AMERICAN HEALTH CONSULTANTS

DRUG UTILIZATION REVIEW

Pharmaceutical Care Across the Continuum

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# Informing patients about black box warnings and recalls can be difficult

*Notification is only as good as your database*

The Food and Drug Administration (FDA) has issued a new black box warning. If you are not doing your best to notify patients taking the drug, you may become liable, says one health system pharmacist.

Not many hospitals have established a formal system to handle black box warnings and recalls. Some post information around the facility. Others include information about it in publications sent to patients. Still others try to identify and notify physicians and pharmacists who have written or dispensed prescriptions for the medication with the black box warning.

"If we have a black box warning, we have been able to search our state Medicaid files to specifically look for the patients who are on the medication," says **Julie Kuhle**, RPh, senior vice president of Clinical and Quality Assurance Programs, Iowa Pharmacy Association in Des Moines. "We may then send out letters to pharmacists and physicians providing care to those patients."

The key is whether your system allows you to search for patients taking the drug, says **Barry A. Browne**, PharmD, coordinator of Drug Information Services, Scott & White Hospital in Temple, TX. "We have an integrated health care system with informatics capabilities to identify patients who are on these drugs. Stand-alone operations may not have the ability to identify and notify those patients and to notify medical staff."

Browne discovered the limitations of Scott & White's previous information system when Janssen Pharmaceutica added a black box warning to cisapride (Propulsid), which eventually was pulled off the market. A pediatrician in the health system became concerned about locating his patients who were taking the drug. Browne found that he could identify patients in the Scott & White Health Plan who were taking cisapride. Unfortunately, 50% or fewer of the health system's patients were covered by this health plan.

The health system sent a letter to the physicians, along with a list of their patients on the drug. Browne discovered that because of patients'

usual mobility, the physician list wasn't as precise as it could be. "The teaching point from this experience is that no matter what you do, it is only as good as the data you have," he says.

### *An upgrade in system and responsibility*

Scott & White then upgraded to an electronic medical record. Now the health system can identify all patients on a particular drug. "When a physician dictates his note at the end of the clinic visit, it goes into a searchable, central computerized repository. If we then want to know all of the patients in the year 2001 who were on the antidepressant nefazodone HCL (Serzone), we can pull up all the names of those patients and link them with a physician."

Because of the system's information-gathering capabilities, Browne now feels a medical and legal responsibility to inform patients of black box warnings and recalls. The health system's formal policy dictates that all appropriate physicians and patients be notified about black box warnings and recalls. "The specifics of how we do it differ depending upon the drug."

Recently, the health system notified patients of nefazodone's potential hepatotoxicity problem. "We are sending a letter to those patients on the drug and telling them about the black box warning. We are telling them that they need to come in and have blood work drawn. We phrase it by saying, '[This effect] is very rare, but to be careful, we want you to come in and have blood work drawn.' Any abnormal results will be followed up with the patient."

Browne also feels like Scott & White has an obligation to send out immediate notification to medical staff, to make them aware of the new black box warning and the drug's potential for hepatotoxicity.

"It could be a difficult situation if a patient received a drug from your pharmacy and you had the ability to retrieve the list of those patients from the last year, and you didn't do it." The letter may not have to say more than, "You need to contact your physician."

Browne advises against relying on patients to hear about the warnings and recalls through the lay press. That did not work in the case of many patients taking troglitazone (Rezulin), which had a black box warning added about hepatotoxicity and eventually was removed from the market.

"There have been a number of cases of patients who, after the black box warning was added, stayed on the drug, didn't have any liver monitoring, didn't know about the risk, and have filed suit," Browne says. "Relying on the warning being adequately publicized in the lay press would be a tenuous position if you had the ability, within 15 or 20 minutes, to produce a list of the patients who had been on that drug in your system in the last year."

### *Technology has limits*

Hospitals without electronic medical records, however, still have limitations in identifying patients on drugs that have black box warnings. One pharmacist says she sees limited information about patients' medications, even when she is working in an outpatient clinic in a hospital. "We don't see the inpatient chart when we see the patient in the clinic," says **Carla B. Frye**, PharmD, professional practice associate, professional practice and scientific affairs, American Society of Health-System Pharmacists in Bethesda, MD. "We don't always know [about the medications] unless the patient tells us." The situation won't be fixed until all the medical records are electronic, she says.

A community pharmacist also depends on the correct information being loaded into his database. "Although I am still ultimately responsible for knowing black box warning information, the system has to be designed so it gets that information for me when I am screening that prescription," says **Dennis Bryan**, RPh, pharmacy manager at Albertson's in Chicago.

The possible adverse effects should be caught even before they reach the pharmacist, he adds. "It's a technology issue. The Palm Pilots are here; the database interlinks are here. It's just a matter of money [to implement them]." ■

## *COMING IN FUTURE MONTHS*

- FDA approves a dosing system
- Drug company mergers squeeze drug availability
- Multitasking and pharmacists' personalities
- A cost-cutting success story
- News from the American Stroke Association meeting

# A tale of insulin warnings

Insulin manufacturers say patients shouldn't be switched from one type of insulin to another without proper medical supervision. Marketplace politics, however, have threatened to diminish the warnings, a pharmacist claims.

**R. Keith Campbell**, RPh, FAPhA, CDE, professor and associate dean of pharmacy practice at Washington State University in Pullman, watched in dismay when he says at least one drug manufacturer encouraged pharmacists to switch patients to its brand of insulin. A diabetic himself, he repeatedly has informed colleagues of the possible legal and clinical consequences of making such a switch.

Campbell first wrote an article when he heard that sales representatives from the drug manufacturer were telling pharmacists that it was "ok" to switch patients from Eli Lilly insulin to its brand. Many pharmacists then turned to diabetic specialists for their opinion. "The answer was, 'It probably won't be too big of a deal for most patients. But if you change someone and you don't tell the patient and the physician and something goes wrong with the patient, you would legally be dangling in the wind.'"

Switching is in a big gray area of legality and clinical impact, he explains. "There are different levels of protamine and different quality of protamine from one brand to another. There are different preservatives."

