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IN THIS ISSUE

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Drug-induced diseases have become an increasing problem

Pharmacists create a resource, suggest process for determining AEs

Much has been written about drugs and their adverse effects (AEs). But two pharmacists saw the need for a central source of information for an important subset of adverse effects: drug-induced diseases.

The resulting reference book, *Drug-Induced Diseases: Prevention, Detection, and Management*, was published this summer by the American Society of Health-System Pharmacists (ASHP). "The impetus for this book was an increasing awareness of drug-induced diseases as a significant cause of morbidity and mortality. Drug-induced diseases are associated with significant human costs and have a substantial financial impact on the health care system," says **James E. Tisdale**, PharmD, BCPS, FCCP, professor of pharmacy practice at Purdue University in West Lafayette, IN. Tisdale co-edited the book with Douglas A. Miller, PharmD, a professor in the department of pharmacy practice at Wayne State University in Detroit.

Tisdale and Miller define a drug-induced disease as an adverse drug reaction that may cause death, require hospitalization, or result in symptoms severe enough to prompt a patient to seek medical attention. "We wanted to create a comprehensive source that clinicians — pharmacists, physicians, nurses, and others — could use to review information regarding drug-induced diseases," Tisdale says. "The overall objective was to make it easier for practitioners to determine whether a patient's symptoms are being caused by a drug that the patient is taking."

The book includes more than 50 chapters that cover a plethora of drug-induced diseases. "Drugs can cause diseases in just about every system in the body," Tisdale says. "[For example], drugs can cause a number of dermatologic conditions that are serious enough to require patients to seek medical attention. Some may even require hospitalization or result in death. [In addition], almost any cardiac arrhythmia can be caused by drugs, and drug-induced diseases can resemble many neurologic and psychiatric disorders. The list just goes on and on.

"Some drugs [induce diseases] at higher-than-recommended doses,

while others can cause problems even at their usual and customary doses," he continues. Drug-induced diseases are becoming more prevalent, most likely because a greater number of drug products are available and more drugs are prescribed today than ever before. And, drug use is expected to continue to increase in the future as the population ages.

Determining drug-induced diseases

Many health professionals, including pharmacists, could be better informed about drug-induced diseases, Tisdale says. "In the past, many pharmacy schools had stand-alone courses in drug-induced diseases. Today, much of the information regarding drug-induced diseases is interspersed with other material concerning pharmacology and therapeutics. This can make it more challenging for those who have to learn how to differentiate a drug-induced disease from diseases that are normally occurring."

For this reason, the book has been designed to try to make it easier for clinicians to apply a logical thought process in their efforts to determine whether a drug is the likely cause of a given symptom and how to treat those drug-induced diseases that do occur. The book has been organized around the approach Tisdale teaches his students to use in evaluating their patients.

"I teach my students that any time a patient develops new symptoms or experiences an exacerbation of an existing disease, drugs must be ruled out as a potential cause or contributor," he says. To help, Tisdale and Miller have included in the book tables of drugs known to cause specific diseases.

Tisdale teaches his students to use a systematic approach in making a determination as to whether a suspect drug is the likely actual cause of a patient's disease. The system involves answering questions that include, "What is the likelihood that the disease could be caused by a drug to which this patient has been exposed? Is this drug-induced disease relatively common or is it rarely reported? Is there a temporal relationship between the exposure to the drug and the onset of symptoms? Is that relationship consistent with a drug-induced disease in this patient?"

"The symptoms the patient experiences with a drug-induced disease are not always the same as those experienced by patients who have the naturally occurring disease," Tisdale says. "I teach students to sort through patients' signs and symptoms, to determine whether the clinical presentation is consistent with drug-induced disease."

An offending drug often needs to be discontinued in patients who experience a drug-induced disease. In some situations, however, other treatments can be employed to help alleviate symptoms.

"There is a risk/benefit equation to consider," Tisdale says, "It's not always possible to discontinue drug therapy and sometimes you have to look for other ways to manage a patient's drug-induced disease." When applicable, authors have discussed those management approaches in the book.

Tisdale will discuss drug-induced diseases further at ASHP's Midyear Clinical Meeting and Exhibition in Las Vegas this month. "I want to give people an overall perspective of drug-induced diseases — how prevalent might they be, and at what

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cost to health care and society," he says. The session at the meeting will focus on two specific drug-induced diseases. One session discusses drug-induced dermatologic conditions. The other addresses drug-induced liver disease. For more information about the program or the book, see www.ashp.org. ■

Enrollment begins for Medicare Part D

Seniors looking to physicians, pharmacists for info

Seniors finally had the opportunity to enroll in a Medicare Part D plan beginning Nov. 15. More than half of those eligible, however, still are confused about the government's new prescription drug plan benefit, according to a Kaiser Health Poll Report conducted in August.

