FOR MORE THAN 20 YEARS

DRUG FORMULARY R•E•V•I•E•W™

Utilization, Criteria and Outcomes

THOMSON™
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

Statement of Financial Disclosure: Barry A. Browne, PharmD (Pharmacist Editor), John Hope (Editor), Lee Landenberger (Editorial Group Head), Paula Cousins (Managing Editor), and Tiffani Twilley (Author) report no relationships with companies related to this field of study.

JUNE 2006
VOL. 22, NO. 6 • (pages 41-48)

Pharmacists should become 'immunization advocates'

With concern rising about the possibility of an influenza pandemic, pharmacists must be immunization advocates and provide pharmaceutical care that includes evaluation of immunization status, according to a *Pharmacotherapy* article by two members of the U.S. Army Medical Command Military Vaccine Agency.

Stephen Ford, PharmD, and **John Grabenstein**, PhD, wrote that influenza epidemics occur each year and account for more illness in the developed world than all other respiratory diseases combined.

Pandemics occur when influenza viruses undergo either antigenic drift or antigenic shift that results in a new viral strain that infects humans, when they are capable of sustained transmission from person to person, and when they are introduced in populations with little or no pre-existing immunity. As many scientists have warned, an avian influenza A (H5N1) now circulating in Asia has pandemic potential, although no evidence currently exists that a pandemic is occurring.

Seasonal influenza infections and related complications result in some 36,000 deaths each year in the United States and between 3 million and 5 million severe flu cases worldwide, resulting in 250,000-500,000 deaths. So far, human H5N1 infection has involved 147 confirmed cases and 78 deaths, all in east Asia and Turkey.

No one knows for sure about avian flu

Although no one can yet say whether the next pandemic is imminent or even whether it will be caused by H5N1, pharmacists and other health care professionals have an obligation to evaluate current medical and scientific evidence, take inventory of available treatment and prevention interventions, and make rational treatment and prevention decisions focused on what is most beneficial now.

Ford tells *Drug Formulary Review* that immunization and sanitation are two of the most important achievements in controlling infectious diseases and improving public health. But he says this success is potentially at risk due to an expanding public focus on rare serious adverse events following immunization.

He recommends that pharmacists initiate practice changes including evaluation of immunization status/history as part of delivering pharmaceutical care. Pharmacists must understand basic immunization science and be well versed in immunization safety to effectively promote immunization and its importance in individual and public health. And pharmacists must work to improve immunization rates against vaccine-preventable diseases in vulnerable populations such as the elderly and children with chronic cardiopulmonary diseases. Pharmacists also must be immunized themselves.

According to Ford, hospitalized patients are often representative of the vulnerable populations and hospital pharmacists should actively promote immunization of hospitalized patients, if unprotected and not contraindicated, before hospital discharge or during follow-up appointments after an acute, serious illness has resolved.

Drug Formulary Review (ISSN#1548-2790), including **Drug Criteria & Outcomes**™, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Drug Formulary Review**, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (ahc.customerservice@thomson.com) **Hours of operation:** 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday.

Subscription rates: One year (12 issues), $499. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $83 each. (GST registration number R128870672.)

Editor: **John Hope**.
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@thomson.com).
Managing Editor: **Paula Cousins**, (816) 237-1833, (paula.cousins@thomson.com).
Senior Production Editor: **Nancy McCreary**.

Editorial Questions

Questions or comments? Call **Lee Landenberger** at (404) 262-5483.

Select populations at greatest risk

The risk of hospitalization and even death resulting from influenza complications is higher in people older than age 65, young children, and people of any age with certain underlying medical conditions including chronic disorders of the pulmonary or cardiovascular systems, including asthma; chronic metabolic diseases, including diabetes mellitus; renal dysfunction; hemoglobinopathies or immunosuppression; any condition that can compromise respiratory function or the handling of respiratory secretions or that can increase aspiration risk; and children or adolescents receiving long-term aspirin therapy. Influenza-related deaths often result from pneumonia or from worsening of underlying chronic disease. Effective influenza immunization programs that target high-risk people reduce the frequency of severe complications in vulnerable individuals.

WHO recommendations

The World Health Organization (WHO) has published recommendations for non-pharmaceutical public health interventions. The recommendations resulted from consultation with experts and evaluation of historic and current observations and data obtained from influenza disease models, as opposed to data from controlled studies. The authors said the effectiveness of individual measures will not be known until precise epidemiologic characteristics (attack rate, virulence, modes of spread within a community, affected age groups) of the pandemic virus are identified; thus, the WHO recommendations should be considered general guidance rather than formal WHO advice.

The WHO advice provides strategic guidance to limit international spread, including travel screening and restrictions. Unfortunately, according to the report, travel screening may have a limited impact because infected people may shed a virus before the onset of symptoms. Measures within affected communities include rapid case detection and isolation of infected people, contact tracing, quarantining those who are symptomatic, use of antivirals for treating cases and prophylaxis of others in the affected community, restrictions on movement and exit screening of people leaving the area where clusters of human cases are occurring.

Once a pandemic is declared, WHO may recommend any or all of these measures within affected countries: N95 respirator masks for health care workers and first responders, surgical masks for those seeking medical care, voluntary home confinement for people with fever and respiratory

systems as well as their contacts, deferring nonessential domestic travel to areas with disease; travel health alerts for incoming travelers describing symptoms and giving instructions on where to report if symptoms develop, and for people with known exposure on an aircraft or cruise ship, consideration of daily fever checks and prophylactic antiviral treatment if available.

In a scenario in which all countries are affected, WHO recommends stopping patient isolation, contact tracing, and quarantining contacts because those measures no longer will be possible or useful. Additional recommendations include social distancing (such as closing schools and canceling events involving large gatherings or crowds), reinforcing hand hygiene, and reinforcing respiratory hygiene. The WHO does not recommend the general public wear masks, as this intervention would have negligible transmission impact.

Immunization remains the primary intervention for preventing severe influenza illness and its complications, the report says. No H5N1-specific vaccine has been licensed by FDA, although the National Institutes of Health, through the National Institute of Allergy and Infectious Diseases, and vaccine manufacturers are working on development and clinical investigation of H5N1 vaccines.

Ford wrote that because no surveillance evidence indicates that a pandemic is occurring now, and because the circulating H5N1 viral strain is not involved in sustained human-to-human transmission, it's not clear whether the H5N1 vaccine being developed would be protective in a future pandemic. "It is generally believed that this vaccine will provide at least partial protection in those immunized and serve as a bridge until a tailored pandemic vaccine could be developed," he says. "This 'priming' dose could be considered the first in a two-dose strategy much like seasonal influenza immunization in children younger than 9 years old not previously immunized against influenza. In such children, two doses one month apart are recommended to achieve adequate antibody response because they are unlikely to have ever encountered H1N1 or H3N2 influenza viruses earlier in life."