Campbell's article looked at the issue of switching insulins and talked about the black box warnings. "I said that if you are going to do this, you have to talk to the patient about the switch." He says the manufacturer then offered legal help for anyone who switched a patient and got sued — as long as the pharmacist followed the guidelines in the package insert. Campbell wrote another article advising that the offer seemed deceptive. "If you read the package insert of the product, it says 'Warning, do not switch.'"

Now some retail pharmacy chains are being offered their own brand of insulin, a change that has upset some chain pharmacy managers, Campbell says. For example, Nova Nordisk provides Wal-Mart with ReliOn insulin. "If you go to a Wal-Mart pharmacy, they would switch you to their brand," Campbell says. "That would save you a few dollars." The black box warning, however, remains.

"The stupidity of the situation is that we have a shortage of pharmacists. They are overburdened with counting and pouring and are having a hard time doing disease state management and counseling patients about following the standards of care," Campbell says. "If they are going to do the switch right, they have to take the time to call the doctor." Contacting the physician costs the chain the time of the pharmacist. That reduces the profit margin of an already highly competitive product.

Lilly wrote a strongly worded statement in response to Wal-Mart pharmacists possibly switching Lilly insulin patients to ReliOn. "All insulin brands are NOT the same. We at Lilly firmly believe that a pharmacy should not switch your brand of insulin without your physician's involvement," the statement says. "The *type* and *brand* of insulin you use has been carefully selected by your personal physician, based on your diabetes history and need for blood sugar control. Thus, your physician — not your pharmacist — is the medical professional who should be primarily responsible for any changes in your insulin therapy. In fact, a statement mandated by the Food and Drug Administration on every insulin product cautions that changing type or manufacturer of insulin should be done only under medical supervision."

Physicians also are upset that they may prescribe a brand of insulin, only to have the patient switched without their knowledge. If something happens to the patient because of the switch, the physicians wouldn't know the reason unless they saw the patient's bottle, Campbell says.

There also is concern of ending up with 20 brands of insulin that can confuse everyone. Wal-Mart has to carry more inventory for patients who refuse to switch brands of insulin, Campbell adds. "If I go to Wal-Mart and get insulin, I am going to request my own brand. I'm not willing to change. That means they have to carry twice as many bottles of insulin."

A cost-impact study would show Wal-Mart that switching patients to its own brand of insulin costs them money, he says. "One HMO thought it would save about $30,000 a year by switching. They then tracked all the expenses and it cost them $67,000 to educate all the health care providers and all the pharmacists and the patients about the switch." ■

# Usefulness of black box warnings is questioned

*System could do more to alert pharmacists*

Black box warnings may be the strongest type of labeling. That doesn't mean they are well-publicized to the health care community, pharmacists say.

Black box warnings have been created to alert and inform health professionals of potentially severe, life-threatening adverse events associated with a particular medication. In addition, black box warnings convey important safety information as well as revised prescribing instructions.

When a black box warning is issued, the Food and Drug Administration (FDA) often posts information about it on the FDA web site. The media often report it, too, depending on the severity of the warning. The FDA and drug manufacturer also send out "Dear Doctor" letters to health care providers that address the warning.

Not everyone is impressed with the letters. "The 'Dear Doctor' system that the FDA and the manufacturers use doesn't seem that effective to me," says **Barry A. Browne**, PharmD, Coordinator of Drug Information Services, Scott & White Hospital, Temple, TX. "Often it comes in the same type of envelope as other drug company propaganda, and sometimes it doesn't get opened."

Once the manufacturer and/or the FDA send out the initial warning or recall information, it is added to the package insert, too. Unless pharmacists have information systems that continue to notify them of the warning when they dispense the drug, however, some lesser-publicized warnings may lose their priority — especially since some black box warnings pertain to small segments of the population.

Access to patient information can give hospital and health care system pharmacists a better handle on black box warnings than their retail counterparts. "Hospital pharmacists can check the progress notes the physician wrote. They can look at lab results. They can look at the patient's history," says **Carla B. Frye**, PharmD, professional practice associate, professional practice and scientific affairs, American Society of Health-System Pharmacists, Bethesda, MD. "Medication order review is a part of every new order."

One pharmacist is angry that black box warnings are needed at all. "Sometimes I get the feeling that the black box warnings are more like a last-ditch effort on the part of the manufacturer to try and keep its product on the market before it gets pulled," says **Dennis Bryan**, RPh, pharmacy manager at Albertson's in Chicago. Bryan also spent 20 years working in a hospital pharmacy setting.

"The FDA says it has issues with the product; you need to do something about it. The manufacturer creates a black box warning and hopes that it plugs the hole in the dam, so to speak. If the problem continues, then the drug is going to get pulled."

He faults a clinical research system that allows Phase III trials to involve only small populations. "When the drug hits the general population where the numbers exponentially increase, some of these problems start popping up."

If black box warnings are needed, why was the drug prescribed in the first place, Bryan asks. "If there is indeed that level of a problem, why isn't something more stringent done instead of passing it down the ladder and putting someone else at risk — not only the patient, but the pharmacist, too?" This indicates the influence of drug manufacturers, he says.

He uses clozapine (Clozaril) as an example of what manufacturers can do to further reduce risk. Clozapine is used in psychiatric patients, but it can adversely affect white blood cell counts.

"That particular product has to come with a screening tool that says health care providers have done a blood work-up within so many days of the issue of that prescription," Bryan says. "In this case, that brings ultimate protection because the tool jumps out at us. The manufacturers don't like that level of warning because it diminishes the amount of prescriptions being written." ■

# Foreign-born pharmacy students find challenges

*Educator tries to ease their transition into school*

As hospitals continue to report severe pharmacist shortages, the pharmacy field is wide open for many foreign-born students. But one educator finds that cultural factors can challenge them in school.

Nova Southeastern University College of Pharmacy in Fort Lauderdale, FL, has expanded

its classes based on the recommendation of the American Council on Pharmaceutical Education (ACPE) in Chicago. Its traditional class now has about 160 students, up from 120.

Of the students in the first- and second-year classes now, about 55% were born outside the United States, in places such as Romania, Cuba, and Trinidad, says **Carsten Evans**, MS, PhD, assistant dean for professional affairs. "A great percentage had not learned English by the time they were 8 years old."

As a group, they sometimes take more time to learn certain courses, especially ones with a math base, such as statistics and pharmacokinetics, he says. He also has found that the majority of students taking remedial courses are foreign-born.

