DRUG FORMULARY REVIEW™
Utilization, Criteria and Outcomes

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IN THIS ISSUE

Drug Utilization Review has a new name, *Drug Formulary Review*, as we now are concentrating on providing information that supports formulary decision making and compliance. We hope you will find this shift in focus helpful and welcome your questions and comments. Call Lee Landenberger at (404) 262-5483 or e-mail at lee.landenberger@thomson.com.

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Computer prompt promotes switch from intravenous to oral medications

Physicians less likely to respond with antimicrobial agents

Researchers from Harvard Medical School's teaching hospital in Boston decided to test if they could encourage physicians to switch appropriate patients from intravenous (IV) to oral (PO) medications.

They found that the physicians responded to a computer prompt almost 36% of time, either making the switch to PO administration or canceling the order altogether. The physicians, however, were less likely to change the order when it involved an antimicrobial agent. The results of the study were published in the Nov. 24 issue of the *Archives of Internal Medicine*.

It was clear from observation that patients were receiving expensive IV medications upon admission — when they were sickest, needed the highest concentrations of drugs, and might have trouble taking PO medications, says **Jonathan M. Teich**, MD, PhD, one of the researchers and a physician in the department of emergency medicine at Brigham and Women's Hospital in Boston. Teich also is an assistant professor of medicine at Harvard University and a senior vice president and chief medical officer of HEALTH*vision*, in Irving, TX. Then, even when the patients improved and were in better condition, the IV medications were continued rather than being switched to oral administration.

"Our pharmacists and our informatics leaders talk frequently about key problems and possible improvements," Teich says. "Through these discussions, the pharmacists expressed their concern about unnecessary costs from this practice, and we in the informatics division suggested that an algorithm could be developed and put into play." The hospital performs formal studies on many of its interventions, particularly if they are new or unique.

Five medications chosen

The researchers targeted five medications with equal oral and intravenous bioavailability: fluconazole, levofloxacin, metronidazole,

ranitidine, and amiodarone. The researchers programmed an algorithm in the hospital's computerized order entry system (CPOE) to prompt physicians to convert appropriate IV medications to PO.

The first algorithm was fairly simple, Teich says. It looked for orders for the target IV drugs for patients who also were taking oral medications or nutrition — indicating that they could handle taking medications by mouth.

In the first phase of the study, the prompts for the IV-to-PO conversion were given to the pharmacists, who then could decide which ones needed follow-up, Teich says. Although the pharmacists were enthusiastic about the study, they were short-staffed at the time of the original study and had a hard time getting even a few minutes to do the review. "When we moved the prompting over to physicians — who are used to getting all sorts of prompts from the computer — they responded well, but only after we had tightened up the algorithm to eliminate more conditions where the doctor was likely to reject the alert," he says. "Our physicians, and physicians everywhere, are generally happy to get prompts like these from the computer, if they are not excessive and if most of them are valid."

Tangible results

The researchers then measured the total use of the five medications via each route in the four months before and after the implementation of the intervention. They also measured the rate at which physicians responded to the intervention when prompted.

The researchers found that the average IV-defined daily dose declined by 11% during the intervention period, while the average oral-defined daily dose increased by 3.7%. These figures came at a time when the overall length of stay, case-mix index, and total drug use at the hospital increased.

Physicians responded to the prompts in 35.6% of the 1,045 orders, by either converting from IV to PO administration or canceling the order altogether. The responses, however, differed depending on the medication. More than 20% of the amiodarone orders were canceled, but none were directly converted to the oral route.

The researchers surmised that the automated IV-to-PO conversion prompt did not provide physicians with the dose recommendations they needed for this drug.

Among the other four medications, physicians were willing to replace or cancel ranitidine more often than the three antimicrobial agents, the researchers say. Orders for ranitidine were changed or canceled 42.5% of the time, followed by those for levofloxacin (30.3%), metronidazole (27.0%), and fluconazole (18.2%).