If a pandemic occurs before a vaccine is available, the article warns, substantial numbers of illnesses, hospitalizations, and deaths may occur. For that reason, public health control measures such as social distancing, use of respirator masks, isolation, and quarantine, and use of antiviral drugs would be the best available interventions to limit disease spread until adequate vaccine supplies become available.

Tamiflu is the only neuraminidase inhibitor licensed for prophylaxis of influenza in the United States, although several large, controlled, clinical trials have given evidence that both Relenza and Tamiflu are effective in preventing influenza illness among healthy adults, children, and high-risk elderly or chronically ill people. In those studies, both Relenza and Tamiflu were 70-90% effective in preventing illness either before or after exposure to influenza A or B viruses. Limited information is available documenting these drugs' effectiveness in human H5N1 infections.

Manufacturers have limited production ability

Limited production capacity among four major flu vaccine manufacturers — Sanofi Pasteur, Chiron, GlaxoSmithKline, and MedImmune — in combination with greater limitations on surge capacity, seriously limit the rate of pandemic influenza vaccine production, according to the article. Production and delivery delays of seasonal influenza vaccine that occurred last year dramatically emphasized the limitations. Also, regulatory requirements for evaluating new vaccine production methods such as cell culture and other nonegg-based techniques represent significant barriers to rapid pandemic vaccine development and production.

Ford says pharmacists are uniquely positioned to implement near-term interventions that may mitigate the impact of a future pandemic. Increasing the rates of pneumococcal and seasonal influenza immunizations in vulnerable populations may reduce the likelihood of severe influenza complications in the event of a pandemic. And increased seasonal influenza immunization rates or a universal immunization program resulting in increased market demand would prompt vaccine manufacturers to increase both influenza production and production capacity. Thus, in Canada, health officials negotiated a contract with the country's only domestic producer of trivalent influenza vaccine guaranteeing purchase of 5 million doses a year for the next 10 years. Ford says vaccine manufacturers respond to such demand by increasing production when less financial risk exists in an otherwise unpredictable vaccine market. "In addition," he says, "pharmacists and all health care professionals must become effective risk communicators. Public confidence in health officials and health care providers is often shaken when contradictory recommendations are made in the face of public health and other disease threats."

There are a number of levels of immunization advocacy that pharmacists can assume, Ford says.

At a minimum, all pharmacists should ensure that vulnerable people are immunized against diseases that are the most significant sources of preventable mortality. That includes routine determination of immunization status and referral for recommended immunizations, identification of high-risk groups requiring targeted immunizations, and, most important, protecting themselves and those they come in contact with by being appropriately immunized. Pharmacists working outside a hospital can be immunization facilitators and host others who immunize. And consistent with state laws, pharmacists can become immunizers and assume an active role in protecting vulnerable people, recognizing that vaccine delivery by pharmacists is associated with higher immunization rates among those younger than age 65 receiving chronic drug therapy.

Ford cites a study comparing influenza immunization rates in states where laws permit pharmacists to administer immunizations compared with states without such legislation. The results indicated a statistically significant increase in influenza immunization rates in people ages 65 and older in states allowing pharmacist immunization. A positive result also was received from a pharmacist-managed immunization campaign that showed an increased influenza vaccination rate after the intervention (54% of patients) compared with baseline (28%) in high-risk patients identified through chart review.

Despite vaccine administration by a nurse in that campaign, Ford says, there is no reason to believe that a similar positive result would not be achieved if the pharmacists had administered the immunizations. The pharmacists in the campaign designed, initiated, implemented, and managed the logistics of the program to the point of immunization, including conducting intake surveys, providing disease and vaccine information, and resolving individual clinical issues, as well as providing clinic administrative oversight.

Pharmacists and other health care providers must be effective risk communicators, Ford says. Failure to communicate risks effectively may inadvertently increase public fears and undermine public confidence. Pharmacists must be trustworthy and authoritative sources for disease and drug information and communicate information in a way that empowers people to make informed and independent judgments about risks to their health and safety. That can range from dispelling myths about routine immunizations to communicating disease risk during a public health emergency such as a pandemic.

Ford concludes that if a pandemic virus reaches our communities, the best defenses will be local, with cities and counties effectively distributing vaccine and/or antiviral drugs, treating infected patients, and doing this efficiently and on an unprecedented scale. "If a pandemic virus attacks now, most cities and counties will have several months to prepare and progressively implement their responses," he says. "If, however, this virus waits a few more years, the national defenses will be considerably stronger."

[Editor's note: Contact Ford at (703) 681-5101, or e-mail Stephen.Ford@us.army.mil.] ■

Staff buy-in key to USP 797 implementation

While some aspects of implementing USP 797 ended up being surprisingly easy at Baytown, TX-based San Jacinto Methodist Hospital, and others were quite challenging, the major lesson learned from the experience was the importance of getting the staff involved and having them take ownership of the changes, according to **Charles Hines**, PharmD, RPh, the hospital's pharmacy clinical coordinator.

After reading the new standards **(see article, p. 46)**, Hines says, hospital officials knew they would need a collaborative effort on the part of pharmacy management, pharmacist, and technician staffs, and cooperation and coordination with various hospital departments.

Before implementing USP 797, he tells *Drug Formulary Review,* the situation at San Jacinto Methodist basically was the same as in all hospital pharmacies. "What we needed to change was our procedures as to exactly how we would prepare IVs based on this new regulation," he says. "We also needed to change how trash was removed from the room, how and when the room was cleaned, what needed to be monitored and how we were going to monitor it, education of our staff regarding the new procedures, updating our policies and procedures to reflect the new procedures being performed, and to reinforce with all the staff who was responsible for each piece and the part that each of us must play in ensuring compliance."

The hospital formed a committee composed of members of pharmacy management, pharmacists, and pharmacy technicians. That committee was

divided into subcommittees assigned to particular areas of focus. The subcommittees were given a specific time in which to complete their work and bring the results to the full committee for review and discussion. Each subcommittee's report was reviewed and discussed by the full committee and the appropriate actions were planned to ensure completion of each part of the process.

Planning followed by obtaining needed items

Completion of the project's planning phase led next to the acquisition phase, in which the hospital obtained new shelving units, carts, bins, and all other materials necessary to comply with the new guidelines. This step also included performing particle counts throughout the entire cleanroom.

The next step in the process was implementing new gowning, gloving, and cleaning procedures outlined in USP 797 and ensuring staff compliance with these elements.

"All of this work has paid off in seeing a decrease in our particle counts throughout the entire clean room as well as allowing our department to work together to accomplish this task," Hines reports. "Also, our hospital underwent a survey by JCAHO in April 2005, and they were pleased with our plan and all the work that had been put into this project. The continuation of this process as we review and implement the quality control portion of our program will assist the staff with understanding why the changes were necessary and the impacts made on patient care as a result of these changes, and allow them to take pride in the hard work they have put into this project."

