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IN THIS ISSUE

■ How safe is your pharmacy? . . . . . cover

■ Be on alert for hospital impostors 43

■ Get a jump-start on improving your pharmacy informatics 43

■ Take a look at the patient when assessing renal function 44

■ **Research News:** Investigators release data on unexpected adverse drug and device reactions 45

■ **News Briefs** 46

■ **Inserted in this issue:**
— *Drug Criteria & Outcomes*
— January-June 2005 CE Test and Evaluation form for CE subscribers

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How safe is your pharmacy? Be on the lookout

Impostors raise red flags about overall hospital security

The Joint Commission on Accreditation of Healthcare Organizations recently sent out an alarm about three instances in which impostors posing as surveyors tried to gain access to different hospitals. The impostors left the hospitals when questioned or pressed for identification.

The incidents did not seem to involve the pharmacy area, says **John Fishbeck**, associate project director of the Joint Commission's Division of Standards and Survey Methods. Per Joint Commission standards, hospitals need to make sure they can identify their staff and visitors. **(For further instruction about possible impostor situations, see p. 43.)**

"We allow each organization to take a look at the risk associated with the services they provide. It's fine if they take a look at what's needed and then implement it," Fishbeck says.

With the red flags being raised about the impostors, *Drug Formulary Review* decided to review the state of pharmacy security today. **Fred Roll**, CHPA-F, CPP, president of the International Association for Healthcare Security and Safety (IAHSS) in Glendale Heights, IL, weighs in on this issue.

DFR: What is the biggest safety concern today for hospital pharmacy directors and managers?

Roll: Diversion. You can have diversion in the pharmacy proper or, more likely, on the floor. To track diversion problems, more hospitals are going now to automated dispensing systems such as Pyxis and to Pyxis CII Safe for their narcotics. As long as they effectively use either the Pyxis-provided software or other software that works with Pyxis dispensing, it's going to help identify areas of potential problems.

I would suggest they consider an automated system if they can afford it and, more importantly, use the software that tracks potential diversions and med errors.

DFR: What is another security problem for hospital pharmacies?

Roll: Access control issues — letting the wrong people have access to the pharmacy. [Pharmacy staff], for example, will let staff members in the house come into the pharmacy while the pharmacy staff is getting the product ready for them, rather than keep the hospital staff at the perimeter and only have authorized people within the pharmacy.

Hospital pharmacies may also lock their doors, but have problems at the transition windows. The windows can be left open, allowing someone to jump over the counter and come in. If product is left on the counter, someone can reach in and take it.

DFR: What types of protection options are available for transaction windows?

Roll: I have seen pharmacy windows be open and have nothing for protection to what I call a "customer-friendly" partition, which is usually a piece of Plexiglas that only keeps someone from jumping over or crawling under. On the other end is bulletproof glass and thin trays and bullet-resistant metal behind the fascia — a real fortress. There are all of these different levels. I am a big proponent in what is reasonable and appropriate in a given environment. When I assess security for hospitals and look at the pharmacy, I am primarily concerned with access control and with the pharmacy being able to deliver the product back and forth.

DFR: What about protection methods for other access issues?

Roll: There are several methodologies for securing access control: You can give everyone a key. You can give everyone a computerized card. You can combine a card with a PIN number, such as with an ATM.

A crook, who often is [mistaken about the type and quantity] of drugs he can get from a hospital pharmacy, may wait around in the hallway for the door to open. Or he may knock on the door; customer service then opens the door to see who is knocking. Once you open the door, you have breached the perimeter and it is an open portal.

I like to see TV cameras viewing the hallway outside of all exit points from the pharmacy with a small monitor close to eye level inside the pharmacy. If someone is knocking on the door, a pharmacy staff member can then look at the monitor. He or she can even check the monitor before leaving to see if anyone is lingering in the hall.

Some people use the cheap solution of putting a peephole in the door. In my experience, I have found that people don't generally use that. They don't like to put their eyes close to things. Overall, the camera and monitor is not an expensive project these days given technology costs.

If you are keeping the wrong people out and only granting access to the appropriate people, you are meeting access control and are also making the staff more comfortable and safe.

DFR: Do you recommend any type of alarms?

Roll: I am a big believer in having hold-up alarms at the transaction area of the pharmacy. If it's a large pharmacy, I like to see those same kinds of buttons strategically placed throughout the area.

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Thomson American Health Consultants has designated up to 6 contact hours annually for this program. Participants will receive ACPE statements of credit within 6 weeks after receipt of the post-test and evaluation form, provided a passing grade of at least 70% is achieved. Health system pharmacists and pharmacy benefits managers are the target audience of this activity; however, anyone involved in prescribing, dispensing, patient counseling, formulary selection, or reimbursement processes might benefit from participation. Drs. Gilchrist, Holder, and Cramer (authors) report no relationships with companies related to the field of study covered in *Drug Criteria & Outcomes.*

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Be on alert for hospital impostors

Take these steps if you have a concern

In an e-mail sent to all Joint Commission-accredited organizations on March 3, Joe Cappiello, Joint Commission's vice president of accreditation field operations, advised hospital personnel to make sure they verify the credentials of anyone reporting to be Joint Commission surveyors. Cappiello recommended hospital personnel take these steps:

- Ask the surveyors to show their Joint Commission ID badge.
- Ask for the surveyors' letter addressed to the head of the organization signed by Russell Massaro, MD, executive vice president of Accreditation Operations for the Joint Commission, explaining who they are and why they are there.
- Call Cappiello at (630) 792-5757 or their Joint Commission account representative if they experience a similar situation or if they have any questions about whether an individual is a surveyor. ■

If a pharmacy is not 24/7, I also really like to see an intrusion alarm in that area. Satellite pharmacies around the hospital are a good application to have intrusion alarms as well, because the satellite pharmacies may be tucked away [in areas that don't have consistent traffic]. If you are going to install an intrusion alarm, it is a good idea to add a hold-up panic alarm, too.

DFR: What about staff training?

Roll: The staff needs hold-up training so they know what to do, how to do it, etc., in case anything happens. If they don't have some kind of formalized training, [someone in the pharmacy may try to control the situation]. Pharmacy managers and supervisors, therefore, should have a discussion about this with their staff.

DFR: Do these types of robberies happen often?