Seniors must sign up for a Medicare Part D plan by May 15, 2006, to be eligible for coverage in 2006. Those signing up in 2005 would be covered under their plan beginning Jan. 1, 2006. After May, the next opportunity to enroll would be Nov. 15 to Dec. 31, 2006.

Plans have begun marketing to seniors, and Medicare is trying to set up a one-stop source of information about the prescription drug plan benefit and its participating plans on its web site, www.medicare.gov.

The survey from the Kaiser Family Foundation in Menlo Park, CA, shows mixed feelings about the benefit, which should pay half of a senior's drug costs, according to the Medicare web site. More than six in 10 (65%) of the seniors surveyed say it will be "somewhat" or "very" helpful for a typical person on Medicare, and even more think the benefit will be helpful for people on Medicare with very high prescription drug costs (75%) or no drug coverage (74%) and for low-income people (70%).

However, they are less sure the benefit will help them personally. Twenty-two percent say the benefit will be "very" helpful, while more than three in 10 (35%) say it will not be helpful at all to them personally.

The survey also found gaps in seniors' understanding of the benefit. Currently, about six in 10 seniors say they do not have a good understanding of the new benefit, and do not have enough information to understand how the new benefit will affect them personally (62%).

More than half (55%) of seniors seem to recognize that they need to sign up to receive the new Medicare prescription drug benefit. Just more than one in seven (15%) seniors believe that coverage will begin automatically, and about three in 10 (31%) don't know.

A lot of seniors had not made up their minds to enroll, according to the survey. More than two in 10 (22%) seniors say they plan to enroll for the new benefit, more than double the share that said the same in April 2005 (9%). However, four in 10 seniors have currently not decided whether to enroll in the new prescription drug benefit, and one-third (33%) say they will not enroll.

More than half of the 73% of seniors who say they will not enroll, or who haven't heard enough to decide whether to enroll in a Medicare prescription drug plan, say they already have help paying for prescription drugs from an insurance plan or program (55%). Other reasons include that they don't think a Medicare drug plan will save them money (42%) or they don't know enough about the new benefit (41%).

Of special note in the survey, nearly half of seniors (49%) said they would be "very" likely to turn to their doctor for information, and one-third said they would turn to their pharmacist (33%).

Helping patients navigate their choices

Pharmacists, however, can be confused about the benefit and its plans, too. That is why pharmacist organizations such as the American Pharmacists Association (APhA) in Washington, DC, have offered information resources on its web site (www.aphanet.org).

"With anything this big, both patients and health care providers will be faced with challenges," says **Kristina E. Lunner**, APhA's director of federal government affairs. Some of the confusion has been that the Medicare web site, with its Drug Plan Finder and Formulary Finder features, has not totally been updated with the detailed information about each participating plan.

"There is also a lot of confusion about whether seniors should sign up," Lunner says. "There is a lot of going on — that's the bottom line."

The prescription drug benefit is for outpatients. However, hospital pharmacists also need to have familiarity with local Medicare Part D plans.

"Physicians and pharmacists who are working with patients in the hospital will need to be cognizant of what medications the patients' Part D plan covers for them when they are released," explains

Susan K. Bishop, MA, APhA's associate director of regulatory affairs.

"Pharmacists in general won't have all the formularies memorized because there are so many Part D plans in each region," she continues. Pharmacists, health care providers, or even consumers should instead be able look up the individual plan on the Medicare web site and get the formulary information from the Formulary Finder feature.

The more familiar pharmacists become with the plans in their area, the better equipped they will be to answer questions from their patients, Lunner adds. She suggests that pharmacists use the Formulary Finder feature to identify the top 20 or so drugs they dispense to Medicare beneficiaries right now. "The results will give them a quick reference as to which plans cover which drug." ■

FDA predicts more vaccine production than last year

Shipments suspended after reports of hoarding

Don't expect a repeat of last year's shortage of influenza vaccine this winter. Do expect, however, to hear more about preparing for a possible avian flu pandemic.

The FDA announced in October that it expects "significantly" more flu vaccine to be produced for the 2005-2006 influenza than was available last year. Four manufacturers are distributing influenza vaccine this year: Sanofi Pasteur, MedImmune Vaccines, GlaxoSmithKline Biologicals, and Chiron Corp. The FDA says it does not know the exact number of doses that will be distributed because Chiron had lowered its projections.