San Jacinto Methodist is a 315-bed private, nonprofit, suburban community hospital that is part of a four-hospital system located in the United States' fourth-largest metropolitan area. The process Hines and his colleagues followed was to review resources and current practices, prepare a gap analysis and budget, develop a compliance/implementation timetable, make committee assignments, make decisions on level of care and service, implement a quality management program, prepare and execute needed education, and implement a continuous quality improvement element.

The gap analysis showed that the main campus pharmacy had an area for sterile admixture with a 90% limit to external access. It was compliant for ceiling, wall, and floor conditions. There were separate physical areas for HLAFH, VLAFH, processing, and storage. Exposure of materials and equipment in the buffer area to less controlled environments required improvement.

A long-term care pharmacy needed a major physical facility upgrade to become compliant with USP 797.

Monitoring was compliant with LAFH ISO Class 5. Environment testing for particulate/airborne microorganisms had not been previously done and was started in September 2004. There was no written plan in place and environmental air quality needed improvement.

The gap analysis showed that in terms of cleaning, elimination of paper particulate was needed, and materials, methods, and frequency for cleaning by pharmacy and housekeeping required significant changes.

While personnel were compliant with hand washing and hair and foot cover requirements, changes were needed for gowning and re-entry issues.

When they evaluated processing and responsibilities in the gap analysis, they found employees had an annual skills evaluation, but that needed to be upgraded to meet the new requirements. Policies and procedures needed to be updated to meet USP 797 and JCAHO standards.

Finally, employee education was needed as was continuous monitoring and quality improvement of the environment, equipment, and personnel.

Subcommittees were formed to work on processing, personnel/equipment, monitoring, environment, cleaning, and quality measurement/management. The subcommittees were charged with developing solutions to gap issues in their areas of focus. They met with vested individuals, groups, and manufacturers, and found suppliers to review contracts and sales terms. The subcommittees estimated costs and drafted proposed standard operating procedures. They also provided education and testing materials for didactic and physical testing.

Decisions made by the committee on subcommittee recommendations included: 1) management would communicate to medical staff; 2) Level 3 items must be purchased by the physician or patient externally; 3) patients must be transferred to an in-network facility with Level 3 capability; 4) education must be provided to the housekeeping and pharmacy staffs; 5) there should be a routine scheduled cleaning of all surfaces; 6) nonshedding, nonaerosolizing germicidal materials should be used; 7) furniture and equipment should be restricted to the ISO 8 area; 8) all stock entering the ISO 8 area should be wiped down; 9) corrugated cardboard should be eliminated from the ISO 8 area and the surrounding

environment; 10) personnel-borne particulate should be reduced through use of tacky mats, operating room-style nonshed gowns, bouffant hats, changing the cover on reentry, and no talking in hoods; 11) all employees required six hours of didactic education from an ACPE provider; 12) all employees were required to pass written and practical tests; 13) environmental air should be tested monthly; 14) personnel microbial testing should be performed annually; 15) routine reports should go to quality management, management, and pharmacy staff; and 16) out-of-compliance items required immediate changes and retesting.

In summary, Hines says, the gap analysis greatly helped identify areas needing improvement to meet USP 797 standards, the division of labor in problem-solving facilitated a timely resolution that had buy-in from all department members; application of the guidelines and avid follow-up of noncompliance areas resulted in meeting air quality and microbial standards; and the gap analysis aided resolution of difficult compounding issues with physicians.

Hines tells *DFR* that he was surprised to find that the item that was the easiest to change was informing the medical and nursing staffs that the pharmacy would no longer be able to provide compounded sterile products considered to be High Risk by the USP 797 guidelines. The hardest issue to address and change was the new rules for personnel gowning and gloving in the cleanroom. In the past, he says, gowning and gloving were only required when preparing chemotherapeutic agents, but now is required with preparation of all IV products.

Start with gap analysis

For facilities still working to implement USP 797, Hines stresses the value of the gap analysis — a good, hard look at exactly what you are doing as compared with what the guidelines require. "Be honest about what you need to implement these changes and help your administrators understand why it is necessary," he says.

The staff, as many as are willing, need to be included in the evaluation, planning, and implementation of these new processes. If they are unwilling to volunteer, it should be assigned to them. The staff working on the project needs to include management, supervisors, staff pharmacists, and technicians. Be sure to include any and all necessary departments in the initial process so they will be aware of the upcoming changes and your needs.

Lastly, be sure that your policies and procedures reflect actually what you are doing so when JCAHO comes to inspect your facility they will look, evaluate, and then make suggestions on what they would like to see changed rather than write you up for not doing what you say in your policies and procedures.

[Editor's note: Contact Hines at (281) 420-8680 or e-mail him at chines@tmh.tmc.edu.] ■

USP 797 is the first enforceable standard

An overview of USP Chapter 797 prepared by pharmacist **Mike Hurst**, RPh, MBA, for pharmacy supplier Baxa Corp., says the chapter, which became effective Jan. 1, 2004, is the first enforceable standard for sterile compounding. Following years of patient safety recommendations and professional guidelines, the intent of USP 797 is to lay out procedural and practical requirements for safe compounding of sterile preparations. The requirements apply to all practice settings where sterile preparations are compounded, raising concerns about the cost and ease of complying.

Hurst said it's important to recognize that the goal of USP 797 is improving the compounding of sterile products. Like any change, he said, it can be misinterpreted and thus feared. He said the biggest misconception seems to be that 797 requires a sophisticated cleanroom. For the most part, it contains many procedural, training, and quality assurance requirements that Hurst said are not unreasonable for a quality IV operation.

Like other USP standards numbered below 1,000, USP 797 is enforceable by state Boards of Pharmacy or the FDA. While FDA does not routinely inspect individual pharmacies, it may intervene in the case of injuries, a death, or a complaint. In addition, USP standards often are cited as evidence of national standards in legal actions, and the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) adopted them for use after July 1, 2004. JCAHO accreditation is required for Medicare reimbursement and almost all state Medicaid programs.

Hurst exploded some of the myths about USP 797, telling both what it is and what it is not. What 797 is, he said, is long (18 pages with 13 single-spaced and in a small-text font);

paperwork- and process-intensive; intended to upgrade pharmacy admixture processes to reasonable precautions; and based on three risk categories (low, medium, and high) for compounded sterile products.

But 797 isn't some of the things it's rumored to be, he maintained. Thus, it does not require sophisticated cleanrooms to be installed, instead calling for environmental controls, that is, a separate area for compounding that meets a defined level of cleanliness, and monitoring to ensure that control is maintained.

Facility baseline is first step

The first step in dealing with USP 797, according to Hurst, is to prepare a baseline on the existing facility to determine what remediation steps of facility and procedural redesign will be required to meet the environmental controls.

There are six levels of ISO (International Organization for Standardization (ISO) cleanrooms, from ISO Class 3 to ISO Class 8. The net result of the guidelines is that sterile mixing takes place in a properly maintained laminar airflow hood (ISO Class 5) situated in a relatively clean room (ISO Class 8). For most pharmacies, Hurst said, this requirement is neither difficult nor unreasonable. He expressed concern that some interpretations of the requirement have made it seem more onerous than it is.

