updated recommendations for their appropriate use, including cautions, contraindications and safety monitoring for statin therapy. The advisory's purpose is not to discourage the appropriate use of statins, which have life-saving potential in properly selected patients, particularly those with established coronary heart disease (CHD) and others at high risk for developing CHD. The advisory is available online at www.americanheart.org/downloadable/heart/1027113715726statins_july02.pdf.

Two Childhood Vaccine Shortages End

On July 12, the Centers for Disease Control (CDC) announced the end of a two-year shortage of two commonly used childhood

vaccines – Measles, Mumps and Rubella (MMR) and Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP). Current supplies are now adequate for the resumption of routine vaccinations, as recommended by the Advisory Committee on Immunization Practices. However, the CDC is advising physicians not to schedule children for missed vaccinations for at least the next two months to allow inventories to return to normal.

Vaccination guidelines, published in the July 12 issue of *MMWR*, are available online at www.cdc.gov/mmwr/preview/mmwrhtml/mm5127a5.htm.

Comments: There were multiple reasons for the vaccine shortage, including manufacturing problems, temporary suspension of production of some vaccines due to facility upgrades, and a recommendation by the CDC and the American Academy of Pediatrics to remove mercury-based preservatives from all vaccines.

NuvaRing Now Available

On July 16, Organon announced that NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) is now available in pharmacies. NuvaRing was approved in October 2001 and is the first monthly vaginal ring for contraception. It releases estrogen and progestin in amounts similar to those found in oral contraceptive pills.

Committee Recommends Pravachol/Aspirin Combination

On July 18, an FDA advisory committee recommended the approval of a combination package of Bristol-Myers Squibb's Pravachol (pravastatin 20mg, 40mg and 80mg) and aspirin 81mg and 325mg (ASA). Bristol-Myers Squibb initially plans to sell the two in a combination package but later would like to combine the two drugs into one tablet. The combination is intended to help some patients improve compliance, especially when they're required to take multiple medications each day. The FDA usually follows committee recommendations.

Comments: This is the second time Bristol-Myers Squibb's Pravachol/ASA combination package has been reviewed by the FDA advisory committee. In January, the committee voted against approval of a single-pill formulation (Pravachol 40mg and ASA 81mg or 325mg) because of the limited dosage forms and the potential for excessive bleeding if the product was not discontinued prior to a surgical procedure.

Clinical News

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