Much of the attention, though, has already shifted to planning for a possible pandemic caused by the H5N1 avian influenza virus. Millions of wild birds and poultry have been culled or killed. The virus remains primarily an animal disease for now and most cases have been reported in Asia and Europe; however, H5N1 has infected 125 people and killed 64, according to statistics published Nov. 9 by the World Health Organization (WHO). The cases of bird flu infection in humans have primarily been attributed to contact with infected poultry or contaminated surfaces. Health officials, however, are concerned that virus strains could mutate to become transmissible between humans.

At a November meeting in Geneva, the WHO said the world is taking the threat of an influenza pandemic seriously. The goal of the meeting was to work toward a global consensus for controlling the disease in animals while simultaneously preparing for a potential human pandemic, the organization says.

Because such a human-transmissible virus strain would be new, it may be resistant to existing antiviral medications. Four different influenza antiviral medications (amantadine, rimantadine, oseltamivir phosphate, and zanamivir) are currently approved by the FDA for the treatment and/or prevention of influenza, according to the Centers for Disease Control and Prevention (CDC) in Atlanta. The four usually work against influenza A viruses. However, H5N1 viruses identified in humans in Asia in 2004 and 2005 have been resistant to amantadine and rimantadine, the CDC says.

Media coverage of the bird flu has prompted concern about H5N1 among the public. News agencies are reporting that demand for zanamivir (Relenza) and particularly oseltamivir phosphate (Tamiflu) has risen, fueling fears that some patients, and even health officials and organizations, are trying to stockpile the drugs. In response, oseltamivir manufacturer Roche Holding AG announced in October that it had temporarily suspended shipments of oseltamivir to private buyers in the United States and Canada to ensure that enough of the antiviral drug would be available for patients with seasonal influenza. Roche also stopped supplying oseltamivir to private doctors and pharmacies in Hong Kong, saying it would only fill orders for government stockpiles, according to *Reuters*.

Infectious disease societies in the United States are urging the public not to panic, while also asking that federal policy-makers and local health care institutions have sufficient stockpiles to treat sick people and maintain the health care system in the event of a pandemic. On that end, the Senate approved nearly $8 billion in late October to stockpile vaccines and other drugs.

The Department of Health and Human Services (HHS) has announced plans to buy enough H5N1 influenza vaccine for 20 million people and enough influenza antivirals for another 20 million people. These supplies will be placed in the nation's Strategic National Stockpile where they will be available for use in the event of an influenza pandemic. At time of publication, HHS had awarded a $100 million contract to Sanofi Pasteur and a $62.5 million contract to Chiron to manufacture an avian influenza vaccine. In addition, the FDA announced

in October that it had formed a Rapid Response Team to work in partnership with HHS, the CDC, the National Institutes of Health, and industry, to "ensure every necessary measure is taken to provide an adequate and timely supply" of antiviral drugs to treat avian flu, should it emerge in the United States.

The agency anticipates that oseltamivir production can be in full gear within 12 months.

Roche also announced in early November that it will increase its own production capacity by the end of 2006 so that it can produce 300 million treatments of oseltamivir annually. This is a 10-fold increase over the capacity in 2004.

Bush plan will cost billions

Also in November, President Bush announced a $7.1 billion plan to guard against pandemic influenza. The request includes $6.7 billion in additional 2006 appropriations for HHS.

Approximately $4.7 billion would go toward investments in creating vaccine production capacity and stockpiles, $1.4 billion to stockpile antiviral drugs, and $555 for surveillance, public health infrastructure, and communications, including $100 million for state and local preparedness.

Some groups criticized Bush's plan, saying that preparedness for a pandemic would take too long. The plan also largely bypasses international institutions, including the World Health Organization and the Global Fund to Fight AIDS, Tuberculosis and Malaria, which have expertise in supporting the development of health systems, says the Global AIDS Alliance in Washington, DC.

The Infectious Diseases Society of America in Alexandria, VA, however, applauds the president for giving the issue the attention it warrants. "The president's strategy provides an initial framework with strong potential. Success will require a long-term commitment and coordinated effort from the state and local government, the medical profession, business, and the American people." ■

■ Research News ■

Trastuzumab trial results 'stunning' in early-stage HER2-positive breast cancer

Results from recent published trials have shown much promise in the use of trastuzumab (Herceptin) plus adjuvant chemotherapy in patients with HER2-positive early-stage breast cancer.

Patients are considered HER2-positive if they have overexpression of the HER2 protein, amplification of the *HER2* gene, or both, researchers say. This occurs in about 15-25% of breast cancers, and is an aggressive form of the disease.

The results of these trials were published in the Oct. 20 issue of the *New England Journal of Medicine*. The first Phase III trial, HERA, involved women with HER2-positive early-stage invasive breast cancer who completed therapy (surgery with or without radiotherapy) and a minimum of four courses of chemotherapy. Endocrine therapy, primarily tamoxifen, was given after chemotherapy to women with hormone receptor-positive disease unless contraindicated.