He pointed out that USP 797 is not a radical departure from what most admixture programs are already doing. "There are basic steps in quality sterile compounding that many inpatient pharmacies have unfortunately not had the time or interest to implement. Regulatory agencies such as FDA and state Boards of Pharmacy have long recognized this need. USP 797 simply puts the requirements in a format that inspectors can check against."

Hurst cautioned that USP 797 cannot be fully met by outsourcing. USP 797 does not cover legitimate first doses, and other doses can be outsourced, he said. But almost any pharmacy will still need to make many doses such as those subject to change, short-expiration drugs, some antineoplastics, etc., that are not candidates for outsourcing. Other expensive and specialized drugs may be hard to outsource, also. Sterile compounding activities can be minimized through an outsource arrangement, Hurst said, but not entirely eliminated. Thus, nearly all hospital pharmacies have to comply with USP 797 requirements.

Can't use only isolators for compliance

Pharmacies need to be aware that isolators alone will not ensure compliance with USP 797. Hurst said that using an isolator for sterile compounding handles only part of the requirements for USP 797. Issues such as process validation, training, expiration setting, product quality maintenance after the sterile compounded product leaves the pharmacy, caregiver training, patient monitoring, and quality assurance remain the same as for products compounded in standard laminar flow hoods. Also, the special requirements for cleaning the isolator itself and for cleaning materials entering the isolator make it a demanding alternative to standard pharmacy flow hoods. Also, he said, many users find isolators physically difficult to work in and inappropriate for medium-to-large institution workloads.

Hurst said compliance with USP 797 is expected to be achieved through completion of steps on a timeline running through January 2008. The requirements allow pharmacies to plan appropriately for compliance, understanding that changes of this magnitude will not be accomplished overnight. JCAHO surveyors began surveying facilities for compliance with 797 on July 1, 2004.

The October 2004 issue of *Joint Commission Perspective* listed five items that the USP 797 advisory group recommended that organizations focus on for compliance: personnel training and evaluation, beyond-use dating and labeling, verification of automated compounding devices, finished preparation release checks and tests, and aseptic technique. Hurst said that list recognizes that the task of developing a comprehensive plan for USP 797 compliance is daunting. While all chapter components must be addressed for compliance, listing priority activities will allow organizations to make the most significant progress toward achieving the goal of improving the quality of sterile compounded products.

COMING IN FUTURE MONTHS

- New University of Michigan system reduces medication-use process errors
- Consider physiochemical properties of inhaled anesthetics when selecting one
- Know the latest developments in poison control
- Some states considering 'conscience bills' to allow pharmacists to decline filling Rx
- Optimizing antibiotic treatment for ventilator-assisted pneumonia

"USP 797 is a profound change for the profession of pharmacy," Hurst said. "The key is using aseptic technique with the right equipment in an environment that's appropriate." ■

Examples of USP 797 Tasks

CAPS (Central Admixture Pharmacy Services) list these examples of what it will take to comply with USP 797:

Daily

- ☐ Every bottle, vial, syringe, bag, etc. brought into the clean room must be decontaminated.
- ☐ Storeroom carts can't go into the buffer room and vice versa.
- ☐ No cardboard, paper towels, or cotton items in the buffer zone or clean room.
- ☐ Minimize traffic flow into and out of the buffer zone.
- ☐ No gum, candy, or food in the buffer area.
- ☐ Arrange items in hood to avoid blocking air flow.
- ☐ Daily cleaning and sanitizing of all buffer room carts, equipment, hoods, work surfaces, and floors.
- ☐ Daily calibration and verification of accuracy of all automated compounding equipment.
- ☐ Documentation of all compounding activities.
- ☐ No makeup or jewelry.
- ☐ Scrub hands and arms to elbow.
- ☐ Hair covers, shoe covers, knee-length coats or coveralls, and gloves.
- ☐ Sterile or nonsterile gloves. (Nonsterile gloves must be sanitized with sterile filtered alcohol.)
- ☐ Re-sanitize gloves frequently with sterile filtered alcohol.
- ☐ Coveralls can be reused throughout the day, but all other items should not be reused.
- ☐ Verification of compounding activity conducted by someone other than the compounder to ensure proper measurement, reconstitution, and component usage.
- ☐ Visual inspection: no PM, no leakage, accuracy and thoroughness of labeling.
- ☐ For high-risk compounding, sterility and bacterial endotoxin testing, filter integrity testing.
- ☐ Labeling in compliance with storage and expiration dating requirements.

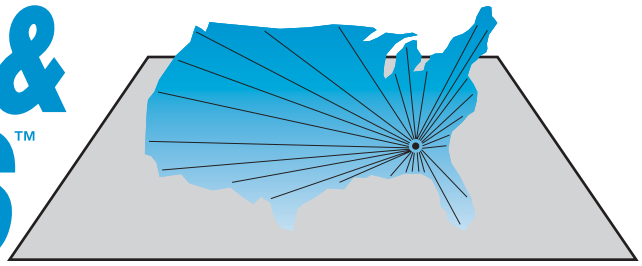
Ongoing

- ☐ Clean and sanitize anteroom weekly and shelving monthly.
- ☐ Clean and sanitize buffer room shelves at least weekly.
- ☐ Routine disinfecting and air quality testing: weekly air bio-burden for high-risk areas, and monthly for low- and medium-risk areas.
- ☐ Review of environmental monitoring and enforcement of alert and action limit contingency programs.
- ☐ Review of calibration data and enforcement of contingency programs.
- ☐ Review of cleaning logs and compounding documentation to ensure compliance, with enforcement of contingency plans for noncompliance.
- ☐ Patient monitoring and adverse event reporting.

Semiannually/Annually

- ☐ High-risk compounding training and documentation for all personnel involved in compounding sterile preparations initially and semiannually — written and didactic review.
- ☐ Semiannual media fills for high-risk compounding.
- ☐ Low- and medium-risk compounding training and documentation for all personnel involved in compounding sterile preparations initially and annually — written and didactic review.
- ☐ Annual media fills for low- and medium-risk compounding for all personnel involved in compounding sterile preparations.
- ☐ Room, hood, and equipment certification.
- ☐ Analysis of Quality Assurance program and effectiveness. ■

DRUG CRITERIA & OUTCOMES™



Pegaptanib (Macugen®) Formulary Evaluation

By **Tiffani Twilley**, PharmD Candidate
Samford University
Written while on clinical rotations
at Huntsville (AL) Hospital

Description

• ***Pegaptanib sodium injection (Macugen®)*** **is** a sterile, aqueous solution for intravitreous injection.[1]

• ***Verteporfin (Visudyne®)*** is a light-activated drug for injection used in photodynamic therapy (PDT).[2]

Indications

• *Pegaptanib:* Treatment of neovascular (wet) age-related macular degeneration.[1,3-5]