There are several conditions associated with physicians rejecting the suggested conversion, Teich says. Included among these are patients in the intensive care unit, patients in very recent postoperative status, patients taking drugs for a gastrointestinal problem, and others.

"We determined these factors from a review of the initial data. More refinement [to the algorithm] would lead to a consistent set of rules, usable or all target medications, that would further concentrate the alerts so that their specificity is very high," he adds.

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Lessons from the study

Pharmacists can discern from this study that in many cases, doctors are happy to switch to PO medications when reminded to do so, Teich says. "The fact that they don't do it without prompting may be more a matter of 'not changing what's working,' and concentrating on acute clinical problems, than a deep belief that the IV drug is still superior."

The study also shows that computer algorithms are great tools for screening patients, he adds. "Even if not all of the selected patients should have the IV-to-PO change made, it is much easier to review a small number of patients [after the computer has pre-screened them] than to try and look at the entire service by hand."

Finally, there are many examples of how CPOE benefits patient care, Teich says. "Usually, CPOE concentrates on immediate alerts: The doctor writes an order, and the system tells the doctor that the patient is allergic. This is a different kind of clinical decision support, and takes a little more thought to put into play, but it can be very powerful." ■

Pharmacist interventions increase dramatically with new technology

Automation frees time for prospective chart review

Integrating new automated dispensing technology with an already established computerized physician order-entry system (CPOE) has changed the way pharmacists work at El Camino Hospital, a community facility in Mountain View, CA. Freed from most dispensing duties, pharmacists now spend much of their time reviewing patient information before drugs are dispensed.

The hospital has seen a 250% increase in clinical interventions by pharmacists between 2002 and 2003. These interventions have resulted in a 500% increase in direct cost avoidance.

El Camino, located in the heart of Silicon Valley, was one of the first hospitals in the nation to begin using a CPOE tool in 1971. The system has a strong compliance rate with clinical users, says **Mark Zielazinski**, chief information officer. The pharmacists, as well as nurses and physicians, use this tool.

Drug dispensing tools, which had simple inventory dispensing capabilities, were added in the early 1990s. However, the hospital had the goal of moving toward bedside medication verification. The first step was the recent addition of new patient safety technologies. These technologies include a biometric drug dispensing system, a bedside drug bar-coding system, and an automated pharmaceutical and supply replenishment system that integrates with the CPOE system.

The hospital did three things simultaneously, Zielazinski says. It first upgraded the dispensing tools from being drawers of drugs to a patient profile tool. Next, it forced a complete medication verification process through the CPOE tool. "We were always verifying the orders, but now we are verifying them within a given time frame," he says. "We set our target to be 15 minutes. The mean, since setting the target, has been less than eight minutes, and the maximum time in the last quarter was 13 minutes."

Third, the hospital updated the process of how pharmacists interact with the system. "In the current quarter, they intervene at about four times the previous level of the same quarter last year," Zielazinski says.

Challenging implementation pays off

The implementation was at times challenging, but the updated system has been a positive change for the hospital pharmacists, according to **Mei Poon**, PharmD, director of pharmacy. With the exception of controlled substances, most of the medications had previously been dispensed directly from the pharmacy to the floors.

Now when the pharmacists receive the electronic orders from the physicians, the pharmacists have the medical profile history and patient notes available for review from the CPOE system. "After we had the interface, we were able to review all the medication orders prior to the nursing getting access to the medication," Poon says. This helps ensure the five rights before verifying the order: the right patient, the right medication, the right dose, the right route, and the right frequency.

The pharmacists' verification of an order allows nurses on the unit to access and dispense the medications for the patients. The cubicles of the medication-dispensing machine will only open for the drugs listed for that particular

patient. More than 85% of the drugs are now being dispensed on the unit, Poon says.

The automated pharmaceutical and supply replenishment system also largely bypasses the pharmacy. The system, for example, will tell a wholesaler exactly how many tablets it needs to deliver for a particular med station, she explains. The tablets will be delivered already prepackaged and bar-coded. When they arrive, pharmacy technicians simply refill the medication station on the unit. "Our goal is to maximize that process," Poon says. The technicians regularly make about three runs to the unit a day.