Researchers randomly assigned 1,694 women to two years of treatment with trastuzumab, 1,694 women to one year of trastuzumab, and 1,693 women to observation. The published findings, however, report only the results of treatment with trastuzumab for one year or observation.

As compared with observation after primary therapy, trastuzumab given after primary therapy reduced the rate of recurrence by approximately 50%. A total of 127 disease-free survival events were reported in the trastuzumab group and 220 in the observation group. The unadjusted hazard ratio for the risk of an event in the trastuzumab group, as compared with the observation group, corresponded to an absolute benefit in disease-free survival of 8.4 percentage points at two years. Overall survival in the two groups was not significantly different (29 deaths with trastuzumab vs. 37 with observation). Severe cardiotoxicity, a possible side effect of the drug, developed in 0.5% of the women who were treated with trastuzumab.

The second article presents the combined results of two trials that compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER2-positive breast cancer.

The National Surgical Adjuvant Breast and Bowel Project trial B-31 compared doxorubicin and cyclophosphamide followed by paclitaxel every three weeks (Group 1) with the same regimen plus 52 weeks of trastuzumab beginning with the first dose of paclitaxel (Group 2). The North Central Cancer Treatment Group trial N9831 compared three regimens: doxorubicin and cyclophosphamide followed by weekly

paclitaxel (Group A), the same regimen followed by 52 weeks of trastuzumab after paclitaxel (Group B), and the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (Group C). The studies were amended to include a joint analysis comparing Groups 1 and A (the control group) with Groups 2 and C (the trastuzumab group). Group B was excluded because trastuzumab was not given concurrently with paclitaxel, the researchers say.

The results included 2,043 patients enrolled in trial B-31, 1,736 of whom with at least one follow-up evaluation. In trial N9831, 1,633 patients had been enrolled in Groups A and C; 1,615 of these patients had follow-up data submitted.

The median follow-up was 2 years (2.4 years in trial B-31 and 1.5 years in trial N9831). There were 261 events in the control group and 133 events in the trastuzumab group. The absolute difference in disease-free survival between the trastuzumab group and the control group was 12% at three years. Trastuzumab therapy was associated with a 33% reduction in the risk of death. (There were 62 deaths in the trastuzumab group, as compared with 92 deaths in the control group.) The three-year cumulative incidence of Class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1% in trial B-31 and 2.9% in trial N9831.

Results might change treatment plans

The results of the studies are stunning, says **Gabriel N. Hortobagyi**, MD, professor of medicine and chairman of the department of breast medical oncology at the University of Texas M.D. Anderson Cancer Center in Houston. His comments appeared in an editorial accompanying the trial results.

"On the basis of these results, our care of patients with HER2-positive breast cancer must change today," he writes. "Certainly, patients with lymph node-positive, HER2-positive breast cancer should receive trastuzumab as part of optimal adjuvant systemic therapy, unless the antibody is clearly contraindicated. Patients with negative lymph nodes, whose estimated risk of recurrence after optimal chemotherapy and endocrine therapy comfortably exceeds the risk of the cardiac toxic effects of trastuzumab, should also be offered the antibody. Since most HER2-positive tumors have other adverse prognostic factors, this risk-benefit scenario is likely to apply to many patients with node-negative breast cancer."

The results do raise some questions, Hortobagyi says. What is the optimal schedule for therapy with trastuzumab: Should it be given with or after chemotherapy? More research should also determine how to deal with the trastuzumab-induced heart problems that trastuzumab can cause, he adds.

The results of these studies are not "evolutionary but revolutionary," concludes Hortobagyi. "The rational development of molecularly targeted therapies points the direction toward continued improvement in breast cancer therapy. Other targets and other agents will follow. However, trastuzumab and the two reports in this issue will completely alter our approach to the treatment of breast cancer." ■

NEWS BRIEFS

FDA: Manufacturers must use electronic drug labels

The FDA has begun requiring drug manufacturers to submit prescription drug label information to the agency in a new electronic format. This electronic format will allow health care providers and the general public to more easily access the product information found in the FDA-approved package inserts for all approved medicines in the United States, the FDA says.

Under the new regulations, drug manufacturers are now required to submit to FDA prescribing and product information in a structured product labeling (SPL) format that uses standardized

COMING IN FUTURE MONTHS

- How pharmacists contaminated the drug supply
- Heart failure patients may benefit from beta-blocker first
- Ramelteon (Rozerem) drug evaluation
- Cost of new injectable drugs

medical terminology. Using embedded computer tags, the prescribing and product information in the SPL format can be electronically managed, allowing a user to search for specific information. These tags can instruct computers to read specific sections of a drug label including product names, indications, dosage and administration, warnings, description of drug product, active and inactive ingredients, and how the drug is supplied.