• *Verteporfin:* Treatment of predominantly classic subfoveal choroidal neovascularization (CNV), which is a type of neovascular (wet) degeneration, caused by age-related degeneration, pathologic myopia, or presumed ocular histoplasmosis. Unlabeled uses include treatment of: psoriasis, psoriatic arthritis, rheumatoid arthritis, nonmelanoma skin cancers, circumscribed choroidal hemangioma.[2,3]

Mechanism of Action

Pegaptanib is a selective vascular endothelial growth factor (VEGF) antagonist that binds to extracellular VEGF165, which is thought to be the primary isoform in neovascularization. VEGF is a protein that is secreted and selectively binds to and activates receptors on the surface of vascular endothelial cells inducing angiogenesis, increasing vascular permeability, and inflammation. These processes are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration (AMD), a common cause of blindness. Through inhibition of VEGF binding to VEGF receptors, pegaptanib was found to be effective at suppressing pathological neovascularization in animal studies.[1,3-5]

Verteporfin is transported in the plasma primarily by lipoproteins. It is activated by light in the presence of oxygen and generates highly reactive, short-lived singlet oxygen and reactive oxygen radicals. Once activated, local damage occurs in the neovascular endothelium resulting in selective vessel occlusion of the newly formed vessels. It is these vessels that can hemorrhage, which leads to vision loss. Damaged endothelium is known to release procoagulant and vasoactive factors through the lipo-oxygenase (leukotriene) and cyclooxygenase (eicosanoids such as thromboxane) pathways, resulting in platelet aggregation, fibrin clot formation, and vasoconstriction.[2,3]

Pharmacokinetics

To date, most pharmacokinetic studies have been conducted in animals.

• ***Absorption***

Following intravitreous administration, pegaptanib is slowly absorbed from the eye into systemic circulation. The rate of absorption from the eye of pegaptanib appears to be the rate-limiting step in the disposition of the drug. Within 24 hours after intravitreous administration of labeled pegaptanib, most of the drug was distributed throughout the retina and the vitreous and aqueous fluid. Within one to four days following a 3 mg monocular dose (10 times the recommended dose), the mean maximum plasma concentration was 80 ng/mL. The mean area under the curve is about 25 ug hr/mL at this dose.[1,3-5]

The extent of exposure and the maximal plasma concentration of verteporfin are proportional to the dose between 6 and 20 mg/m^2.[2,3]

• ***Distribution***

Within 24 hours after intravitreous

administration of radiolabeled pegaptanib to both eyes of rabbits, most of the drug was distributed throughout the retina and vitreous and aqueous fluid. Follow-ing intravitreous and intravenous administration of radiolabeled pegaptanib, the highest concentrations were obtained in the kidneys, excluding the eye for the intravitreous dose.[1,3,4]

Verteporin appears to preferentially accumulate in neovasculature including choroidal neovasculature.[2,3]

Metabolism

Pegaptanib is metabolized by endo- and exonucleases, presumed to be present in most tissue types, producing 2'- fluorouridine as one metabolite. This finding is based on preclinical data.[1,3,4]

Verteporfin is metabolized to a small extent to its diacid metabolite by liver and plasma esterases. NADPH-dependent enzyme systems (including the cytochrome P450 isoenzymes) do not appear to play a role in the metabolism.[2,3]

• ***Elimination***

The average (± standard deviation) half-life of pegaptanib is 10 (±4) days following a 3 mg monocular dose (10 times the recommended dose). Based on animal studies, pegaptanib is excreted as parent drug and metabolites primarily in the urine.[1,3,5]

Verteporfin exhibits a bi-exponential elimination with a half-life of approximately five to six hours. Elimination is by the fecal route with less than 0.01% of the dose recovered in urine.[2,3]

Dosage[1-5]

Pegaptanib is supplied in a single-use 1 mL glass syringe containing 0.3 mg of the drug in a volume of 90 mcL. It is administered 0.3 mg every six weeks by intravitreous injection into the affected eye. The length of therapy is based on clinical judgment; however, efficacy has only been proven for two years. The patient's medical history for hypersensitivity reactions should be evaluated prior to administration. In the special populations that have been studied (e.g., gender, renal insufficiency, and elderly), no dose adjustments were required. Studies have not been conducted in patients with hepatic impairment. The safety and efficacy of use in both eyes concurrently has not been studied.

Verteporfin is supplied in a single-use glass vial containing 15 mg of verteporfin. Intended for intravenous injection only, a course of verteporfin therapy is a two-step process requiring administration of both the drug and light. A desired dose of 6 mg/m^2 body surface area is then drawn from the vial and diluted with 5% dextrose for injection to a total infusion volume of 30 mL. The full infusion is then given intravenously over 10 minutes at a rate of 3 mL/min using an appropriate syringe pump and in-line filter. The laser light is then initiated 15 minutes after the start of the 10-minute infusion of verteporfin that activates the drug. The laser is directed toward and confined to the specific target area within the eye. Verteporfin should be used cautiously in patients with moderate-to-severe hepatic impairment due to lack of studies in this population.

Contraindications[1-3]

Pegaptanib is contraindicated for use in patients with ocular or periocular infections, or with known hypersensitivity to pegaptanib or any other excipient in this product.

Verteporfin is contraindicated in patients with porphyria or a known hypersensitivity to any component of this preparation.

Warnings/Precautions

Pegaptanib[1,3]

• For ophthalmic intravitreal injection only.

• Pegaptanib intravitreous injections have been associated with endophthalmitis. To prevent, utilize proper aseptic technique when administering pegaptanib. Monitor patients during the week following the injection to identify and treat infections early.

• Increases in intraocular pressure have been seen within 30 minutes of injection with pegaptanib. Monitor intraocular pressure as well as the perfusion of the optic nerve head and manage appropriately.

• Rare reports of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in association with pegaptanib administration in conjunction with administration of other drugs as part of the procedure. A direct causal relationship between pegaptanib and these reactions has not been established.

• Safety and efficacy in children has not been studied.

Verteporfin[2,3]

• Extravasation is a risk, and methods to avoid this include: establish free-flowing IV line before starting infusion, use the largest arm vein possible (preferably antecubital), and avoid small veins in the back of the hand. If extravasation occurs, stop infusion immediately and apply cold compresses.

• Possible hemodynamic effects may occur when verteporfin is administered in anesthetized patients. Supervise patients during infusion.

• Photosensitivity risk is increased; exposure of skin or eyes to direct sunlight or bright indoor light should be avoided for five days. If extravasation occurs, the area must be thoroughly protected from direct light until the swelling and discoloration have faded to prevent local burn.

• In patients who experience a severe decrease of vision of four lines on the eye chart (5 letters = l line) or more within one week after treatment, re-treatment should be delayed until vision completely recovers to pretreatment levels.

• Incompatible lasers that do not provide the right characteristics of light may result in incomplete treatment.

• Risk of mutagenesis, due to the fact that PDT is used, has been reported to result in DNA damage. It is not known how the potential for DNA damage with PDT translates into human risk.