The struggles are not from a lack of hard work, Evans explains. Instead, they can result from entering a compressed, fast-paced program while trying to deal with differences in culture.

Communication is one challenge pharmacy schools face with this kind of diversity, says **Jeffrey W. Wadelin**, PhD, ACPE's executive associate director. "Many of the schools have gone to using not only the TOEFL [Test of English as a Foreign Language] but the test of spoken English as an university entrance requirement." These tests attempt to assure at least a minimal level of competence in English as a second language.

### *Pre-empt the problems*

When Evans greets pharmacy students in the first year, he attempts to ward off future problems. For example, he tries to help supporting family members understand the pressures the pharmacy students face, especially in the first year of the program. Many of these students have attended community colleges and have not experienced the pace of a compressed program.

The family members know that the students will attend classes from 8 a.m. until noon. They don't realize that the students also will be studying much of the remainder of the day and on the weekends. At least three female students divorce every year because the spouse didn't expect the time commitments, Evans says.

For this reason, Evans encourages students to bring their family members to school so they can see the pressure firsthand. "Let them sit in a class for just an hour. Take them to the library. I try to get them to involve the family."

He encourages students not to work, as well, at least during the first year. "It is essential that they don't work. It is a rare exception that someone can work and go to a professional school."

First-year students do go on-site and spend a couple of hours with a preceptor who has been assigned to them. "It's like working without the responsibilities," Evans says.

Some foreign-born students find the last year a challenge, too, Wadelin says. "Most of the last year in the program is spent in actual pharmacy practice experiences, applying the knowledge that students have gained over the first three years." If the practice model in the students' home country is significantly different than that of the United States, the students may struggle with how the health care system works and how pharmacy fits in with medicine in this country. ■

## Pharmacist shortages remain high, survey says

A good pharmacist is still hard to find. According to recent data recorded in "The Healthcare Workforce Shortage and Its Implications for America's Hospitals," the mean vacancy rate for pharmacists is 12.7%. Nineteen percent of hospitals reported severe shortages (more than 20% vacancy rate) of pharmacists.

The survey was faxed to 5,980 hospitals nationwide; it was conducted during late August and early September 2001. Twenty-five phone interviews were conducted with hospital CEOs, nurses, pharmacists, and human resources executives.

A pharmacy director at a prestigious Los Angeles medical center told the researchers that it takes two years to recruit for a night pharmacist. The operations director at another California medical center has been recruiting pharmacists for eight months and has had no applicants.

This report was produced by First Consulting Group for the American Hospital Association, the Association of American Medical Colleges, the Federation of American Hospitals, and the National Association of Public Hospitals and Health Systems. Copies of the report are available on all of these organizations' web sites. ■

# NEWS BRIEFS

## FDA recounts 2001 approvals

During 2001, the Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research approved 66 new drugs, 24 of which were new molecular entities (NMEs) with ingredients never before marketed in the United States.

Ten of the 66 new drugs (seven of the NMEs) received priority status and were reviewed and approved in the median time of six months. The other 56 approvals were reviewed under a standard status. Their median review time was 12 months (15.7 months for the 17 standard NMEs), and their median total approval time was 14 months (19 months for the NMEs).

The FDA's Center for Biologics Evaluation and Research reviewed a total of 16 complex biological license applications (BLAs) in the median time of 13.8 months and approved them in the median time of 20.3 months. Two of the BLAs, which were classified as priority products, were reviewed in the median time of 11.5 months and approved in the median approval of 13.2 months. Approvals of 10 of the BLAs, six BLA supplements for new or expanded uses, and three premarket approval applications (PMAs) were considered major actions. Most of the products approved by CBER were designed to detect or treat infectious diseases.

Finally, FDA's Center for Devices and Radiological Health approved 54 PMAs, of which 24 were for devices with novel technologies or new uses. The median total approval time for the 54 products was 11.3 months. ▼

## Study: Aspirin as effective as warfarin/aspirin

A new study appearing in the Feb. 5 issue of *Circulation* found that aspirin alone was as effective as aspirin combined with warfarin, a prescription blood thinner, in reducing the risk of a recurrent heart attack.

The open-label study compared the efficacy of warfarin (target international normalized ratio 1.5-2.5 IU) plus aspirin (81 mg daily) with the efficacy of aspirin monotherapy (162 mg daily) in reducing the total mortality in 5,059 patients enrolled within 14 days of infarction and followed for a median of 2.7 years. Secondary endpoints included recurrent myocardial infarction (MI), stroke, and major hemorrhage.

Four hundred thirty-eight of the 2,537 patients assigned to the aspirin group died, as did 444 of the 2,522 patients assigned to the combination group. Recurrent MI occurred in 333 patients taking aspirin and in 33 patients taking the combination therapy. Stroke occurred in 89 patients taking aspirin and in 79 patients taking the combination therapy.

This research follows another study published last month in the *British Medical Journal*, which indicated that a significantly lower strength of aspirin — between 75 and 150 milligrams — is just as effective as regular strength 325 mg aspirin, for long-term cardiovascular therapy. This is significant

because higher doses of aspirin, while no more effective, are associated with significantly higher risk of serious gastrointestinal side effects. ▼

## HHS approves Medicaid expansion prescription in IL

Health and Human Services Secretary Tommy G. Thompson has approved a demonstration program in Illinois that will give an estimated 368,000 low-income seniors prescription drug coverage through the Medicaid program. He also launched a new initiative to make it easier for other states to take similar steps to aid seniors.

In addition, Secretary Thompson announced a model demonstration application form, Pharmacy Plus, which will allow states to immediately expand Medicaid coverage for prescription drugs to Medicare beneficiaries and other individuals with family incomes up to 200% of the federal poverty level. The streamlined application, available electronically, is designed to allow states to move quickly to implement effective programs expanding prescription drug benefits to low-income people.

Eligibility for the Illinois demonstration program would be limited to individuals and families with incomes up to twice the federal poverty level ($23,220 for a family of two). Individuals could pay an annual enrollment fee of $5 or $25, depending on their income levels.