Roll: Robberies in hospital pharmacies don't happen often, but when they do, they are a major deal. Security protocols that have been implemented have prevented many problems. ■

Get a jump-start on improving your informatics

The Internet may provide a partial solution

The transition into the digital information world has not been smooth for most hospital pharmacists — or health care in general.

"If you look at the ability for integrated information systems to allow the power that can be brought on by both information technology and automation to make people more efficient and effective, pharmacists like every other health care provider are struggling to bring their practice into fully supported digital workflow and workload," says **Bill G. Felkey**, MS, professor of pharmacy care systems at Auburn (AL) University.

Felkey made a presentation at the 2005 meeting of the American Pharmacists Association in April about how to best use supportive technology.

Initially health care leaned in the direction of using large mainframe computers, he says. Because of the need for better clinical department support, however, health care went to more stand-alone departmental solutions. Now the pendulum is swinging back to where the pharmacy's information provision needs to become more completely integrated in the whole information system.

The system should have the ability to have a multidisciplinary care team approach, in which work is sent for the pharmacist to do electronically, Felkey says. "If a prescription or medical order requires specific dosing, it would be more appropriate for that to be turfed to the pharmacist," he says. "Other things like documentation systems, pharmacokinetic calculations, and clinical references all need to become more integrated so that the support that is needed arrives more in a just-in-time manner."

Pharmacists may have had the will, but not always the ability to make changes to their information systems. "One of the biggest barriers is that because of the diverse hardware, software, and operating systems, we have a variety of information standards," he says. "With new HIPAA [Health Insurance Portability and Accountability Act of 1996] concerns, we have systems that are not talking well to each other."

Information barriers also exist that keep health care from meeting coding requirements that are necessary for truly integrating resources, he adds.

Even when vendors pass on their vision of what

can be possible in information technology, pharmacists may be disappointed in the implementation. For example, computerized prescribed order entry can be useful for helping patient safety, Felkey reports. Some health systems have adopted it, but without first acquiring an electronic medical record. The result has been frustration. "We all know what is possible, but it is not necessarily implemented at the level it can be," he says.

Pharmacists now can have everything become more "Net-centric," which describes those things that operate on web browsers and the Internet. The Internet may become one component of the solution since it involves a smaller set of standards than other information systems.

A pharmacist who has a Macintosh computer at home, for example, would be able to use an Internet browser on his or her own machine to talk to the hospital system. A thin client (low-level workstation) is all that it takes to make this type of communication possible. Similarly, if pharmacists have patient responsibility and are sitting in a restaurant with their pocket PCs or Palm handheld operating systems, they should be able to connect to the system and get the information they need to reduce their uncertainty when making clinical decisions, Felkey says.

"We need a pervasive computing platform — and the Internet does provide that, to be able to move those data to where they are needed for better use and better timeliness of the information," he says.

Whatever they decide, pharmacists need to keep heading toward a solution, Felkey advises. "There is enough change in the technology that it would be detrimental to wait until the perfect system has been developed and then move to it. It's better to look for areas right away where you can get a return on investment and to keep piloting interesting technology so you can keep your pharmacy department moving and used to change. Look for new solutions on a continual basis, knowing that the systems are getting better.

"Redirecting an organization that is already moving is easier," he concludes, "than taking one that is at a total standstill and trying to get it jump-started." ■

Take a closer look when assessing renal function

Prediction should be adjusted based on muscle mass

Two men are admitted to the hospital. One is a bodybuilder and looks like Arnold Schwarzenegger. The other is obese and describes himself as a "couch potato." They have the same body weight. What is the best way to predict their creatinine clearance?

Muscle mass makes a difference, says **John E. Murphy**, PharmD, professor and head of the Department of Pharmacy Practice and Science at the College of Pharmacy at the University of Arizona-Tucson. For the best prediction, he advises pharmacists to look at the actual patient first instead of just saying, "Predict their creatinine clearance on ideal body weight or actual body weight."

Because the input side is the skeletal muscle mass, each of the men would have the same creatinine clearance prediction if a pharmacist used the lean body weight or actual weight, Murphy explains. At the same serum creatinine level, however, Arnold Schwarzenegger types would have a much higher creatinine clearance.

"If you have a patient who looks like Arnold and has a lot of muscle, I suggest using his actual body weight to predict creatinine clearance and maybe even assume it's higher," Murphy says. "A patient who's very obese and more like a couch potato won't have as much muscle mass relative to his total weight. You might want to use ideal body weight for him or some adjustment in between if he has some degree of muscle increase with his increase in body weight."

Murphy made a presentation about the notion of muscle mass as an important factor in creatinine clearance estimates at the 2005 meeting of the American Pharmacists Association in April. His presentation was part of the "Clinical Pearls for Acute Care Pharmacists" section of the meeting.

The talk stemmed from a course Murphy teaches in clinical pharmacokinetic application. One of the subjects he tackles is, "What is the best way to make predictions of drug dosages and concentration outcomes?" His advice to assess the degree of a patient's muscle mass is just a way to slightly improve predictions, he says.

"A lot of hospitals have dosing programs based on renal function, and pharmacists alter doses in patients with reduced function based on an estimated creatinine clearance," he says. "It would be good for them to take the opportunity to look at the patients and enhance their predictions."

Murphy doesn't think that predicting creatinine clearance without considering a patient's body makeup is necessarily harmful to patients. Estimating dose adjustments, however, might allow pharmacists to make more sophisticated decisions in their dosing approaches. He would also like to see more researchers make a distinction in their clinical results about which weight they used when predicting creatinine clearance so that clinicians can best adapt the research results to patient care.

Most overweight patients treated with the more general approach to predicting creatinine clearance would receive no more than about a 20% difference in dosing, Murphy says. "People aren't going to go over the edge necessarily [with this difference], but you might refine your predictions and give them a better dose from the start." ■

■ Research News ■

Investigators release data on unexpected ADRs

Ten percent of patients died from adverse reactions

In 1998, a multidisciplinary team of investigators initiated RADAR (Research on Adverse Drug events And Reports), a clinically based postmarketing surveillance program that is funded independently of the pharmaceutical industry. RADAR systematically investigates and disseminates information describing serious and previously unrecognized adverse drug and device reactions (ADRs).