Number of errors reduced

This system has dramatically reduced the number of errors and the amount of "shopping" for a medication that had gone on in the past, Zielazinski says. "Nurses opened the drawer and had access to all the drugs that were in that particular drawer. Now the particular cubicle only opens for drugs listed for that patient and will not give out drugs until a pharmacist verifies the order." Nurses have the ability to override the system, but the overrides are tracked, and the number of overrides has decreased in the last two quarters.

New system allows prospective review

Dispensing the drugs on the unit also has allowed pharmacists to devote most of their time to prospective review, resulting in the 250% increase in clinical interventions. Many of the documented interventions address patients' medication allergies, Poon says. "[With the new system,] we have on-line drug interaction and allergy cross-checking. We are able to catch a lot of the allergies/drug interaction potential problems and intervene ahead of time." Some of the interventions have prevented serious adverse effects, such as a warfarin (Coumadin) overdose.

In addition, some of the pharmacists have a window of time in which they do drug utilization review on specific high-risk drugs, such as warfarin or enoxaparin (Lovenox), Poon says. "They are able to devote the time just to do a focused review of patients who are on these high-risk drugs. They are able to correct dosing, make recommendations, and intervene when there is a problem."

The interventions, such as switching routes of administration or finding alternative therapies, have led to more cost-effective drug therapy — 500% in cost avoidance compared to 2002 levels. "That is just based on raw acquisition drug costs," Poon says. "It does not take into consideration the reduction of hospital days and length of stay."

The prospective chart review doesn't take the place of having a pharmacist present on the unit, such as in a university setting, Poon says. But since El Camino does not have teams of physicians and residents going on patient rounds, the system is an efficient way of doing clinical review.

The automated dispensing system acts as a gatekeeper at the point of care, she explains. "Important information relevant to each patient's medication regimen is available to front-line practitioners, since pharmacists are seeing the same data the physicians are seeing. This way, orders are reviewed before the medication is dispensed, rather than after the medication has been given to the patient at the bedside," Poon says. "The potential safety effects on patient care are profound."

Another benefit from the new system is that Poon has been able to expand the pharmacy hours without adding any FTEs (full-time equivalents). "We were able to restructure our workflow by becoming more staggered. We still are not open 24 hours, but we are close." The pharmacy is now only closed three hours a day, during the night shift.

El Camino plans to move ahead with improving its system in 2004. Next on the docket is a fixed patient station at the bedside. The hospital also plans to have medications bar-coded on a unit-dose basis. ■

Abbott stands firm in ritonavir price increase

500% increase for patients taking 100 mg a day

Abbott Laboratories is not backing down from its decision to increase the price of ritonavir (Norvir) by 500% monthly for patients who take 100 mg a day. Ritonavir is used in almost all protease inhibitor combinations for treating HIV infection.

Ritonavir is unusual because it was approved

as an HIV protease inhibitor but it is actually being used as an inhibitor of the cytochrome P450 system, says **Daniel Kuritzkes**, MD, director of AIDS research at Brigham and Women's Hospital in Boston, and director of the Program in Retroviral Therapeutics at Harvard Medical School. Ritonavir is the most potent of the cytochrome P450 inhibitors, and it has now become a component of protease inhibitor-based regimens.

The HIV Medicine Association (HIVMA) in Alexandria, VA, had called on Abbott to rescind the price hike, which took effect Dec. 4. In the letter, **Paul Volberding**, MD, and Kuritzkes, who are chairman and vice chairman, respectively, of the HIVMA board of directors, tell Abbott that, "While we recognize the value of ritonavir, we are alarmed by your decision to raise the cost of protease inhibitor regimens to the point where many people who need these life-saving drug combinations will struggle to pay for them or won't have access to them at all. In addition to our particular concern about the price increase for ritonavir, we are generally concerned about continuing upward pressure on prices as each new HIV drug is approved."