In Illinois, Medicaid would pay virtually all the costs of prescriptions up to a total of $1,750 each year, with enrollees responsible only for a copayment of $3 or less for each prescription. Medicaid would pay roughly 80% of the costs of additional prescriptions, with enrollees paying 20% plus the co-payment. ▼

## Link between physicians and drug companies

A survey of doctors who wrote treatment guidelines for common diseases such as diabetes and arthritis found that most had ties to drug companies, but few thought those ties influenced their recommendations.

However, researchers evaluating the survey, published in the Feb. 6 *Journal of the American Medical Association*, suggest that academicians and physicians may underestimate the impact of their drug company connections. "Unfortunately, bias may occur both consciously and subconsciously, and therefore, its influence may go unrecognized," the researchers say.

Among those who responded to the survey, 58% said they had received research funding from drug companies and 38% said they had served as company employees or consultants. In addition, 59% of the doctors said they had ties to pharmaceutical companies whose drugs were considered in the drafting of the guidelines they wrote.

Of these authors, 96% said the relationships were formed before the guidelines were created. Only 7% thought the ties affected their own guideline recommendations, although 19% thought such ties influenced their co-authors' recommendations.

The researchers suggest that the results of this study be interpreted cautiously because of its relatively low response rate. The results were based on a survey mailed to 192 doctors involved with creating

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### Editorial Questions

Questions or comments? Call **Paula Cousins** at (816) 960-3730.

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Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcpub.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@ahcpub.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@ahcpub.com).
Production Editor: **Emily Palmer**.



THOMSON
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44 "clinical practice guidelines" for treating diseases. The guidelines were for the treatment of asthma and chronic obstructive lung disease, cardiovascular disease, heart failure, depression, diabetes, peptic ulcers, high cholesterol, high blood pressure, osteoarthritis, and pneumonia. Only 100 doctors provided usable responses, and whether they accurately assessed drug companies' influence over them is not known, the survey authors said. ▼

# Training on adverse drug reactions found lacking

Only a small percentage of the curriculum at many U.S. medical schools is dedicated to recognizing and reporting adverse drug reactions, says a study conducted at Georgetown University Medical Center and published in the January 2002 issue of *Clinical Pharmacology & Therapeutics*.

Researchers surveyed the responses of 79 directors of third-year internal medicine clerkships and the directors of 200 internal medicine residency programs and found that 53% of the medical schools did not have clinical rotations that included clinical pharmacology or adverse drug reactions training. Of the schools that did offer clinical pharmacology and adverse drug reactions curriculum during clinical training years, only 8% of these rotations were mandatory; the others were elective programs that offered 11 hours of didactic lectures.

In addition, 29% of inpatient and 55% of ambulatory programs provided residents with little or no opportunity for contact with clinical pharmacists. Sixty percent of responding programs did not have hospital or clinic electronic systems designed to detect drug interactions. Twenty-five percent of program directors have never reported an adverse drug reaction; 23% believed it was difficult to report; and 18% of programs did not review adverse drug reactions that occurred in the hospital during mortality and morbidity conferences. ■




• InterMune has begun enrolling patients in its Phase II clinical trial of Interferon gamma-1b (Acti-mmune) injection for the treatment of **severe liver fibrosis, or cirrhosis**, caused by hepatitis C virus.

• Transgene has initiated a Phase I clinical trial of its Adeno Interferon gamma (Ad-IFNg) immunotherapeutic product candidate for the treatment of **cutaneous lymphoma**.

• AstraZeneca announced that the FDA has granted Fast-Track Designation for its drug anastrozole (Arimidex), for the treatment of postmenopausal women with early **breast cancer**.

• Peptor will begin a multicenter Phase II clinical trial in the United States of its experimental diabetes drug DiaPep277. The peptide-based drug has been shown in a published study to stop the progression of **Type 1 diabetes**.

• Alexion Pharmaceuticals and its partner Procter & Gamble Pharmaceuticals have completed enrollment in their first Phase II **acute myocardial infarction** trial with pexelizumab. The 900-patient Phase II trial is known as the COMPLY trial, or "COMPlement Inhibition in Myocardial Infarction Treated with ThromboLYtics."

• Genaera Corp. has initiated a clinical trial for squalamine, its antiangiogenic agent, in **fibrodysplasia ossificans progressiva**. ■

DRUG CRITERIA & OUTCOMES™

# Exogenous Lung Surfactants in the Management of Neonatal Respiratory Distress Syndrome

By **Monique Cannon**, PharmD
Written as a PharmD candidate at Auburn University School of Pharmacy, Auburn, AL

## *Surfactant preparations*

• Beractant (Survanta) — natural bovine lung extract

• Calfactant (Infasurf) — natural surfactant from calf (bovine) lungs

## *Objectives*

Evaluate and compare the efficacy, safety, and costs of the two most commonly used exogenous surfactants (beractant and calfactant) in respiratory distress syndrome (RDS).

• Select an exogenous surfactant to be used primarily in the Huntsville Hospital System in the prevention and treatment of RDS.

## *Surfactant compositions*

Both beractant and calfactant use bovine lung as a source. They are similar in that they both contain phospholipids, neutral lipids, fatty acids, and hydophobic surfactant apoproteins. However, the proportions of the active ingredients are different.

## *Significant differences in constituents*

**Beractant**: Lung tissue mince extract with a modified lipid profile.

Total protein: 1% of total phospholipids (wt / wt)

Surfactant apoprotein: C (SP-C) 99%

Surfactant apoprotein: B (SP-B) trace amounts, < 0.5%

Beractant contains phospholipids from lung cells as well as lung surfactant. It has higher levels of nonphosphatidylcholine, and these phospholipids limit the lowest surface tension attainable in bovine surfactant preparations.

The step in the beractant process that removes cholesterol likely removes the SP-B.

**Calfactant**: Extract of the surfactant lavaged from the alveolar spaces (contains the same lipid profile as natural surfactant).

Cholesterol: 5%

Total protein: ~2% of total phospholipids (wt / wt)

SP-C: 60%

SP-B: 40%

## *Indications*

Both products are indicated for the prevention and treatment ("rescue") of RDS in premature infants.

**Beractant:**

Prophylaxis — In premature infants weighing less than 1,250 g or with evidence of surfactant deficiency. Give as soon as possible, preferably within 15 minutes of birth.

Treatment — In infants with RDS confirmed by X-ray and requiring mechanical ventilation. Give as soon as possible, preferably within 8 hours of birth.