The investigator team evaluates initial reports of the ADRs, identifies additional reports of each ADR, develops hypotheses for mechanistic pathways, evaluates related laboratory and pathologic findings, and derives reporting and incidence rate estimates. They then synthesize summary safety information into reports disseminated in medical journals, revised package inserts, and Dear Doctor letters. The information also is presented at medical conferences and at meetings with officials of the FDA, the relevant pharmaceutical manufacturers, and to officials in the public sector who are evaluating pharmaceutical safety issues.

In the May 4 issue of the *Journal of the American Medical Association*, the 25 core investigators described the RADAR project and gave statistics about their findings: Between 1998 and 2004, they identified serious ADRs associated with 16 different drugs that affected 1,699 patients, 169 (10%) of whom died. The toxicities affected multiple organ systems and included TTP (thienopyridines), hypersensitivity (drug-eluting cardiac stents), interstitial pneumonitis (nonsteroidal anti-androgens and gemcitabine), sinusoidal obstructive syndrome (gemtuzumab), immune-mediated anemia (epoetin), thrombocytopenia (megakaryocyte growth and development factor [rHu-MGDF]), thromboembolism (thalidomide), hepatotoxicity (nevirapine), optic neuritis (amiodarone), pseudoaneurysms (enoxaparin), jaw osteonecrosis (zolendronate), and lymphoproliferative disorders (rHu-MGDF).

ADRs associated with 16 drugs

Initial cases were identified by seven RADAR investigators, four collaborating physicians, two attorneys, and by reviewing three published reports, the investigators said. Additional sources included queries of occupational health programs and medical directors of interventional cardiology laboratories (three types of ADRs), published manuscripts and clinical trials (11 types of ADRs), review of medical records at a RADAR site (two types of ADRs), unpublished clinical trial reports (three types of ADRs), and reports from attorneys, family members, or patients (four types of ADRs).

Incidence estimates, ranging from 0.4% to 33%, were derived from five clinical trial reports, two physician queries, and two observational databases. Laboratory support for hypotheses included identification of three neutralizing antibodies and three histopathological findings. ADR reports were disseminated as eight revised package inserts, seven Dear Doctor letters, and nine peer-reviewed articles.

"In conclusion," the investigators said, "our investigations exemplify the potential benefits of establishing clinically based, postmarketing surveillance collaboratives that focus on serious ADRs. The RADAR group has identified and evaluated 16 serious ADRs and in response, package insert revisions, Dear Doctor letters, and peer-reviewed medical articles describing our findings have been disseminated. It is hoped that the efforts of the RADAR project will ultimately improve safety through early detection and treatment of serious ADRs." ■

NEWS BRIEFS

Gefitinib for advanced lung cancer trial closes early

Researchers have closed a randomized clinical trial comparing gefitinib (Iressa) vs. placebo following chemotherapy and radiation for patients with non-small cell lung cancer (NSCLC) that had spread only to nearby tissues or lymph nodes. Review of interim data indicated that gefitinib would not improve survival.

Based on a review of the limited data available from the Phase III clinical trial, the Data Monitoring Committee overseeing the trial recommended the closure. Detailed results from the study were presented at the American Society of Clinical Oncology Annual Meeting on May 14.

The study was designed to assess whether maintenance therapy with gefitinib would improve overall survival and progression-free survival as compared to placebo in patients with stable or responding disease. These patients had inoperable stage III NSCLC and already had completed the combined chemotherapy regimen of cisplatin and etoposide with radiation, followed by docetaxel. A total of 672 patients in this study were to be randomized to one of two treatment arms following chemotherapy and radiation: One arm would receive gefitinib daily and the other arm would receive a placebo daily. As of March 10, 611 patients were entered and 276 were randomized to one of the two arms.

The National Cancer Institute sponsored the trial. ▼

Survey: Patients struggle with drug compliance

One in three (33%) U.S. adults who have been prescribed drugs to take on a regular basis reported that he or she is often or very often noncompliant with the treatment regimen, according to a recent Harris Interactive on-line survey. In addition, nearly half (45%) of the respondents said they have failed to take their medications because of concerns they had about the drugs themselves, and 43% reported having not complied with their regimens because they felt the drug was unnecessary.

The survey of 2,507 U.S. adults was conducted between March 16 and 18 for *The Wall Street Journal* Online's Health Industry Edition.

Of the 63% of adults who have had prescription drugs prescribed to them in the last year — drugs that should be taken regularly — nearly two-thirds (64%) reported that they have simply forgotten to take their medication. Eleven percent said this has happened "often" or "very often." Other top reasons respondents cited for noncompliance with their treatment regimens include:

- I had no symptoms or the symptoms went away (36%).
- I wanted to save money (35%).
- I didn't believe the drugs were effective (33%).
- I didn't think I needed to take them (31%).
- I had painful or frightening side effects (28%).
- The drugs prevented me from doing other things I wanted to do (25%).

"These barriers leading to noncompliance present significant challenges to physicians and the U.S. health care system as a whole that will be difficult to address," says **Katherine Binns**, senior vice president of healthcare research at Harris Interactive. ▼

Bevacizumab with chemotherapy improves breast cancer survival

Preliminary results from a large, randomized clinical trial for patients with previously untreated recurrent or metastatic breast cancer show that those patients who received bevacizumab (Avastin) in combination with standard chemotherapy had a longer time period before their cancer progressed than patients who received the same chemotherapy without bevacizumab.

Preliminary results suggest that patients in the study who received bevacizumab in combination with standard chemotherapy consisting of single-agent paclitaxel had a delay in worsening of their cancer by four months, on average, compared to patients treated with paclitaxel chemotherapy alone. This difference is statistically significant.

A total of 722 women with recurrent or metastatic breast cancer who had not previously received systemic chemotherapy for their recurrent or metastatic disease were enrolled in this study between December 2001 and May 2004. Patients were randomized to one of the two treatment arms. One patient group received standard

treatment consisting of single-agent paclitaxel. The second group received the same regimen of paclitaxel with the addition of bevacizumab.

The National Cancer Institute sponsored this trial. ▼

PharMEDium Services recalls all lots and strengths of IV solution

PharMEDium Services of Houston is recalling all strengths of 50 mL admixtures of magnesium sulfate in 5% dextrose solution because of a potential lack of sterility assurance for these products. In addition, the company is voluntarily ceasing production and distribution of the product until it can determine and correct the source of this problem.

Two previously distributed lots of this product have been associated with outbreaks of *Serratia marcescens* infection, which can potentially cause serious or life-threatening conditions in patients (particularly among the immune-compromised).