The new electronic product labels will be the key element and primary source of medication information for "DailyMed" — a new interagency on-line health information clearinghouse that will provide up-to-date medication information free to consumers, health care providers, and health care information providers. This information can be accessed through the National Library of Medicine at http://dailymed.nlm.nih.gov.

Updated product labels will be posted on the site within one business day of an approval action by FDA or submission to FDA of a product label change that does not require prior approval. Within one year, product labels for most approved prescription medications will be posted on DailyMed.

In the future, this new product information will also be provided through facts@fda.gov, an Internet resource designed to give one-stop access for information about all FDA-regulated products. ▼

Sales, marketing stopped for pemoline products

The FDA has concluded that the overall risk of liver toxicity from pemoline (Cylert) and generic pemoline products outweighs the benefits of this drug. In May 2005, Abbott chose to stop sales and marketing of Cylert in the United States. All generic companies have also agreed to stop sales and marketing of this product.

Pemoline, a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), is considered second-line therapy for ADHD because of its association with life-threatening hepatic failure. Health care professionals who prescribe Cylert, or any of its generics, should transition their patients to an alternative therapy.

Cylert will remain available through pharmacies and wholesalers until supplies are exhausted. No additional product will be available.

For more information, see www.fda.gov/medwatch/safety/2005/safety05.htm#Cylert. ▼

Hepatic injury linked to duloxetine hydrochloride

Eli Lilly and the FDA have notified health care professionals of revisions to the Precautions/Hepatotoxicity section of the prescribing information for duloxetine hydrochloride (Cymbalta), indicated for treatment of major depressive disorder and diabetic peripheral neuropathic pain.

Postmarketing reports of hepatic injury (including hepatitis and cholestatic jaundice) suggest that patients with pre-existing liver disease who take duloxetine may have an increased risk for further liver damage. The new labeling extends the precaution against using duloxetine in patients with substantial alcohol use to include those patients with chronic liver disease. It is recommended that duloxetine not be administered to patients with any hepatic insufficiency.

For more information, see www.fda.gov/medwatch/safety/2005/safety05.htm#Cymbalta. ▼

Warning added to ibritumomab tiuxetan label

Biogen Idec and the FDA have notified health care professionals of revisions to the Boxed Warnings, Warnings, and Adverse Reactions sections of the Prescribing Information to describe severe cutaneous or mucocutaneous reactions, some with fatal outcome, that have been reported in association with the ibritumomab tiuxetan (Zevalin) therapeutic regimen in the post-marketing experience.

Patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further components of the ibritumomab tiuxetan therapeutic regimen and should seek prompt medical evaluation.

For more information, see www.fda.gov/medwatch/safety/2005/safety05.htm#Zevalin. ■

IN THE PIPELINE

• AEterna Zentaris has initiated a European multicenter Phase II trial of perifosine, a novel, first-in-class, oral signal transduction inhibitor, in combination with radiotherapy, in **non-small cell lung cancer**.

• CytRx Corp. has announced that the FDA has granted "fast-track" designation for the company's leading drug candidate arimoclomol for the treatment of **amyotrophic lateral sclerosis**.

• CuraGen Corp. and TopoTarget A/S have announced the initiation of patient dosing in a Phase Ib open-label, multicenter, proof-of-concept clinical trial evaluating PXD101, a small molecule histone deacetylase inhibitor, for the treatment of **advanced solid tumors**, including colorectal cancer.

• CuraGen Corp. expects to complete the enrollment of patients in its Phase II randomized, double-blind, placebo-controlled clinical trial evaluating a single dose of velafermin (CG53135) for the prevention of oral mucositis in cancer patients undergoing **bone marrow transplantation**.

• ChemGenex Pharmaceuticals Limited has launched a new Phase II study evaluating the use of sHHT (Ceflatonin) in patients with **accelerated-phase chronic myeloid leukemia** who are resistant to the first-line therapy imatinib mesylate (Gleevec).

• Coley Pharmaceutical Group has initiated a five-arm Phase Ib clinical study of CPG 10101 (Actilon) alone and in combination with the current standard of care for the treatment of **chronic hepatitis C virus**.

• XTL Biopharmaceuticals Ltd. has initiated the Phase 1a clinical trial of XTL-6865 for the treatment of **hepatitis C virus**.

• ActivBiotics has announced plans to pursue a Phase II trial of its lead product, rifalazil, as a novel medical treatment for **peripheral arterial disease**.