**Calfactant:**

Prophylaxis — In premature infants younger than 29 weeks of gestational age and at significant risk for RDS. Administration should be as soon as possible, preferably within 30 minutes of birth.

Treatment — In infants younger than 72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

## *Mechanism of action*

Endogenous lung surfactant is essential for effective ventilation because it modifies alveolar surface tension, stabilizing the alveoli. Lung surfactant deficiency is the cause of RDS in premature infants. Exogenous surfactants (calfactant and

beractant) restore surface activity to the lungs of these infants by adsorbing to the surface of the air-liquid interface, modifying surface tension similarly to natural lung surfactant.

### *Dosage*

**Beractant**

- 25 mg phospholipid / mL.
- 4 mL / kg of birth weight (100 mg of phospholipid / kg).
- Four doses can be administered in the first 48 hours of life.
- Doses should be given no more frequently than every six hours.
- The total calculated dose is divided into four quarter-doses (1 mL / kg aliquots), each given with the infant in a different position.

**Calfactant**

- 35 mg phospholipid / mL.
- 3 mL / kg of birth weight (105 mg of phospholipid / kg).
- Usually dosed every 12 hours for a total of up to three doses (as frequently as every six hours has been used for a total of four doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a $PaO_2 \leq$ 80 torr).
- The total calculated dose is given in two aliquots of 1.5 mL / kg each, given with the infant in a different position.

### *Administration*

Dosing procedures are the same between the products, with the exception of:

- The total beractant dose is divided into four aliquots; the total calfactant dose is divided into two aliquots.
- Calfactant does not require warming before administration.

The following applies to both products:

- For intratracheal adminstration only; these products should not be instilled into a mainstream bronchus.
- Store refrigerated (2-8°C).
- If settling occurs during storage, swirl the vial gently (do not shake) to redisperse.
- Date and time should be recorded on the vial whenever removed from the refrigerator.
- Unopened, unused vials that have been warmed to room temperature may be returned to the refrigerator within 24 hours of warming, and stored for future use.
- Surfactant preparations should not be removed from the refrigerator for more than 24 hours or warmed and returned to the refrigerator more than once.
- Vials are single-use and should be entered only once.
- Reconstitution or sonication is not required before use.
- Draw dose into a plastic syringe through a large-gauge needle (at least 20 gauge). Do not filter.
- Do not suction the infant for one hour after dosing unless signs of significant airway obstruction are present.

### *Beractant only*

Before administration, beractant vials should be warmed by standing at room temperature for at least 20 minutes or hand warmed for at least 8 minutes. Artificial warming methods should not be used.

### *Overdosage*

There have been no reports of overdosage with either product.

**Beractant** — Overdosage may result in acute airway obstruction. Treatment should be symptomatic and supportive.

**Calfactant** — Overdosage would result in overloading the lungs with an isotonic solution. Ventilation should be supported until clearance of the liquid.

### *Pharmacokinetics*

Marked improvements in oxygenation may occur within minutes of administration **(see Table 1, below)**. Therefore, frequent and careful clinical observation and monitoring of systemic oxygenation are essential to avoid hyperoxia. These values are not reported in the package insert, but are listed in a Drugdex drug evaluation from Micromedex that includes references.

### *Distribution*

Endotracheal administration — surfactants are distributed uniformly to all lobes of the lung, distal

**Table 1. Onset/Peak/Duration**

| Drug | Onset of Action | Peak Response | Duration of Action |
|---|---|---|---|
| Beractant treatment | 30 minutes | 3-4 hours | 48-72 hours |
| Calfactant prophylaxis | 1-2 hours | N/A | 24-72 hours |
| treatment | 1-4 hours | N/A | 24-72 hours |

airways, and alveolar spaces; gravitation to the dependent areas of the lung does not occur.

Surfactant concentrations are highest at the alveolar air-liquid surface, where it exists as a monolayer.

More even distribution is observed following prophylactic administration at birth as opposed to after birth when lung fluid rapidly decreases.

### *Metabolism*

The metabolism of these products is not completely understood — it is thought to occur in the lungs, on the surface of alveoli or small airways.

Metabolism also may occur following uptake by alveolar type II pneumocytes.

Recycling may be a dominant pathway by which surfactant is taken up by type II pneumocytes and reused.

### *Contraindications*

There are no known contraindications to calfactant and beractant therapy.

### *Precautions/warnings*

Precautions and warnings are printed in the package inserts, but are not all representative of the comparative clinical trial of beractant vs. calfactant.

Both agents are for intratracheal use only.

Foreign proteins in bovine surfactants potentially can induce protein sensitization, and the risk of immunization may increase with retreatment. However, no cases of immunologic or allergic phenomena have been described.

Administration of exogenous surfactants often rapidly improves oxygenation and lung compliance. Therefore, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.

Transient episodes of reflux of surfactant into the endotracheal tube, cyanosis, bradycardia, or airway obstruction have occurred during the dosing procedures. These events require stopping administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing can proceed with appropriate monitoring.

### *Beractant*

Rales and moist breath sounds may occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in beractant-treated infants was observed in the controlled clinical trials. The increased risk of sepsis among beractant-treated infants was not associated with increased mortality. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Incidences of sepsis in the beractant vs. calfactant clinical trial were similar and not statistically significant.

Use in infants weighing less than 600 g or greater than 1,750 g at birth has not been evaluated in controlled trials.

No information is available on the effects of doses other than 100 mg phospholipids / kg, more than four doses, dosing more frequently than every six hours, or administration after 48 hours.

### *Calfactant*

When repeat dosing was given in the calfactant vs. colfoseril palmitate (Exosurf) trial, transient episodes of cyanosis, bradycardia, reflux of surfactant in the endotracheal tube, and airway obstruction were observed more frequently among infants in the calfactant-treated group. Incidences of cyanosis, bradycardia, reflux of surfactant into the endotracheal tube, and airway obstruction in the beractant vs. calfactant clinical trial were similar and not statistically significant.

An increased proportion of patients with both intraventricular hemorrhage and periventricular leukomalacia was observed in calfactant-treated infants in the calfactant vs. colfoseril palmitate controlled trial. These observations were not associated with increased mortality. (These events were not reported in the beractant vs. calfactant clinical trial.)