The products subject to recall are those labeled under the following service codes:

- 2K2410
- 2K2411
- 2K2412
- 2K2413
- 2K2419

These products were manufactured by PharMEDium Services of Houston and were distributed to several hospitals around the country.

On March 18, the FDA issued a nationwide alert regarding PharMEDium Services Magnesium Sulfate 1 g in 50 mL D5W (piggyback) IV solution, lot number 100504900049 and expiration date 4/4/05, after it was associated with five cases of *S. marcescens* infection in a hospital in New Jersey.

The company is working with the FDA, the U.S. Centers for Disease Control and Prevention, and other public health authorities. Hospitals with questions may contact the company at (847) 457-2300. ▼

Enrollment stopped in drotrecogin alfa (activated) pediatric trial

Eli Lilly and the FDA have notified health care professionals that enrollment has been stopped in a randomized, double-blind, placebo-controlled trial of drotrecogin alfa (activated) (Xigris) in pediatric patients with severe sepsis. Drotrecogin alfa (activated) is not indicated for use in pediatric severe sepsis.

A planned interim analysis showed that drotrecogin alfa (activated) was highly unlikely to show an improvement over placebo in the primary endpoint of "Composite Time to Complete Organ Failure Resolution" over 14 days.

A numerical increase in the rate of central nervous system bleeding in the drotrecogin alfa (activated) vs. the placebo group was also noted. Over the infusion period the number of patients experiencing an intracranial hemorrhage event was four vs. one for the overall population (drotrecogin alfa (activated) vs. placebo), with three of the four events in the drotrecogin alfa (activated) group occurring in patients age 60 days or younger. Mortality, the rate of serious adverse events, overall serious bleeding events, and major amputations appeared to be similar in the drotrecogin alfa (activated) and placebo groups.

For the complete MedWatch 2005 Safety summary, see www.fda.gov/medwatch/SAFETY/2005/safety05.htm#biologics. ▼

FDA updates albumin administration advice

The FDA issued a notice on May 16 to update an earlier correspondence and to revise its previous advice about the safety of albumin administration in critically ill patients. The action was taken following the FDA's review of recent studies on the safety of albumin; it also is consistent with recommendations made on

COMING IN FUTURE MONTHS

- Flu vaccine supply questionable for next year
- Formulary evaluation for ziconotide (SNX-111)
- CPOE system introduces new errors, study says
- More news from the 2005 American Pharmacists Association annual meeting
- Another study confirms benefits of aggressive statin therapy

March 17 by members of the Blood Products Advisory Committee (BPAC).

In an Aug. 19, 1998, letter to health care providers, the FDA had expressed serious concern over the safety of albumin administration in critically ill patients and urged physicians to exercise discretion in its use.

This advice was based on a meta-analysis published in the July 25, 1998, issue of the *British Medical Journal.* The researchers found that compared to normal saline, albumin administration was associated with a 6% increased risk of dying; similar findings were noted for patients with hypovolemia, hypoproteinemia, and burns.

Then the *New England Journal of Medicine* published the SAFE study in its May 27, 2004, issue. SAFE is the largest randomized controlled trial to date to address the safety of albumin. In this trial, 6,997 critically ill subjects were randomized to receive either 4% albumin or normal saline for the treatment of hypovolemia.

The results presented by the principal investigator at the BPAC meeting on March 17, 2005, indicate that for patients in the general intensive care unit requiring fluid resuscitation, the mortality rate of those who receive albumin is the same as for those who receive saline.

Secondary analyses of pre-specified subgroups of patients with acute respiratory distress syndrome (ARDS), severe sepsis, and trauma were consistent overall with this finding.

Two additional findings deserve mention, according to the FDA. First, results of an exploratory analysis of trauma patients with concomitant traumatic brain injury showed increased mortality in the albumin treatment arm. Second, a higher survival rate was observed in the albumin-treated patients with severe sepsis, but since this finding was not statistically significant, its clinical significance remains uncertain.

Based on these data, the BPAC voted unanimously that the SAFE study had resolved the prior safety concerns raised by the 1998 researchers. However, the relative safety of albumin for use in patients with burns cannot be determined at this time as this group was excluded from the SAFE study.

Additionally, further evaluation of albumin in patients with traumatic brain injury and septic shock will have to be performed to determine the safety of albumin administration in these patient populations. ■

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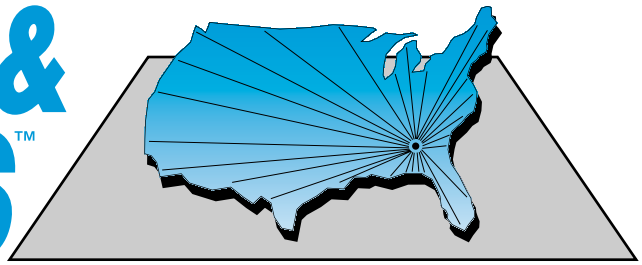

Poractant alfa (Curosurf) Formulary Evaluation

By **Penny Jones**, PharmD candidate
Harrison School of Pharmacy
Auburn (AL) University

Background

Respiratory Distress Syndrome (RDS), also known as hyaline membrane disease, is one of the leading causes of infant mortality in the United States. The incidence of RDS is approximately 1% of live births. Between 60,000 and 80,000 infants in the United States are diagnosed with the syndrome each year, the majority of whom are born prematurely. Approximately 60%-80% of infants born at fewer than 28 weeks develop RDS, compared to only 5% of infants born between 37 weeks and full-term.

RDS is caused by a deficiency in pulmonary surfactant that results in poor lung compliance and an increased effort to breathe. Surfactant reduces surface tension and stabilizes alveoli at low lung volumes, allowing alveoli of all sizes to inflate. Premature infants often produce insufficient surfactant, resulting in the collapse of alveoli (atelectasis), decreased functional residual capacity, and increased dead space within the lungs. This review will compare poractant alfa (Curosurf) are calfactant (Infasurf).

Similar drugs in class

Drugs that are similar to poractant alfa are calfactant, beractant (Survanta), and colfosceril palmitate (Exosurf). Curosurf is manufactured sby DEY. Infasurf is manufactured by Forest Pharmaceuticals.