• Verteporfin should be considered carefully in patients with moderate-to-severe hepatic impairment or biliary obstruction because no clinical studies have been conducted in these patients.

Reduced effect has been seen with increasing age.

Drug Interactions

Pegaptanib[1,3]

Although no drug interactions have been found, drug interaction studies have not been conducted. Pegaptanib is metabolized by nucleases and is not affected by the CYP450 system in general.

Verteporfin[2,3]

Drug interaction studies in humans have not been conducted, and CYP450 does not appear to play a role in verteporfin metabolism. However, based on the mechanism of action of this drug, many drugs, if used concomitantly, could have an effect on therapy (e.g., calcium channel blockers, polymyxin B, and radiation therapy), which could enhance the uptake of verteporfin by the vascular endothelium.

Efficacy may be decreased by drugs that decrease clotting, cause vasoconstriction, or inhibit platelet aggregation (i.e., thromboxane A_2 inhibitors). Photosensitizing agents could increase the risk for photosensitivity reactions. Drugs such as dimethyl sulfoxide, beta-carotene, ethanol, and mannitol that activate oxygen species or scavenge radicals, decrease verteporfin activity.

Adverse Effects

Pegaptanib[1-4]

• Serious adverse effects include: endophthalmitis (1.3%), retinal detachment (0.7%), iatrogenic traumatic cataract (0.6%), anaphylaxis/anaphylactoid reactions including angioedema (rare).

• Most frequently (10-40%) reported adverse events include: blurred vision, cataract, conjuctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased ocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbances, vitreous floaters, and vitreous opacities.

• Approximately 6-10% of patients reported the following: blepharitis, conjunctivitis, photopsia, vitreous disorder, bronchitis, diarrhea, dizziness, headache, nausea, and urinary tract infection.

Verteporfin[2,3]

• Severe vision decrease (of four lines or more) within seven days of treatment was reported in 1-5% of patients.

• Photosensitivity in the form of sunburn following exposure to sunlight.

• Back pain during infusion.

• Most frequently (10-30%) reported adverse events include: injection site reactions including extravasation and rashes, and visual disturbances such as blurred vision, decreased visual acuity, and visual field defects.

• Approximately 1-10% of patients reported: blepharitis, cataracts, conjunctivitis, diplopia, dry eyes, ocular itching, severe vision loss, atrial fibrillation, hypertension, sleep disorder, vertigo, constipation, nausea, anemia, increased or decreased WBC count, albuminuria, increased creatinine, arthralgia, and cough.

Pregnancy/Lactation

Pegaptanib is pregnancy Category B. It is unknown whether pegaptanib is excreted in breast milk; caution is recommended when administering to nursing women.[1,3]

Verteporfin is pregnancy Category C. It is unknown whether verteporfin is excreted in breast milk; caution is recommended when administering to nursing women.[2,3]

Administration

Pegaptanib[1,3]

Pegaptanib should be inspected prior to administration for visible particulate matter and/or discoloration. To administer, attach the threaded plastic plunger rod to the rubber stopper inside the barrel of the syringe. Do not pull back on the plunger and remove the syringe needle cap.

Verteporfin[2,3]

For administration, reconstitute each vial with 7 mL of sterile water for injection to provide 7.5 mL

Table 1

Rate of Visual-Acuity Loss, Measured as the Loss of Fewer Than 15 Letters, in 1,186 Patients

Time	Pegaptanib 0.3 mg (n = 294)	Pegaptanib 0.3 mg (n = 294)	Pegaptanib 1.0 mg (n = 300)	Pegaptanib 1.0 mg (n = 300)	Pegaptanib 3.9 mg (n = 296)	Pegaptanib 3.0 mg (n = 296)	Sham Injection (n = 296)
	No. (%)	P Value	No. (%)	P Value	No. (%)	P Value	No. (%)
Week 12	256 (87)	0.01	259 (86)	0.04	251 (85)	0.13	237 (80)
Week 24	242 (82)	< 0.001	239 (80)	< 0.001	224 (76)	0.003	190 (64)
Week 36	220 (75)	< 0.001	229 (76)	< 0.001	222 (75)	< 0.001	175 (59)
Week 54	206 (70)	< 0.001	213 (71)	< 0.001	193 (65)	0.03	164 (55)

Note: The difference between the doses of pegatanib were not significant.

containing 2 mg/mL. Once reconstituted (opaque and dark-green), protect from light and use within four hours. The full infusion should be given intravenously over 10 minutes at a rate of 3 mL/min using an appropriate syringe pump and in-line filter.

Storage

Pegaptanib should be stored in the refrigerator. Do not freeze or shake vigorously.[1,3]

Verteporfin should be stored between 20° and 25° C (68° and 77° F). Reconstituted verteporfin must be protected from light and used within four hours.[2,3]

Patient Instructions

Following administration of pegaptanib, the patient is at increased risk of developing endophthalmitis.[1,3] Seek immediate medical care if the eye becomes red, sensitive to light, painful, or develops a change in vision.

Following verteporfin treatment, photosensitivity will increase.[2,3] Avoid direct sunlight and bright lights for five days. Patients should protect all parts of the skin and eyes by wearing protective clothing and sunglasses. UV sunscreens are not effective in protecting against photosensitivity. Encourage patients to expose their skin to ambient indoor light to help inactivate drug in the skin.

Clinical Studies

Trial 1: Gragoudas ES, Adamis AP, Cunningham ET, et al. **Pegaptanib for neovascular age-related macular degeneration.** *N Engl J Med* 2004;351:2,805-2,816.

Objective: Two concurrent clinical trials were conducted to evaluate the short-term safety and efficacy of pegaptanib in patients with a broad spectrum of visual acuities, lesion sizes, and angiographic subtypes of lesions at baseline.

Study design: This study was a summarization of two concurrent, prospective, randomized, double-blind, multicenter, dose-ranging, controlled clinical trials conducted at 117 different sites in the United States, Canada, Europe, Israel, Australia, and South America.

Intervention: Patients were randomly assigned to receive either sham injection or intravitreous injection of pegaptanib into one eye every six weeks over a period of 48 weeks, for a total of nine treatments. Those in the pegaptanib intervention group received one of three strengths: 0.3 mg, 1 mg, or 3 mg.

Adjunctive therapy: All patients underwent an ocular antisepsis procedure and all received injected subconjunctival anesthetic.

Patient Population

Inclusion criteria for the study were as follows:

- Patients 50 years of age or older and had subfoveal sites of choroidal neovascularization secondary to age-related macular degeneration and a range of best-corrected visual acuity of 20/40 to 20/320 in the study eye and 20/800 or better in the other eye.
- Patients with all angiographic subtypes of lesions with a total size up to and including 12 optic-disk areas (including blood, scar, or atrophy, and neovascularization).

Outcomes and Results

The primary endpoint was the proportion of patients who lost fewer than 15 letters of visual acuity (defined as three lines on the study eye chart) between baseline and week 54. Results can be found in **Table 1, above**.