Data from controlled trials on the efficacy of calfactant are limited to doses of approximately 100 mg phospholipid / kg body weight and up to a total of four doses.

### *Adverse effects*

The percentages of adverse effects associated with the use of calfactant that are listed in the package insert are those that occurred in a trial comparing colfoseril palmitate and calfactant **(see Table 2, p. 4)**. In this trial, calfactant was administered in the same manner as colfoseril palmitate, causing over-treatment and a higher incidence of adverse effects.

Incidences of adverse effects between calfactant and beractant were similar and not statistically

significant in the comparative clinical trial.

### *Hydrophobic apoproteins as constituents of exogenous surfactants*

**Background.** The content of surfactant proteins SP-B and SP-C in exogenous surfactants is a distinguishing feature among these products. SP-B is believed to enhance the absorption of the major phospholipid, dipalmitoyl phosphatidylcholine (DPPC), to the air-liquid interface and promote film spreading. It also may contribute to metabolic behavior.

**Study design.** Biophysical properties and physiologic effects of three exogenous surfactants (calfactant, beractant, and colfoseril palmitate) were compared in excised lungs to determine the importance of the hydrophobic proteins SP-B and SP-C.

**Discussion/conclusions.** Results of this study show that hydrophobic surfactant apoproteins SP-B and SP-C are important components of exogenous surfactant preparations.

All three surfactants studied contain DPPC as a major constituent.

Significant evidence supports that DPPC (a rigid saturated phospholipid) is the component primarily responsible for lowering surface tension to the low levels of < 1 mN / m.

DPPC can lower surface tension to this extent only if it reaches the air-liquid interface and subsequently is compressed in a surface film.

Though DPPC adsorbs poorly on its own, the hydrophobic surfactant apoproteins have been shown to be highly effective in enhancing the adsorption process.

**Study limitations/weaknesses.** The calfactant formulation used was composed of 30 mg phospholipid / mL, but the available product formulation contains 35 mg phospholipid / mL.

Pressure-volume mechanics studies were done using excised, lavaged rat lungs. Therefore, the possibility of the positive interactions between the exogenous surfactants with endogenous surfactant (usually present in patients) cannot be determined.

### *Surfactant Protein-B supplementation improves in vivo function of a modified natural surfactant*

**Background**. SP-B and SP-C are critical for surface adsorption and lowering surface tension. Evidence that demonstrates the significance of SP-B in surfactant includes: 1) antibodies to SP-B can cause severe respiratory failure and 2) a genetic deficiency of SP-B causes lethal respiratory failure in term infants. Can beractant be improved by adding surfactant proteins?

**Study design.** The effect of the addition of SP-B or SP-B and SP-C (SP-BC) to beractant was evaluated in 27-day gestation preterm rabbits. Calfactant and beractant (with and without positive end-expiratory pressure [PEEP]) also were compared.

Measured parameters included:

- Ventilatory pressure requirements
- Expiratory time constants
- Dynamic compliance
- Pressure-volume curves
- Lung volume

**Results.** Results are reported in **Table 3, below**.

For all the measurements made with 3 cm $H_2O$ PEEP, the addition of 2% SP-B (Chl) or 3% SP-BC (Chl) enhanced the function of beractant to be equivalent to that of sheep surfactant.

Addition of 2% SP-B ($H_2O$) did not improve dynamic compliance or the expiratory time constant at 15 min of ventilation, indicating that the method of addition (water or chloroform) of SP-B to beractant was important.

For all measurements made with 0 cm $H_2O$ PEEP, beractant + 2% SP-B (Chl)

**Table 2. Adverse effects**

| | Beractant | Calfactant |
|---|---|---|
| Cardiovascular | bradycardia (11.9%) | bradycardia (34%); cyanosis (65%) |
| Respiratory | oxygen desaturation (9.8%); reflux of surfactant into endotracheal tube (< 1%) | airway obstruction (39%); reflux of surfactant into endotracheal tube (21%) |

**Table 3. Study results**

| Parameter | Beractant | Calfactant |
|---|---|---|
| Adsorption | 28 mN/m | 22 mN/m = natural lung surfactant |
| Surface tension | < 2 mN/m | < 1 mN/m |
| Pressure-volume mechanics | Able to restore mechanics by about 50% | Able to restore mechanics almost completely to normal (prelavage levels) |

**Table 4. Results of the treatment arm**

| Parameter | Calfactant (n = 303) | Beractant (n = 305) | P Value |
|---|---|---|---|
| Change in $FIO_2$ after first dose | -18.3 ± 21.1 | -13.0 ± 20.0 | 0.01 |
| Number of Surfactant doses: | | | |
| only 1 dose | 30% | 34% | |
| only 2 doses | 27% | 21% | |
| only 3 doses | 21% | 12% | |
| 4 or more doses | 22% | 33% | 0.002 |
| Dose intervals: | | | |
| hours dose 1 to dose 2 | 13 ± 11 h | 10 ± 9 h | < 0.001 |
| hours dose 2 to dose 3 | 13 ± 11 h | 9 ± 5 h | < 0.001 |
| hours dose 3 to dose 4 | 12 ± 11h | 8 ± 5 h | 0.006 |
| Time-weighted averages: (0-72 hours) | | | |
| $FIO_2$ | 41 ± 16 torr | 44 ± 20 torr | 0.03 |
| Mean airway pressure | 5.9 ± 2.8 cm $H_2O$ | 6.4 ± 3.1 cm $H_2O$ | 0.04 |

performed similarly to sheep surfactant and better than beractant alone or beractant + 0.5% SP-B (Chl).

On 0 cm $H_2O$ PEEP, calfactant performed better than beractant at all measured parameters (all with statistical significance, $P < 0.05$).

**Discussion/conclusions.** Addition of 2% SP-B (Chl) or 3% SP-BC (Chl) to beractant augments its short-term pf performance to be equivalent to that of sheep surfactant.

All indicators of function became essentially equivalent to those of sheep surfactant. Compliance improved with or without PEEP, expiratory time constants became longer, and pressure-volume curves were superimposable.

The results of this study are consistent with the critical role of SP-B in surfactant function.