Description

Poractant alfa is an extract of natural porcine lung surfactant consisting of 99% polar lipids (primarily phospholipids) and 1% hydrophobic low molecular weight proteins (surfactant-associated proteins SP-B and SP-C). It is suspended in 0.9% sodium chloride solution and the pH is adjusted as required with sodium bicarbonate to a pH of 6.2 (5.5-6.5). It is sterile, nonpyrogenic, and contains no preservatives. Each milliliter of poractant alfa contains 80 mg of total phospholipids (including 54 mg phosphatidylcholine, of which 30.5 mg is dipalmitoylphosphatidylcholine) and 1 mg protein, including 0.3 mg SP-B.

Calfactant is a sterile, nonpyrogenic lung surfactant that is an extract of natural surfactant from calf lungs, which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C. It contains no preservatives. It is suspended in 0.9% sodium chloride and the pH is 5.7 (5.0-6.2). Each milliliter contains 35 mg total phospholipids (including 26 mg phosphatidylcholine, of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg proteins, including 0.26 mg of SP-B.

Strengths/dosage forms available

Poractant alfa is available in sterile, ready-to-use rubber-stoppered clear glass vials containing 1.5 mL (120 mg phospholipids) or 3 mL (240 mg phospholipids) of suspension. Calfactant is available in sterile, ready-to-use rubber-stoppered clear glass vials containing 3 mL (105 mg phospholipids) and 6 mL (210 mg phospholipids) of suspension.

Mechanism of action

Poractant alfa and calfactant have the same mechanism of action. As endogenous pulmonary surfactants, they reduce surface tension at the air-liquid interface of the alveoli during ventilation and stabilize the alveoli against collapse at

resting transpulmonary pressure.

Indications

Poractant alfa is indicated for the treatment (rescue) of RDS in premature infants. Calfactant is indicated for the treatment of RDS in neonates ≤ 72 hours of age and for prophylaxis of premature infants < 29 weeks gestational age at significant risk for RDS.

Off-label uses

No off-label uses are known at this time.

Storage

Poractant alfa should be refrigerated at 2°-8° C. Unopened vials may be warmed to room temperature for up to 24 hours prior to use. It should not be warmed to room temperature and returned to the refrigerator more than once. It should be protected from light and should not be shaken. Vials are for single use only and any unused portion after opening should be discarded.

Calfactant should be refrigerated at 2°-8° C and protected from light. Vials are for single use only and any unused portion after opening should be discarded. The 3 mL vial should be stored upright. It is not necessary to warm the vial prior to use. It should not be shaken and unopened, unused vials that have been warmed to room temperature can be returned to refrigerated storage once within 24 hours for future use.

Pharmacokinetics

Poractant alfa has an initial response that usually is seen within 3-6 hours, and effects may persist for up to 48 hours. It is administered intratracheally directly to the target organ, the lung, where biophysical effects occur at the alveolar surface.

No human pharmacokinetic studies to characterize the absorption, biotransformation, or excretion have been performed, due to the medical fragility of premature infants, which prohibits the use of some techniques of clinical pharmacologic investigation. Nonclinical studies have been performed to evaluate the disposition of phospholipids present in poractant alfa.

Calfactant has an initial response that usually is seen within one to four hours, and effects may persist for 24-72 hours. It is administered intratracheally directly to the target organ, the lung, where biophysical effects occur at the alveolar surface. It is extensively and uniformly distributed in the lung. Metabolism occurs in the lungs as well.

Dosage/administration

Poractant alfa has an initial dose of 2.5 mL/kg birth weight (200 mg/kg). Up to two subsequent doses of 1.25 mL/kg birth weight (100 mg/kg) can be administered at 12-hour intervals if needed. It is administered intratracheally by instillation through a 5 French end-hole catheter (cut to a standard length of 8 cm) inserted into the infant's endotracheal tube. The dose should be administered in two equal aliquots of 1.25 mL/kg (100 mg/kg) each. The infant's ventilator settings should be changed before administration to a rate of 40-60 breaths/min, inspiratory time 0.5 seconds, and supplemental oxygen sufficient to maintain oxygen saturation (SaO_2) > 92%.

Briefly disconnect the endotracheal tube from the ventilator. Insert the pre-cut 5 French catheter into the endotracheal tube and instill the first aliquot. After each aliquot is instilled, the infant should be positioned on either the right or the left side, allowing gravity to help distribute the drug. Administration is made while ventilation is continued over 20-30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning should separate the two aliquots. Repeat dosing is by the same procedures but at 1.25 mL/kg (100 mg/kg). Maximum total dose administration is 5 mL/kg (400 mg/kg).

Calfactant has an initial dose of 3 mL per kg birth weight (100 mg/kg). Up to three subsequent doses can be administered at 12-hour intervals if needed. It is administered intratracheally through a side port adaptor of the endotracheal tube. The dose should be administered in two equal aliquots of 1.5 mL/kg (50 mg/kg) each. After each aliquot is instilled, the infant should be positioned on either the right or the left side, allowing gravity to help distribute the drug. Administration is made while ventilation is continued over 20-30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning should separate the two aliquots. Repeat dosing is by the same procedures.

Special populations

No special populations have been identified.

Adverse reactions

Poractant alfa adverse reactions include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. Calfactant adverse reactions include cyanosis, airway obstruction, bradycardia, reflux of surfactant into the endotracheal tube, requirement for mechanical ventilation, and reintubation.

Warnings/precautions

Poractant alfa should be administered intratracheally only; administration of exogenous surfactants can rapidly affect oxygenation and lung compliance. Poractant alfa should be used with caution in the following situations: infants born after more than three weeks of ruptured membranes (to avoid cases of pulmonary hypoplasia), intraventricular hemorrhage of Grade III or IV, and major congenital malformations.

Calfactant should be administered intratracheally only; administration of exogenous surfactants can rapidly affect oxygenation and lung compliance. Calfactant should be used with caution in the following situations: infants born after more than three weeks of ruptured membranes (to avoid cases of pulmonary hypoplasia), intraventricular hemorrhage of Grade III or IV, and major congenital malformations.

Potential for medication errors

If both drugs are stocked, the nurse could mix up dosages or products. Infasurf also is a look-alike/sound-alike to Exosurf.

Drug-drug interactions

No identified interactions.

Drug-food

No identified interactions.