Table 2

Maintenance, Gain, and Severe Loss of Visual Acuity with Pegaptanib and Sham Injection

Endpoints	Pegaptanib 0.3 mg (n = 294)	Pegaptanib 0.3 mg (n = 294)	Pegaptanib 1.0 mg (n = 300)	Pegaptanib 1.0 mg (n = 300)	Pegaptanib 3.9 mg (n = 296)	Pegaptanib 3.0 mg (n = 296)	Sham Injection (n = 296)
	No. (%)	P Value	No. (%)	P Value	No. (%)	P Value	No. (%)
Maintenance or gain ≥ 0 letters	98 (33)	0.003	110 (37)	< 0.001	93 (31)	0.02	67 (23)
Gain ≥ 5 letters	64 (22)	0.004	69 (23)	0.002	49 (17)	0.12	36 (12)
Gain ≥ 10 letters	33 (11)	0.02	43 (14)	0.001	31 (10)	0.03	17 (6)
Gain ≥ 15 letters	18 (6)	0.04	20 (7)	0.02	13 (4)	0.16	6 (2)
Loss ≥ 30 letters	28 (10)	< 0.001	24 (8)	< 0.001	40 (14)	0.01	65 (22)
Visual acuity in study eye ≤ 20/200 (legal blindness)	111 (38)	< 0.001	128 (43)	< 0.001	129 (44)	0.001	165 (56)

The secondary endpoint was the proportion of patients treated with pegaptanib who maintained or gained visual acuity (no change in the number of letters or a gain of one or more letters on the eye chart). Results of the secondary endpoint are shown in **Table 2, above**.

Study Strengths

• Prospective, randomized, double-blind, multicenter study.

• Characteristics of patients at baseline were similar among treatment groups.

• Appropriate inclusion criteria and length of study.

Limitations

• Lack of power to validate statistics.

• Strengths and limitations not included in the article.

• Different administration of the pegaptanib and the sham injection.

• Patients allowed to receive PDT with verteporfin during the trial.

Authors' Conclusion

The results of this study showed the difference in treatment with pegaptanib compared to placebo to be statistically and clinically significant in regards to treatment benefit in a wide range of patients with neovascular age-related macular degeneration, regardless of the size or angiographic subtype of the lesion or baseline visual acuity. However, long-term data are needed to fully demonstrate the safety and efficacy of pegaptanib.

Trial 2: Visudyne in Minimally Classic Choroidal Neovascularization (VIM) Study Group. **Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration.** *Arch Ophthalmol* 2005;123:448-457.

Objective: The purpose of the study was to compare the treatment efficacy and safety of photodynamic therapy with verteporfin using a standard (SF, 600 mW/cm^2) or reduced (RF, 300 mW/cm^2) light fluence rate to placebo in patients with subfoveal minimally classic CNV with age-related macular degeneration. The light fluence rate is the wavelength of photodynamic therapy being administered.

Study design: This study was a Phase 2, multicenter, double-blind, placebo-controlled, randomized clinical trial conducted in 19 ophthalmology practices across North America and Europe.

Intervention: Each patient was randomized to one of two fluence groups: standard (SF, 600 mW/cm^2) or reduced (RF, which is 300 mW/cm^2) light fluence rate. At the same time patients also were assigned to receive either verteporfin infusion 6 mg/m^2 (intervention) or placebo (control). Treatment was repeated every three months, if the treating physician noted fluorescein leakage from CNV on angiography.

Patient Population

Inclusion criteria for the study were as follows:

• Best-corrected visual acuity letter score (following the Treatment of Age-Related Macular

Degeneration with Photodynamic Therapy vision protocol) of at least 30 (Snellen equivalent, which is the standard eye chart used in practice, approximately 20/250 or better) for lesions of four macular photocoagulation study (MPS) disc areas or less and a 30-65 (approximate Snellen equivalent 20/50) for lesions of greater than four but no greater than six MPS disc areas.

• Fluorescein angiographic evidence of subfoveal CNV due to AMD in which at least 50% of the lesion was CNV.

• Fluorescent pattern of some classic CNV (bright area of fluorescence in early-phase frames with leakage at the boundaries of this area through the middle- and late-phase frames) that was less than 50% of the entire area of the lesion using previously defined terms.

Outcomes and Results: The primary endpoint was at least 15 letters (three lines) of visual acuity loss at 12 months. Results are tabulated in **Table 3, below.**

Table 3

Frequency of Distribution of Changes in Visual Acuity from Baseline by Treatment at the 12-Month Follow-up Examination*

	Placebo (n = 38)	RF Verteporfin (n = 36)	SF Verteporfin (n = 36)
Change from baseline in visual acuity‡			
Line increase ≥ 3 but < 6	0	2 (6)	1 (3)
Line increase ≥ 1 but < 3	3 (8)	6 (17)	6 (17)
No change	9 (24)	14 (39)	5 (14)
Line decrease ≥ 1 but < 3	8 (21)	9 (25)	14 (39)
Line decrease ≥ 3 but < 6	6 (16)	0	3 (8)
P values vs. placebo group		0.001•	0.16†
Median change in letters	-13.5	-1.5	-9.0
P values vs placebo group		0.02	0.36
P value between treatment groups		0.03	0.03

Abbreviations: RF = reduced fluence (300 mW/cm²); SF = standard fluence (600 mW/cm²)
*Includes observed data without last observation carried forward. Unless otherwise indicated, data are expressed as number (percentage) of patients.
‡Values are approximate; there are five letters per line.
• Calculated using the Wilcoxon rank sum test. The RF group had the better outcome compared with the placebo group. Compared with the distribution of change from baseline in visual acuity in the SF group, P = 0.05 at the 12-month examination.
†Calculated using the Wilcoxon rank sum test. The SF group had the better outcome compared with the placebo group. Compared with the distribution of change from baseline in visual acuity in the RF group, P = 0.05 at the 12-month examination.

Study Strengths

• Multicenter, double-blind, randomized study.
• Appropriate inclusion criteria.
• Equivalent baseline patient characteristics.

Limitations

• Small sample size.
• Lack of power to validate statistics.

Authors' Conclusion

Based on the findings of this study, verteporfin has been proven to safely reduce the risks of loss of visual acuity (at least 15 letters or at least three lines), as well as progression to predominantly classic CNV for at least two years in patients with subfoveal minimally classic lesions that are caused by age-related macular degeneration that measures six MPS disc areas or fewer. In addition, the VIM Study Group would consider recommending verteporfin as therapy for the treatment of small minimally classic lesions like those enrolled in the trial.

Cost

One pre-filled 1 mL single-use syringe (contains 0.3 mg of pegaptanib) costs $995. One single-use vial containing 15 mg of verteporfin costs $1,678. Approximate costs of a photodynamic therapy laser used in the verteporfin procedure is $28,500 and would be used routinely to perform the procedure. This laser also could be rented for approximately $786/month.