HIVMA outlines its case

The letter acknowledges the role Abbott played in developing the drug regimens, but asks the drug manufacturer to consider these harmful effects of the price hike:

- The decision increases the average wholesale price of ritonavir to $8.55 for 100 mg, which equates to a monthly total of $260 for patients who take 100 mg daily as part of an ATV/RTV regimen. Previously, the monthly price was $45.
- The higher cost will likely raise insurance premiums and increase the amount of ritonavir copayments to a level that most people with HIV/AIDS cannot afford.
- The dramatic increase in price could cause payers to impose restrictions on available HIV/AIDS therapies.
- AIDS Drug Assistance Programs (ADAPs) may have to pay more. The price increase will result in higher profits to the pharmacy and wholesaler, which will translate into higher costs to ADAPs, if the reimbursement rate used for pharmacies is indexed to the average wholesale price.
- The price hike may create budget problems for ADAPs, since the lag time between payments to pharmacies and receipt of rebates from the manufacturer can be as long as six months.

Abbott explains why

Even though Abbott has had a number of discussions with physicians around the country who are concerned about the impact of the price increase, according to Kuritzkes, the drug manufacturer didn't budge.

In a Dec. 23 letter to HIVMA, Abbott says it did not make the price decision easily. The higher price was necessary to support Abbott's ability to continue research to bring a next-generation HIV medication to market, to develop improved formulations of its existing products, and to continue its commitment to the developing world, wrote **John Leonard**, MD, vice president of global pharmaceutical development. He says Abbott currently is investing in new HIV and hepatitis C compounds as well as another new formulation of ritonavir and a new formulation of lopinavir/ritonavir (Kaletra).

The new price also reflects ritonavir's changing role and value, Leonard says in the letter. "In 1996, Norvir was prescribed as a stand-alone protease inhibitor at a recommended daily dose of 1,200 mg and a daily price of $20.52. Today, Norvir is primarily used at low doses of 100 mg to 200 mg in combination with other protease inhibitors, with 100 mg being the most commonly prescribed daily dose. At the new price of $8.57 per 100 mg, Norvir is most often the lowest cost component of a protease inhibitor-based regimen."

Patient access assured

What impact the pricing change will have depends on what ADAPs and other payers do, Kuritzkes says. Abbott says it was taking steps to assure that patients overall were not adversely affected by the decision. First, the company expanded its Patient Assistance Program (PAP) for Norvir to "ensure that all patients without drug coverage can receive this drug for free from Abbott, regardless of their financial status."

Leonard says Abbott has met with ADAP directors and has issued a Memo of Commitment honoring the former price for all ADAPs through June 2005. In addition, the company has told state Medicaid programs that the cost of the drug for them would not change from the former price.

The top private insurance providers contacted by Abbott do not plan to increase copays or premiums based on the pricing action, Leonard says. "[Less] than 10% of privately insured patients pay a percentage of the prescription cost vs. a flat copay. It is expected that these patients are protected and will not pay more annually due to out of pocket maximums." ■

Combination drug therapy prevents BPH progression

A combination of drugs is significantly more effective than either drug alone for preventing progression of benign prostatic hyperplasia (BPH), especially in high-risk men, according to a study appearing in the Dec. 17 issue of the *New England Journal of Medicine*.

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial tested whether finasteride (Proscar), doxazosin (Cardura), or a combination of the drugs could prevent progression of BPH and the need for surgery or other invasive treatments. All treatments were compared to placebo.

Physicians at 17 MTOPS medical centers treated 3,047 randomized men with BPH for an average of 4.5 years, longer than previous studies. Vital signs, urinary symptoms, urinary flow, side effects, and medication use were checked every three months. Digital rectal exams were conducted every year, and serum PSA and urine were checked yearly. Prostate size was measured at the beginning and end of the study by ultrasound. Progression of disease was defined by one of the following: a four-point rise in the American Urological Association's symptom severity score, urinary retention (inability to urinate), recurrent urinary tract infection, or urinary incontinence.