• Koronis Pharmaceuticals has initiated a Phase 1b clinical trial of KP-1461, its novel antiviral therapeutic, in **HIV-positive** patients.

• Alpharma has received clearance from the FDA to advance into a Phase II multidose clinical efficacy trial for an abuse-resistant, extended-release opioid. This product is being developed by the company for the treatment of **chronic moderate-to-severe malignant (cancer-related) and non-malignant pain**.

• Vion Pharmaceuticals has received fast track designation from the FDA for its anticancer agent VNP40101M (cloretazine) for induction treatment of patients older than 60 years of age with **poor-risk acute myelogenous leukemia**.

• Millennium Pharmaceuticals has initiated a Phase I/II, open-label, multicenter study of MLN518 in combination with standard induction chemotherapy in patients with newly diagnosed **acute myelogenous leukemia**.

• Schering-Plough Corp. has discontinued a Phase II study with its investigational CCR5 receptor antagonist, vicriviroc, used in combination with lamivudine/zidovudine (Combivir) in **treatment-naive HIV** patients. This decision was due to a return of detectable virus in some patients late in therapy compared to the control regimen of lamivudine/zidovudine and efavirenz (Sustiva), a current standard of care for treatment-naive patients living with HIV.

• Centocor and Eli Lilly & Co. have announced that patient enrollment in the Phase III trial of abciximab (Reopro) for the treatment of **acute ischemic stroke** has been permanently discontinued. ■

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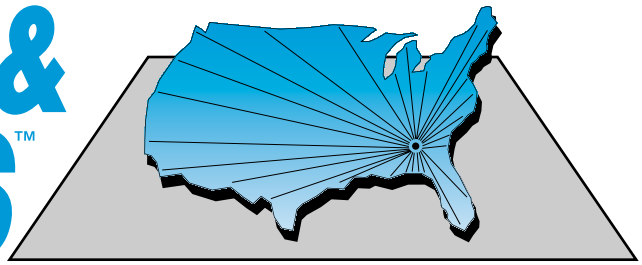

Entecavir (Baraclude) Formulary Evaluation

Mechanism of action, Pharmacokinetics, Dosage, Clinical studies, Strengths, Weaknesses, Drug interactions, Adverse reactions, Warnings/precautions, Monitoring, Cost comparison, Summary and recommendations

By **Summer Johnson Beard**, PharmD Candidate
McWhorter School of Pharmacy
Samford University
Birmingham, AL

Entecavir (Baraclude) is a guanosine nucleoside analog.

Mechanism of action

Entecavir inhibits all three activities of hepatitis B virus (HBV) polymerase:

- Base priming.
- Reverse transcription of the negative strand from the pre-genomic mRNA.
- Synthesis of the positive strand of HBV DNA.

Pharmacokinetics

Absorption: Absorption occurs rapidly after oral administration with a bioavailability of 100%.

Distribution: The volume of distribution is greater than total body water. Entecavir has a low percentage of protein binding.

Metabolism: Metabolism occurs via CYP450, although it is not a substrate, inducer, or inhibitor. Small amounts of sulfate and glucuronide metabolites have been observed. Accumulation half-life is approximately 24 hours, allowing once-daily dosing.

Elimination: Entecavir is primarily eliminated unchanged in the urine. Renal clearance occurs via filtration and net tubular secretion.

Indications: Entecavir is indicated for the treatment of chronic HBV infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Dosage

Oral

- If the patient is HBeAg-positive and nucleoside-naïve, starting dose is recommended at 0.5 mg once daily.
- If the patient is lamivudine refractory, the recommended dose is 1 mg once daily.
- Entecavir should be administered at least two hours after a meal or two hours before the next meal.

Clinical studies

Lai CL, Rosmawati M, Lao J, et al. **Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection.** *Gastroenterology* 2002;123:1,831-1,838.

Purpose: To evaluate the safety and antiviral activity of entecavir as compared to lamivudine in the treatment of adults with chronic hepatitis B infection.

Study design: Twenty-four-week, Phase II, randomized, double-blind, dose-ranging multicenter trial.

Methods: Amplicor PCR Assay and Quantiplex Assay were used to determine viral load and to monitor reductions that occurred over the course of therapy. Cochran-Mantel-Haenszel statistical test and a t-test also were used by the investigators.

Results

Virologic response

• 169 patients.

• Entecavir at doses of 0.1 mg daily and 0.5 mg daily were found to be superior to lamivudine at a dose of 100 mg daily in viral load reduction.

Serologic response: No significant differences were found between comparison groups. Some patients did achieve loss of HBeAg and seroconversion.

Biochemical response

• A trend was found among the two higher doses of entecavir to normalize ALT levels when compared to lamivudine.