### *Comparison of calfactant to beractant in RDS*

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

Treatment arm: infants weighing less than 2,000 g at birth (no minimum) and less than 48 hours of age; with radiographically confirmed RDS requiring endotracheal intubation; and with an $FIO_2 \geq 0.4$, $PaO_2 < 80$ torr, or an a/A oxygen ratio of $\leq 0.22$.

Prevention arm: infants that delivered before 30 weeks gestation and weighed less than 1,250 g at birth or were younger than 15 minutes old.

Administration, storage, and dispensing followed the beractant package insert. Both treatments were administered at the recommended dose for beractant of 100 mg/kg. A special 25 mg/mL concentration of calfactant was used to maintain masking.

**Results.** Results are summarized in **Table 4 (treatment arm), left, and Table 5 (prevention arm), below**. In the treatment arm, no significant differences were noted in the incidence of mortality, chronic lung disease, dosing related events, or complications of prematurity. In addition, infants receiving calfactant required significantly less oxygen and had significantly lower mean airway pressures within one hour of administration.

In the prevention arm, beractant infants required more days of intermittent mechanical ventilation and oxygen supplementation, primarily because of the survival of those weighing less than 600 g at birth. These events data from the prevention arm are skewed due to the unusually high survival rate of those babies weighing less than 600 g in the beractant group. There were no significant differences in the incidence of adverse events, survival to 36 weeks, postmenstrual age without the need for oxygen supplementation, or dosing complications.

**Discussion/conclusions.** The treatment arm showed that calfactant, when administered according to the beractant protocol, produced a greater initial improvement in respiratory status that was better sustained at every dose. This was evidenced by lower oxygen and mean airway pressure (MAP) and by longer intervals between doses.

**Table 5. Results of the prevention arm**

| Parameter | Calfactant (n = 180) | Beractant (n = 194) | P Value |
|---|---|---|---|
| Baseline birth weight | 891 ± 221 g | 845 ± 205 g | 0.04 |
| Dose intervals | | | |
| Hours dose 1 to dose 2 | 15 ± 12 h | 12 ± 12 h | 0.10 |
| Hours dose 2 to dose 3 | 18 ± 19 h | 11 ± 8 h | 0.005 |
| Hours dose 3 to dose 4 | 17 ± 16 h | 11 ± 8 h | 0.04 |
| Duration of intermittent mechanical ventilation | 20 ± 22 d | 27 ± 26 d | 0.012 |
| Duration of supplemental oxygen | 36 ± 39 d | 46 ± 48 d | 0.02 |

**Table 6. Event reports of the prevention arm**

| | Calfactant (n = 180) | Beractant (n = 194) | P Value |
|---|---|---|---|
| Alive at discharge | 86 % | 92% | 0.06 |
| Birth weight < 600 g; alive at discharge | 37% | 74% | 0.007 |
| Respiratory Distress Syndrome deaths | 7% | 2% | 0.01 |

Also, there were fewer patients who required the full calfactant treatment course.

The prevention arm showed that beractant-treated infants had longer duration of mechanical ventilation and oxygen supplementation, most likely as a result of an unprecedented survival rate in those weighing more than 600 g.

The survival rate of this subset of beractant infants (13 out of 19, 74%) is probably not reproducible because all other published data report that a majority of infants weighing less than 600 g die, whether treated with surfactant or not.

Differences between surfactants in biophysical testing and animal models with virtual surfactant depletion are difficult to document in a clinical trial in which almost all patients have endogenous surfactant. It has been proposed that all surfactant drugs, in addition to their independent surfactant activity, interact with existing endogenous surfactant and may serve as substrate for improved endogenous production.

The effect of any surfactant is a combination of surfactant activity, its interaction with endogenous surfactant, and the time for adequate endogenous material to be secreted.

**Study limitations/weaknesses.** Study was funded by ONY, the manufacturer of calfactant. Because of the unprecedented survival of those babies weighing less than 600 g in the beractant-treated prevention arm, the results were skewed and therefore less applicable.

### *Potential medication error?*

In the event that calfactant is chosen as the primary exogenous surfactant used in the Huntsville Hospital System, dosing errors could possibly occur with the change.

With the slight difference in dose, (calfactant dose = 3 mL / kg; beractant dose = 4 mL / kg) an infant weighing 1,400 g may receive a dose of 5.6 mL instead of 4.2 mL. This may not seem significant, but in premature infants this is substantial (33% over the correct dose). Due to the possibility of this error, educational efforts for those who will be dosing / administering calfactant are imperative.

### *Huntsville Hospital cost/usage*

Over the past 12 months, Huntsville Hospital used 348 vials of beractant (146 x 4 mL vials, 202 x 8 mL vials), with total beractant costs of more than $120,000. The manufacturer of calfactant, however, provides an approximate one-month supply of the drug at no cost as a "trial supply." An additional 5% cost reduction is offered for calfactant if it replaces beractant as the neonatal surfactant formulary agent. With these cost reductions for calfactant, it is estimated that neonatal surfactant annual drug purchases would be reduced by approximately $17,000 at Huntsville Hospital.

In addition, as reported in the comparative clinical trial of beractant vs. calfactant, calfactant maintained a longer duration of action, creating longer intervals between doses and fewer patients requiring the full treatment course, meaning fewer calfactant doses were actually given. If these events hold true in actual clinical practice, it is speculated that medication costs may be decreased. However this cannot be predicted and will only be determined with actual calfactant use (possibly in a trial / pilot program with calfactant).

### *Recommendation*

Based on the comparative safety, efficacy, and cost savings of using calfactant over beractant, it is recommended that the neonatologists consider the possibility of calfactant becoming the primary exogenous surfactant used in the prevention / treatment of RDS in the Huntsville Hospital System. However, this recommendation is pending the availability of the 3 mL vial. In addition, it is advised that the neonatologists consider a trial / pilot of calfactant with the free-month supply to assure that the conversion to calfactant is best for the patients and hospital system. Use of the two products can be evaluated through the pilot program comparing usage and outcome issues. If a pilot program is implemented, the results will be reported back to the P&T committee.

### *Pilot program experience*

After four months of experience with calfactant as the primary neonatal surfactant at Huntsville Hospital, neonatologists report similar efficacy and safety outcomes as with those observed with beractant.