Cost

The cost of poractant alfa is $225.00 for a 1.5 mL vial and $450 for a 3.0 mL vial. The cost of calfactant is $245.60 for a 3.0 mL vial and $440 for a 6.0 mL vial. Based on a 200 mg/kg initial dose for a 1 kg infant, the cost of poractant alfa would be $376. Based on a 100 mg/kg initial dose for a 1 kg infant, the cost of calfactant would be $234.

Poractant alfa currently does not have any patient assistance programs, but calfactant does have them available. Last year, $173,000 was spent on 454-6 mL vials of calfactant of which 60 vials were returned, making the total cost of 394-6 mL vials of calfactant $150,140 for one year. Comparing this to poractant alfa, 394-3 mL vials would have cost $177,300 for the same one-year supply. Poractant alfa would have cost an extra $27,160.

Pregnancy/lactation information

No information identified.

Overdose

There have been no reports of overdosage following the administration of poractant alfa. In the event of accidental overdosage (and only if there are clear clinical effects on the infant's respiration, ventilation, or oxygenation), the suspension should be aspirated as much as possible. The infant should be managed with supportive treatment, with particular attention to fluid and electrolyte balance.

There have been no reports of overdosage following the administration of calfactant. Although there are no known adverse effects of excess surfactant, overdosage would result in overloading the lungs with an isotonic solution. Ventilation should be supported until clearance of the liquid is accomplished.

Patient education (special)

No information identified.

Staff education (special)

Staff should be educated on administration requirements. See **dosage/administration, p. 2**.

Clinical trial summary

Trial 1: Ramanathan R, Rasmussen M, Gerstmann D, et al., and The North American Study Group. **A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) vs. beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants.** *Am J Perinatol* 2004;21:109-119.

Objective

To evaluate the effectiveness of a 100 mg/kg initial dose of poractant alfa, by comparing its onset of clinical response to that of a 200 mg/kg initial dose of poractant alfa or a 100 mg/kg initial dose of beractant, for treatment of RDS in infants weighing 750-1750 g.

Study design

Prospective, randomized, masked trial conducted from January 2000 to May 2001 at 20 centers in the United States.

Inclusion criteria

- Birth weight 750 to 1750 g.
- Gestational age < 35 weeks.
- Clinical or radiographic evidence of RDS.
- Intubated and receiving conventional mechanical ventilation.
- Fraction of inspired oxygen (FIO_2) ≥ 0.30 to maintain oxygen saturation by pulse oximeter of 88% to 96% or an arterial to alveolar PaO_2 (oxygen pressure) ratio (a/A ratio) of ≤ 0.33.
- Age 6 hours or younger at the time of randomization.
- Signed informed consent by a parent or legal guardian.

Exclusion criteria

- Respiratory failure not due to RDS.
- Proven fetal lung maturity profile from amniocentesis prior to delivery.
- Suspected lung hypoplasia.
- Prior treatment with an exogenous surfactant.
- Apgar score ≤ 3 at 5 minutes.
- One or more major congenital anomalies considered to be life-threatening.
- Prolonged rupture of membranes, defined as ≥ three weeks in duration.
- Untreated pneumothorax, hypotension, or hypoglycemia.
- Use of high-frequency ventilation prior to first dose of surfactant.
- Severe grades of intraventricular hemorrhage (Grades III or IV) by cranial ultrasound.
- Any condition believed by the investigator to place the subject at undue risk.
- Participation in another clinical trial.

Patient population

- Three hundred and one infants were enrolled in the study.
- Ninety-six infants received low-dose poractant alfa, 99 infants received high-dose poractant alfa, and 98 patients received beractant.
- Birth weight, gestational age, gender, race, baseline FIO_2, and mean airway pressure were similar among all three groups.
- More male infants were treated overall, but there were no differences among the treatment groups.

Outcomes

Primary:

Area of FIO_2 under the curve during the six-hour period ($FIO_2\ AUC_{0-6}$) after the first dose of poractant alfa or beractant.

Secondary:

Mean FIO_2, mean airway pressure (MAP), total number of doses, median durations of oxygen dependence and mechanical ventilation, and complications of prematurity.

Treatment regimen

- Ninety-six infants received poractant alfa 100 mg/kg.
- Ninety-nine infants received poractant alfa 200 mg/kg.
- Ninety-eight infants received beractant 100 mg/kg.
- All repeat dosing was given at 100 mg/kg.

Statistical analysis

- Kruskal-Wallis test.
- Nonparametric rank tests.
- Kaplan-Meier.
- 95% confidence intervals.
- Chi-square test.

Results

- $FIO_2\ AUC_{0-6}$ was significantly lower for both poractant alfa 100 mg/kg ($P < 0.001$) and poractant alfa 200 mg/kg ($P < 0.005$) compared with the beractant group.
- Mean FIO_2 for 100 and 200 mg/kg poractant alfa groups were significantly lower than that for the beractant group at all time points until six hours ($P < 0.05$).
- No significant difference between the mean FIO_2 in infants treated with 100 or 200 mg/kg of poractant alfa.
- $FIO_2\ AUC_{0-6}$ was significantly lower in infants treated with either initial dose of poractant alfa within 2.5 hours of birth compared with beractant ($P < 0.02$).
- Seventy-three percent of infants were successfully treated with only one dose of 200 mg/kg poractant alfa compared with 59% in the poractant alfa 100 mg/kg group and 51% in the beractant group ($P < 0.002$).
- Thirty-six percent of infants received two or more doses of surfactant in the poractant alfa 200 mg/kg group compared with 68% in the beractant group ($P = 0.002$).
- There was no difference in changes in MAP during the six hours after the first dose of surfactant in the three groups.
- Neonatal mortality rate at 28 days was not significant between the three groups.
- Mortality at 36 weeks postconceptional age for infants born ≤ 32 weeks gestation was 3% in the

200 mg/kg poractant alfa group, compared with 11% each in the 100 mg/kg poractant alfa-treated (P = 0.046) and beractant-treated (P = 0.034) infants.

Strengths
- Randomized.
- Comparative.
- Appropriate study population.

Weaknesses
- Repeat doses not masked.
- Surfactant preparations not well-blinded.
- Onset of clinical response only assessed for the first dose.
- Three participants violated entry criteria (one born at 36 weeks gestational age, one had an Apgar score < 3 at 5 minutes, and one was ventilated with high frequency prior to treatment) but their results were included in the analysis.
- Mortality reasons not specified.