• Due to the low population size, this comparison did not relate a significant conclusion.

• Post-treatment follow-up found an increased incidence of elevated ALT in patients discontinuing entecavir when compared to the patients discontinuing lamivudine.

Histologic response: Only a small population size (15%) was able to be evaluated using the Knodell system.

Adverse events: Most common events were headache, abdominal pain, rhinitis, fatigue, fever, diarrhea, nausea, dizziness, cough, and myalgia. These adverse events were mild to moderate in severity and comparative among study groups. The incidence of these adverse events did not reveal a significant drug or dose relationship.

Conclusion: The authors concluded that entecavir is a potent antiviral agent that is effective as monotherapy for the treatment of chronic HBV. The 0.5 mg and 0.1 mg dose of entecavir were found to be superior to lamivudine 100 mg in reducing serum HBV-DNA levels.

Strengths

• Trial included a power analysis of >85%.

• Statistical tests.

• Randomized, double-blind study.

• An extremely small number of participants (four) had to drop out due to adverse events, and only one participant was lost due to noncompliance.

Weaknesses

• The trial was funded by Bristol-Myers Squibb so bias must be considered.

• Length of the clinical trial was too short.

• Confidence intervals were not included.

Drug interaction

Since entecavir is eliminated by the kidneys, coadministration of this drug with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. Coadministration of entecavir with lamivudine, adefovir dipivoxil, or tenofovir disoproxil fumarate did not result in significant drug interactions.

Adverse reactions

The most common adverse events were headache, fatigue, dizziness, and nausea. Other reported side effects included diarrhea, dyspepsia, vomiting, somnolence, and insomnia.

Warnings/precautions

Boxed warnings: Lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B have been reported in patients that have discontinued therapy.

Precautions: The safety and efficacy of entecavir in liver transplant recipients are unknown. Liver function must be closely monitored before and during therapy. Dosage reductions are necessary for patients whose creatinine clearance is less than 50 mL/min.

Pregnancy Category C

Monitoring

Regular monitoring of liver function is needed to make sure that further decompensation is not occurring. If entecavir is being coadministered with a drug that reduces kidney or liver function, the serum concentrations of both drugs should be monitored for toxicity.

Cost comparison

Entecavir costs $592.02 for a month's supply of 30 tablets of the 0.5 mg and the 0.1 mg dosage formulations.

Other agents used to treat HBV: Adefovir dipivoxil (Hepsera) costs $492.26 for a month supply of 30 tablets of the 10 mg dosage formulation.

Summary and recommendations

We recommend that entecavir become a nonformulary medication, and that a small quantity may be made available if absolutely necessary. This recommendation is based on the fact that more clinical experience is needed with this agent and its high cost. Entecavir has been studied and has shown to be effective in the treatment of chronic HBV infection; however, drug resistance already has been reported, and this agent has only been on the market since early 2005. ■

New FDA Approvals

These drugs were recently approved by the FDA:

• ***Nelarabine (Arranon) by GlaxoSmithKline.*** The FDA has approved nelarabine (Arranon) to treat adults and children with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), whose disease has not responded to or has relapsed following at least two chemotherapy regimens. Nelarabine, a cancer chemotherapy drug that kills cancer cells by blocking the cell's ability to reproduce, is the first drug to treat this limited population of patients.

Nelarabine was approved under the FDA's accelerated approval program. Evidence presented for the drug's approval consisted of complete disappearance of cancer cells in some patients, although in most cases the cancer later returned. In those patients who responded to nelarabine, the disappearance of cancer cells was sometimes accompanied by return of normal blood cell counts. The drug's sponsor will complete further studies to verify nelarabine's clinical benefit. Nelarabine had also received orphan drug designation.

The safety and efficacy of this product were demonstrated in two clinical studies, one conducted in children and the other in adults. Both studies enrolled patients with relapsed or refractory T-ALL/T-LBL. All patients received nelarabine. Among the 39 pediatric patients treated, 23% had a complete disappearance of their cancer. Complete disappearance lasted from 3.3 to 9.3 weeks. Of the 28 adult patients treated, the rate of complete disappearance was 21% and lasted from four to more than 195 weeks.

Common side effects reported with nelarabine treatment are fatigue, nausea, vomiting, and diarrhea.

• ***New indication for erlotinib (Tarceva) by OSI Pharmaceuticals and Genentech.*** The FDA has approved erlotinib (Tarceva) in combination with gemcitabine chemotherapy for the treatment of advanced pancreatic cancer in patients who have not received previous chemotherapy.