*Resources*

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# Myopathy, rhabdomyolysis induced by the 'statins'

By **Candace Hodges**, PharmD
Written as PharmD candidate at Samford University, Birmingham, AL

Although hyperlipidemia can be managed with several different treatment options, the most frequently used class of agents is the "statins," a common name for the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Their mechanism of action involves inhibition of this enzyme, which catalyzes the rate-limiting step (conversion of HMG-CoA to mevalonic acid) in cholesterol synthesis.

One of the most important adverse effects of the statins is myopathy, which can lead to rhabdomyolysis. Myopathy is defined as unexplained muscle pain or weakness, accompanied by serum creatine phosphokinase (CPK) levels greater than 10 times the upper limit of normal (200 units/L) and, in some cases, fever and malaise. CPK is the enzyme responsible for catalyzing the regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP).

If myopathy is not treated or diagnosed, it may result in rhabdomyolysis, a syndrome that presents as myopathy, plus some degree of skeletal muscle damage, with myoglobinemia and myoglobinuria. Most commonly, the cause of death associated with rhabdomyolysis is acute renal failure (ARF), which may be caused by myoglobin-induced renal tubule obstruction or direct tubular cell damage.

Although the exact mechanisms involved in statin-induced myopathy/ rhabdomyolysis have not been established, two principle hypotheses exist, both related to the mechanism of action of the drugs. Direct inhibition of cholesterol synthesis results in reduced amounts of cholesterol available for muscle cell membrane synthesis and decreased ubiquinone (coenzyme Q) synthesis, which results in enhanced free-radical damage of myocytes.

Dose-dependent myopathy and rhabdomyolysis have occurred with statin monotherapy and combination therapy with other agents, even while using doses within the recommended ranges. There was an increased reporting rate of rhabdomyolysis at the highest dose (0.8 mg daily) of cerivastatin (Baycol), the statin which was withdrawn from the market Aug. 8, 2001, following 31 deaths from severe rhabdomyolysis.

According to experts at the Food and Drug Adminstration, rhabdomyolysis was about 10 times more common with cerivastatin than with other statins (relative incidence < 1%). Due to a wide variability of adverse reaction reporting with the other statins, it is difficult to determine whether there is a higher risk of myopathy/rhabdomyolysis with some than others.

Data from published case reports of myopathy/rhabdomyolysis secondary to the combination of fibrates (gemfibrozil was responsible in each case) and statins reported that the onset of myopathic symptoms ranged from 36 hours to 36 weeks after initiation of therapy, and the time course of developing rhabdomyolysis was within 2-12 weeks after initiation. Symptoms generally improve over a few days to about a week after drug discontinuation, and CPK levels return to near normal over the course of about two weeks.

Because all statins are metabolized to some extent by the cytochrome P450 (CYP450) enzyme system, concurrent administration with drugs or food that inhibit or are substrates of this system (mainly CYP3A4) may result in an increased incidence of myopathy/rhabdomyolysis **(see Table, p. 8)**. These include erythromycin, clarithromycin, cyclosporine, nefazadone, azole antifungals (e.g., ketoconazole, fluconazole, and itraconazole), protease inhibitors, and grapefruit

juice. Other antihyperlipidemic agents, when used in combination with the statins, also may increase the potential for myopathy / rhabdomyolysis through a different mechanism other than CYP450 interaction. Gemfibrozil has been the causative agent in most cases. However, there also have been documented cases of muscle toxicity with other fibric acid derivatives (i.e., fenofibrate and clofibrate) and niacin.

Other than the combination of statins with certain drugs and use of higher doses, risk factors that predispose patients to statin-induced myopathy / rhabdomyolysis include: advanced age, female gender, renal or hepatic dysfunction, hypothyroidism, and serious infection. According to clinical reports, myopathy / rhabdomyolysis induced by statin-fibrate combination therapy may involve these same risk factors, as well as diabetes, debilitated status, surgery, trauma, excess alcohol intake, and heavy exercise.

To minimize the occurrence of these serious adverse effects caused by the statins, health care providers may take the following steps:

• Carefully screen patients for risk factors that predispose them to myopathies / rhabdomyolysis.

• Be aware of the drugs that can inhibit CYP450 metabolism of the statins, and formulate therapeutic decisions (e.g., appropriate dosage adjustments) based on these potential interactions.

• Provide patient education on the early signs and symptoms of myopathies, such as unexplained muscle pain, weakness, cramping, tenderness, dark urine, fever, and malaise.

• Advise patients to contact their physician if any of the signs and symptoms of myopathies occur.

• Obtain baseline CPK levels and monitor them if the patient complains of signs and symptoms consistent with myopathy. Routine measurements generally are not recommended because severe myopathy usually occurs suddenly and is not preceded by chronic CPK elevations.

• Advise patients to avoid grapefruit juice, if possible. If they insist on drinking it, advise them to only drink it occasionally in order to minimize the effects of this drug-food interaction.

• Avoid the use of statin-fibrate combination therapy unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

• Use the lowest effective dose possible of statins and other drugs in which they may be used in combination.

• Methods to manage situations in which statin-induced myopathy / rhabdomyolysis occur include:

• Discontinue the causative drug, obtain serum CPK levels without delay, and assess renal function.

• Use an antihyperlipidemic agent from a different class, if possible.

• If an agent from a different class cannot be used, rechallenge with a different statin after CPK level normalization, beginning with a low dose and monitoring closely for symptoms and elevated CPK.

• Elevated CPK in the absence of symptoms usually does not require discontinuation of the hyperlipidemic agents, unless it becomes greater then 10 times upper limit of normal or liver transaminases (ALT, AST) become greater than three times upper limit of normal.

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**Table. Metabolism and common inhibitors of the statins**

| Name | Metabolic Enzyme | Common Inhibitors |
|---|---|---|
| Atorvastatin (Lipitor) | CYP3A4 | Clarithromycin, erythromycin, fluconazole, itraconazole, ketoconazole, omeprazole |
| Cerivastatin (Baycol) | CYP3A4, CYP2C8 | Same as atorvastatin |
| Fluvastatin (Lescol) | CYP2C9 | Amiodarone, cimetidine, zafirlukast |
| Lovastatin (Mevacor) | CYP3A4 | Same as atorvastatin |
| Pravastatin (Pravachol) | Limited CYP metabolism | Possibly same as atorvastatin |
| Simvastatin (Zocor) | CYP3A4 | Same as atorvastatin |