Authors' conclusion
Infants < 35 weeks gestation treated with an initial dose of 200 mg/kg poractant alfa are weaned from supplemental oxygen more rapidly during the first six hours after dosing; significantly fewer infants require additional doses if the 200 mg/kg initial dose of poractant alfa is used; and infants ≤ 32 weeks treated with an initial dose of 200 mg/kg poractant alfa have a survival advantage.

Trial 2: Bloom B, Kattwinkel J, Hall R, et al. **Comparison of Infasurf (calf lung surfactant extract) to Survanta (beractant) in the treatment and prevention of respiratory distress syndrome.** *Pediatrics* 1997;100:31-38.

Objective
To compare the relative safety and efficacy of calfactant vs. beractant in reducing the acute severity of RDS when given at birth and to infants with established RDS.

Study design
Prospective, randomized, double-blind, multicenter clinical trial.

Inclusion criteria
- Infants < 2,000 g birth weight and < 48 hours of age.
- Radiographically confirmed RDS.
- Intubation.
- $FIO_2 \geq 0.4$ with a $PaO_2 < 80$ Torr or an a/A oxygen ratio of ≤ 0.22.
- Mothers who presented in labor or were expected to deliver before 30 weeks gestation (no minimum) were asked to enroll their infants in the prevention arm.

Exclusion criteria
- Infant birth weight > 1,250 g birth weight.
- Greater than 15 minutes old before resuscitation was successful.
- Major anomaly that interfered with lung development of function.
- More than one type of surfactant used during retreatment process.
- A dosage error of greater than 50% occurred.
- Major malformation recognized after study entry.
- Diagnosed congenital sepsis or pneumonia.

Patient population
No differences in birth weight, gestational age, sex, racial distribution, maternal conditions, prenatal, intrapartum, and delivery room variables including Apgar scores.

Age and respiratory status were similar at study entry.

Outcomes
- Twenty-five percent reduction between groups in the need for a third dose of surfactant for infants with established RDS.
- Twenty-five percent reduction in the need for a second dose of surfactant for infants who received prophylactic surfactant.

Treatment regimen
The treatment arm enrolled infants of < 2,000 g birth weight with established RDS, and the prevention arm enrolled infants of < 29 weeks gestation with birth weights < 1,250 g.

Three hundred and three infants received calfactant at the recommended dosage of 100 mg/kg along with 180 infants in the prevention arm but in a special 25 mg/mL formulation to provide masking.

Three hundred and five infants received beractant at a dosage of 100 mg/kg in the treatment arm along with 194 infants in the prevention arm, also in a 25 mg/mL formulation.

Statistical analysis
- ANOVA.
- Mann-Whitney *U* test.
- Cochran-Mantel-Haenszel chi square test.

• Intention-to-treat.

Results

In the treatment arm, there was no difference between groups in the number of infants requiring more than two doses of surfactant.

The interval between doses was significantly longer for calfactant, suggesting an increased duration of treatment effect. The inspired oxygen concentration and mean airway pressure were lower in the calfactant infants during the first 48 hours in the treatment arm. There were no significant differences noted in the incidence of mortality, chronic lung disease, dosing re-evaluated events, or complications of prematurity.

In the prevention arm, there were no differences with respect to the number of surfactant doses. The dosing intervals were longer for calfactant infants after the second dose. No difference in inspired oxygen or mean airway pressure was noted during the first 72 hours.

Strengths

- Randomized.
- Double-blinded.
- Appropriate dosages.
- Appropriate study population.
- Comparative.

Weaknesses

Mortality reasons not specified.

Authors' conclusion

Infants treated with calfactant have a modest benefit in the acute phase of RDS. Calfactant seems to produce a longer duration of effect than beractant.

Recommendation

With the current information available, poractant alfa and calfactant appear to have comparable efficacy and safety except for a faster onset of action and longer duration of action for calfactant. Poractant alfa claims to have advantages over other surfactants such as less volume administered and higher phospholipid content; however, these proposed advantages have not been completely studied in clinical trials.

The cost of comparable doses of poractant alfa and calfactant show that calfactant is less expensive than poractant alfa for most situations. Based on comparable one-year cost evaluations and usage figures, poractant alfa would cost the hospital an additional $28,000 with no apparent additional clinical benefit to justify the increased cost. Calfactant has been supplied as both a 3 mL and 6 mL vial, and this availability has contributed to decreasing wastage.

It is recommended that only one neonatal surfactant product by used in the neonatal intensive care unit to minimize confusion among the products and reduce medication error potential. Therefore, it is recommended that calfactant remain the formulary agent instead of changing the formulary agent to poractant alfa.

References

• Bloom B, Kattwinkel J, Hall R, et al. Comparison of Infasurf (calf lung surfactant extract) to Survanta (beractant) in the treatment and prevention of respiratory distress syndrome. *Pediatrics* 1997;100:31-38.

• DEY. Curosurf [package insert]. Napa, CA; February 2002.

• Forest Pharmaceuticals. Infasurf [package insert]. St. Louis; June 2003.

• MICROMEDEX Healthcare Series. Greenwood Village, CO: MICROMEDEX; (edition expires March 2005).

• Ramanathan R, Rasmussen M, Gerstmann D, et al. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. *Am J Perinatol* 2004;21:109-119. ■

IN THE PIPELINE

• Millennium Pharmaceuticals has initiated EVEREST (Evaluation of Velcade [bortezomib] Employed as Retreatment for Efficacy, Safety, and Tolerability). This is a multicenter Phase IV clinical trial of bortezomib in **multiple myeloma** patients who have previously responded to bortezomib and relapsed following a treatment-free remission.

• Pharmacyclics has completed patient enrollment in its pivotal Phase III clinical trial of motexafin gadolinium (Xcytrin) injection for the potential treatment of **lung cancer patients with brain metastases**.

• Genta has announced that LR3001, an antisense compound directed against a gene known as c-myb, has received orphan drug designation from the FDA for the treatment of **chronic myelocytic leukemia**.

• AnorMED has initiated enrollment in a Phase

Ib/IIa trial to evaluate the potential of AMD070, an oral CXCR4 HIV entry inhibitor, in **HIV-infected patients**.

• The Gynecologic Oncology Group has initiated a Phase III clinical trial examining the ability of paclitaxel poliglumex (Xyotax) to maintain remission and prolong the survival of **ovarian cancer** patients.