Erlotinib, which targets the EGFR/HER1 pathway, is the first drug in a Phase III trial to have shown a significant improvement in overall survival when added to gemcitabine chemotherapy as initial treatment for pancreatic cancer, the drug's sponsors say.

Erlotinib is a once-daily oral tablet already approved for use in patients with non-small cell lung cancer whose disease has progressed after one or more courses of chemotherapy. The FDA based its approval decision for erlotinib on results from a randomized double-blind, placebo-controlled Phase III clinical study of erlotinib, in combination with gemcitabine chemotherapy in patients with unresectable locally advanced or metastatic pancreatic cancer. The study met its primary endpoint of improving overall survival.

In the Phase III study in pancreatic cancer, the most common adverse events reported were fatigue, rash, nausea, anorexia, and diarrhea. In addition, severe and potential fatal adverse events included interstitial lung disease-like complications, myocardial infarction or ischemia, cerebrovascular accident, and microangiopathic hemolytic anemia with thrombocytopenia.

• ***New indication for exemestane tablets (Aromasin) by Pfizer.*** The FDA has approved exemestane tablets (Aromasin) for adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer following two to three years of tamoxifen for a completion of five consecutive years of adjuvant hormonal therapy.

The approval was based on the Intergroup Exemestane Study (IES) which showed that patients who switched to exemestane after two to three years of tamoxifen, for a combined total of five years of therapy, had 31% more protection from cancer recurrence than those who remained on five years of tamoxifen therapy.

After the study was published in the *New England Journal of Medicine*, the American Society of Clinical Oncologists and the National Comprehensive Cancer Network updated their guidelines to support the use of a new switch regimen using exemestane adjuvant treatment.

The most common side effects for exemestane, which were mild to moderate, include hot flashes (21.2%), fatigue (16.1%), and arthralgia/bone pain (14.6%). Exemestane should not be administered to premenopausal women and women who are pregnant. Dose modifications should be considered for patients taking concomitant CYP3A4 inducers.

• ***New formulation of lopinavir/ritonavir (Kaletra) by Abbott***. The FDA has approved a new tablet formulation of Abbott's HIV protease inhibitor (PI) lopinavir/ritonavir (Kaletra), which

will allow adult patients to take fewer pills with or without food as part of their treatment regimen.

The FDA approval of the lopinavir/ritonavir tablet formulation was based on data from pharmacokinetic studies in 141 non-HIV-infected, healthy individuals. The studies demonstrated that lopinavir/ritonavir tablets provide similar drug levels in the blood to the capsule formulation. In these studies, lopinavir/ritonavir tablets were generally well tolerated. Tablet benefits include:

- Fewer tablets per dose as part of a treatment regimen in adults. While the total daily dose of lopinavir/ritonavir (800 mg lopinavir/200 mg ritonavir) is unchanged, the number of lopinavir/ritonavir pills adult patients need to take is reduced from six capsules to four tablets per day.
- Lopinavir/ritonavir tablets can be taken with or without food.
- Lopinavir/ritonavir tablets do not need to be refrigerated before or after dispensing. Exposure to high humidity outside the original container for longer than two weeks is not recommended.

The new lopinavir/ritonavir tablets each contain 200 mg lopinavir and 50 mg ritonavir, and the old capsules each contain 133.3 mg lopinavir and 33.3 mg ritonavir. The film-coated tablets are similar in size to the capsules. The color of the new lopinavir/ritonavir tablets in the U.S. is yellow. The old lopinavir/ritonavir capsules are orange.

Taking lopinavir/ritonavir with certain drugs can cause serious problems or death. (See prescribing information for list.) Pancreatitis and liver problems, which can be fatal, have also been reported in patients receiving lopinavir/ritonavir. The most commonly reported side effects of moderate severity with lopinavir/ritonavir are abdominal pain, abnormal bowel movements, diarrhea, feeling weak or tired, headache, and nausea. Children taking lopinavir/ritonavir may sometimes get a skin rash. ■

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This CE program will improve participants' ability to:

- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
- **Perform** cost-effectiveness analyses.

21. Entecavir inhibits which of the following activities of hepatitis B virus (HBV) polymerase?
    A. base priming
    B. reverse transcription of the negative strand from the pre-genomic mRNA
    C. synthesis of the positive strand of HBV DNA
    D. All of the above

22. Metabolism of entecavir occurs via CYP450; entecavir is a/an:
    A. substrate.
    B. inducer.
    C. inhibitor.
    D. None of the above

23. Accumulation half-life of entecavir is approximately 24 hours, allowing once-daily dosing.
    A. True
    B. False

24. Coadministration of entecavir with lamivudine, adefovir dipivoxil, or tenofovir disoproxil fumarate resulted in significant drug interactions.
    A. True
    B. False

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