Formulary Recommendation

Pegaptanib has been proven effective in treating age-related macular degeneration regardless of the lesion size or baseline visual acuity; therefore, it can be used in a broad spectrum of patients. Verteporfin therapy has previously been the treatment regimen for this disease. At this time, pegaptanib administration is considered mainly an outpatient procedure, with the drug cost at about $995 every six months. The procedure with verteporfin is done up to every three months if needed with a drug cost of $1678, and this does not include the cost of laser treatment. Both of these treatments are continued or stopped based upon clinical judgment. At this time, pegaptanib is recommended as nonformulary status for inpatients, with its administration being mainly in the outpatient setting. Each institution should

decide if they will offer the verteporfin plus laser procedure to patients based on hospital-specific factors. The use of these drugs should be restricted to ophthalmic surgeon specialists.

References

• Macugen [package insert]. New York City: Eyetech Pharmaceuticals Inc.; 2004.

• Visudyne [package insert]. East Hanover, NJ: Novartis; 2004.

• Efacts. Facts and Comparisons. Available at: www.efactsonline.com. Accessed Aug. 6, 2005.

• Riley TN, DeRuiter J. Review of select NMEs of late 2004. *US Pharm* 2005;30:HS-12-HS-17.

• Abramowicz M, ed. Pegaptanib sodium (macugen) for macular degeneration. *The Medical Letter* 2005;47:55-56. ■

NEWS BRIEF

Patient safety practices resource available

The Joint Commission International Center for Patient Safety has launched a new "in-development" Patient Safety Practices resource on the Center's web site at www.jcipatientsafety.org/psp. This beta version of the on-line database has a rich collection of practices and interventions for preventing adverse events, while also soliciting user suggestions for enhancing the web site's content and functionality.

There are links to more than 400 established sites that include a wide variety of respected domestic and international patient safety sources. Officials said the database is being introduced as a work in progress to encourage users to submit additional safe practices that can be widely shared and to suggest ways in which the database can become an even more helpful resource.

"This database is a simple way of getting practical information into the hands of health care professionals and other provider organization staff to help them improve patient safety," said Joint Commission International Center for Patient Safety co-director **Peter Angood**, MD. "This initiative underscores the center's commitment to translating available knowledge about patient safety into actionable information." ■

New FDA Approvals

These drugs were recently approved by the FDA:

• ***Pravastatin sodium tablets, Teva Pharmaceuticals' generic form of Bristol-Myers Squibbs' Pravachol***, indicated for treating individuals with high cholesterol levels or who are at increased risk for atherosclerosis-related cardiac and cardiovascular events such as heart attack and stroke in which high cholesterol levels are a factor.

FDA officials said the approval was an example of agency efforts to counter rising health care costs by approving safe and effective generic alternatives as quickly as the law permits. Pravastatin sodium tablets will be available in 10 mg, 20 mg, and 40 mg doses.

• ***Myozyme (alglucosidase alfa, rhGAA) by Genzyme, indicated for treating Pompe disease***, a rare but severely debilitating disease that affects one in 40,000-300,000 individuals, drastically reducing the individual's muscle and respiratory function.

FDA previously granted Myozyme orphan drug designation and gave it priority review. It was approved for administration by intravenous infusion of solution into a vein.

Myozyme's safety and efficacy were assessed in two clinical trials in 39 infantile-onset patients with Pompe disease ranging in age from 1 month to 3.5 years at the time of the first infusion. FDA reported patient survival without needing invasive ventilatory support was substantially greater in the Myozyme-treated infants than would be expected compared to the known high mortality of untreated patients of similar age and disease severity. The drug's safety and effectiveness in other forms of Pompe disease have not been adequately studied, FDA said.

The most serious adverse reactions reported with Myozyme were heart and lung failure and allergic shock. Most common reactions included pneumonia, respiratory failure and distress, infections, and fever. The labeling includes a boxed warning calling attention to the possibility of life-threatening allergic reactions.

• ***Prograf (tacrolimus), Astellas Pharma US, indicated for preventing graft rejection in heart transplant patients.*** Tacrolimus capsules and tacrolimus for injection, the first products

approved in United States for heart transplantation in eight years, previously were approved for preventing graft rejection in liver and kidney transplant recipients.

Company officials said tacrolimus acts by a mechanism similar to cyclosporine, another immunosuppressant used to prevent transplant rejection. Thus, tacrolimus is an alternative to cyclosporine for use in certain combination immunosuppressive regimens in liver, kidney, and heart transplantation.

The safety and effectiveness of tacrolimus-based and cyclosporine-based immunosuppression in heart transplantation were compared in two trials, one in Europe and one in the United States. In the European trial, the survival of patients and grafts 18 months after transplantation in the tacrolimus group (91.7%) was similar to the cyclosporine group (89.8%). In a U.S. study, patient and graft survival at 12 months after transplantation in the tacrolimus group (93.5%) was similar to the cyclosporine group (86.1%).

Use of tacrolimus is associated with increased risk of neurotoxicity, renal function impairment, infection, and post-transplant diabetes mellitus. Like most combination immunosuppressive regimens used in solid organ transplantation, use of tacrolimus-based combination immunosuppression is associated with an increased risk of malignancies, notably of non-melanoma skin cancers.

• ***Zidovudine, Aurobindo Pharma's generic form of GlaxoSmithKline's Retrovir, indicated for use with other antiretroviral agents for treating HIV-1 infection.*** This is the first generic approval for the capsule dosage form of zidovudine. The tablet and oral solution dosage forms were previously approved for sale when the patent on those dosage forms expired last September. ■

CE *Questions*

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers.

Participants must complete a post-test and evaluation form provided at the end of each semester (June and December) and return them in the reply envelopes provided. A statement of credit requires a passing score of 70% or higher. When a passing test and evaluation form are received, a statement of credit and answer guide will be mailed to the participant.

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. Predominantly classic subfoveal choroidal neovascularization (CNV) is a type of neovascular (wet) degeneration caused by:
    A. age-related degeneration.
    B. pathologic myopia.
    C. presumed ocular histoplasmosis.
    D. All of the above

22. To date, most pharmacokinetic studies of pegaptanib and verteporfin have been conducted on animals.
    A. True B. False

23. The length of pegaptanib therapy is based on clinical judgement; however, efficacy has only been proven for:
    A. one year.
    B. two years.
    C. three years.
    D. four years.

24. The CYP450 system:
    A. is involved with the metabolism of pegaptanib.
    B. is involved with the metabolism of verteporfin.
    C. is involved with the metabolism of both pegaptanib and verteporfin.
    D. is not involved with the metabolism of either pegaptanib or verteporfin.

25. Serious adverse effects of pegaptanib include:
    A. endophthalmitis.
    B. retinal detachment.
    C. iatrogenic traumatic cataract.
    D. anaphylaxis/anaphylactoid reactions including angioedema.
    E. All of the above

26. Following verteporfin treatment, patients should be encouraged to expose their skin to direct sunlight to help inactivate drug in the skin.
    A. True B. False