• Cara Therapeutics has initiated dosing in a Phase I clinical trial for CR665, its novel drug candidate for the treatment of **postoperative pain**.

• MediciNova has enrolled patients in a Phase II clinical study with MN-001, a novel, orally administered **asthma** drug that was licensed from Kyorin Pharmaceutical Co.

• Vion Pharmaceuticals has commenced dosing the first patient on the Phase III pivotal trial of its anticancer agent VNP40101M (Cloretazine) in **relapsed acute myelogenous leukemia**.

• Human Genome Sciences has begun dosing patients in a Phase I clinical trial to evaluate the safety, tolerability, and pharmacology of CCR5 mAb in patients who are infected with **HIV-1**.

• ID Biomedical Corp. has completed the enrollment of 1,000 subjects for its Fluviral clinical trial intended to support accelerated approval in the United States.

• Theravance has announced that the FDA has granted fast-track designation to telavancin for the treatment of **hospital-acquired pneumonia** and **complicated skin and skin structure infections**.

• American Pharmaceutical Partners has announced that American BioScience has initiated enrollment in a Phase II study of ABI-007 (Abraxane) administered weekly in combination with trastuzumab (Herceptin) in first-line treatment of **metastatic breast cancer**.

• PharmaMar announced today that its marine-derived anti-cancer drug, trabectedin (Yondelis), has been granted orphan drug designation by the FDA for the treatment of **ovarian cancer**.

• Valentis has initiated patient dosing in a Phase IIb clinical trial to evaluate the safety and efficacy of VLTS-934, a poloxamer, in patients with peripheral arterial disease, specifically **intermittent claudication**.

• Kosan Biosciences has announced that its Phase II clinical trial of KOS-862 (Epothilone D) as monotherapy for patients with **metastatic breast cancer** will proceed to full enrollment of the study following the successful completion of the interim analysis.

• BioMarin Pharmaceutical has randomized the first patient in its Phase III clinical trial of sapropterin hydrochloride (Phenoptin), an investigational oral, small molecule therapeutic for the treatment of the genetic disease **phenylketonuria**. ■

New FDA Approvals

These drugs were recently approved by the FDA:

• ***Entecavir (Baraclude) by Bristol-Myers Squibb Co.*** The FDA has announced the approval of entecavir (Baraclude) tablets and oral solution for the treatment of chronic hepatitis B in adults. Entecavir slows the progression of chronic hepatitis B virus (HBV) by interfering with viral reproduction.

The FDA based its approval of entecavir on the results of three studies in which entecavir was compared to lamivudine. In all three clinical studies, patients treated with entecavir showed significant improvement in the liver inflammation caused by HBV and an improvement in the degree of liver fibrosis. In addition, a higher percentage of patients treated with entecavir showed significant improvement compared to lamivudine.

The major adverse events associated with the use of entecavir were of the type typically seen with HBV therapy. They include severe, acute exacerbation of hepatitis B after discontinuation of entecavir, headache, abdominal pain, diarrhea, fatigue, and dizziness. The labeling for entecavir states that patients who discontinue entecavir should be monitored at repeated intervals over a period of time for liver function. Bristol-Myers Squibb Co. has committed to conducting a large post-marketing study of entecavir to evaluate the risks of cancers and liver-related complications.

• ***A new indication for ropinirole (Requip) by GlaxoSmithKline.*** The FDA has approved ropinirole (Requip) to treat moderate-to-severe restless legs syndrome (RLS). The drug was first approved for Parkinson's disease in 1997.

Ropinirole was found to be effective for RLS in three randomized, double-blind placebo controlled studies in adults diagnosed with moderate-to-severe RLS. The studies measured

effectiveness of the drug using the International Restless Leg Syndrome scale, a patient-rated scale that measures different aspects of RLS including severity of muscle movement and discomfort, sleep disturbance, mood, and overall effect on quality of life. The Clinical Global Impression-Global Improvement scale also was used. This is an investigator-rated scoring of improvement following treatment. All three studies demonstrated a statistically significant difference between the treatment group receiving Requip and the group receiving placebo.

Common side effects reported in clinical trials include nausea, headache, and vomiting. The label for the drug also will include a caution that ropinirole has been associated with sedating effects, including somnolence, and the possibility of falling asleep while engaged in activities of daily living, including operation of a motor vehicle. Syncope or symptomatic hypotension may occur, particularly during initial treatment or dosing.

• ***Exenatide (Byetta) injection by Eli Lilly.*** Amylin Pharmaceuticals and Eli Lilly and Co. have announced that the FDA has approved exenatide (Byetta) injection as adjunctive therapy to improve blood sugar control in patients with Type 2 diabetes who have not achieved adequate control on metformin and/or a sulfonylurea. It is the first in a new class of medicines known as incretin mimetics and became available to pharmacies June 1.

In addition to approving exenatide for use as an adjunct to existing oral medicines, the FDA also stated that exenatide is approvable as a monotherapy for patients with Type 2 diabetes. Any additional data submitted to support a monotherapy indication is expected to receive a six-month review.

Exenatide is formulated for self-administration as a fixed-dose, subcutaneous injection given prior to the morning and evening meals. It will be made available in both a 5-mcg dose and a 10-mcg dose prefilled pen-injector device.

In three 30-week controlled trials, adverse events associated with exenatide were generally mild to moderate in intensity. The most frequently reported adverse event was mild-to-moderate, dose-dependent nausea. With continued therapy in most patients who initially experienced nausea, the frequency and severity decreased over time. Patients also should be advised that treatment with exenatide may result in a reduction in appetite, food intake, and/or body weight and that there is no need to modify the dosing regimen due to such effects. ■

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. Between 60,000 and 80,000 infants in the United States are diagnosed with respiratory distress syndrome each year, the majority of whom are born prematurely.
    A. True
    B. False

22. Premature infants often produce insufficient surfactant, resulting in:
    A. the collapse of alveoli (atelectasis).
    B. decreased functional residual capacity.
    C. increased dead space within the lungs.
    D. All of the above

23. Both poractant alfa and calfactant are indicated for the treatment of RDS in neonates equal to or less than 72 hours of age and for prophylaxis of premature infants younger than 29 weeks gestational age at significant risk for RDS.
    A. True
    B. False

24. Calfactant has which of the following advantages over poractant alfa:
    A. faster onset of action.
    B. longer duration of action.
    C. lower one-year cost.
    D. All of the above