Finasteride and doxazosin together reduced the overall risk of BPH progression by 66% compared to placebo. The combined drugs also provided the greatest symptom relief and improvement in urinary flow rate. Doxazosin alone reduced overall risk of progression by 39% and finasteride alone by 34% relative to placebo. The combination treatment and finasteride alone also significantly reduced the risk of invasive therapy by 67% and 64%, respectively.

MTOPS found that combination therapy was especially effective in men at highest risk for BPH progression — those with prostates larger than 40 mL (30% of participants) or serum PSAs above 4 ng/mL (20% of participants).

BPH progressed in only 5% (49) of men on the two drugs, in 10% (85) of men on doxazosin, in 10% (89 men) of men on finasteride, and in 17% (128 men) of men on placebo. The events signaling disease progression were mostly worsening symptoms (78%), but also included acute urinary retention (12%) and incontinence (9%). ■

Details about Medicare Prescription Drug Discount Card Program released

Department of Health and Human Services Secretary Tommy G. Thompson has announced an interim final regulation for the Medicare Prescription Drug Discount Card Program.

The regulation outlining the new drug discount card program is the first action resulting from the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. While the drug discount benefit will be available this spring, the more significant provision of the law creating new Medicare drug coverage available to all Medicare beneficiaries will take effect in 2006.

Seniors and individuals with disabilities will be able to use these cards to save about 10-15% on their total drug costs, with savings of up to 25% or more on individual prescriptions. All Medicare beneficiaries, except those who already have Medicaid outpatient drug coverage, will be able to enroll in Medicare approved drug discount card programs, with benefits beginning in June, and may continue until the Medicare prescription drug benefit is implemented.

A key component of the Medicare-approved prescription drug discount card program is a

subsidy of up to $600 a year for eligible low-income beneficiaries. Individuals whose income is less than $12,124 each year or married couples whose income is less than $16,363 may qualify for this special help. In addition, Medicare will cover the cost of the enrollment fee for these low-income cardholders.

Medicare beneficiaries will have a choice of at least two Medicare-approved cards, but be allowed to enroll in only one drug card program at a time. The cost of enrollment can be no more than $30 annually. Beneficiaries can change cards during an open enrollment period prior to 2005 or under special circumstances. ▼

Ortho-McNeil adds warning to topiramate

Ortho-McNeil Pharmaceutical has revised the prescribing information for topiramate/topiramate capsules (Topamax) Tablets/Sprinkle Capsules to include a warning that it causes hyperchloremic, non-anion gap metabolic acidosis.

Topiramate is approved and marketed for the adjunctive treatment of partial-onset seizures, generalized tonic-clonic seizures, and seizures associated with the Lennox-Gastaut syndrome in adults and children 2 years of age and older.

Data on hyperchloremic, non-anion gap metabolic acidosis are derived from placebo-controlled trials and post-marketing experience in more than 2.5 million patients.

In clinical trials, the rate of occurrence of a persistently decreased serum bicarbonate ranges from 23% to 67% for patients treated with topiramate and 1% to 10% for placebo. The incidence of markedly low serum bicarbonate in clinical trials ranges from 3% to 11% for topiramate and 0 to less than 1% for placebo.

Generally, decreases in serum bicarbonate occur soon after initiation of topiramate, although they can occur at any time during treatment. Bicarbonate decrements usually are mild to moderate, with an average decrease of 4 mEq/L at daily doses of 400 mg in adults and approximately 6 mg/kg/day in pediatric patients. Rarely, patients can experience decrements to values below 10 mEq/L.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue topiramate in the face of persistent acidosis, alkali treatment should be considered. ▼

Pergolide mesylate (Permax) may cause patients to fall asleep

Eli Lilly & Co. is advising health care professionals of the possibility of patients falling asleep while performing daily activities, including the operation of motor vehicles, while receiving treatment with pergolide mesylate (Permax). The dopamine agonist is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

While somnolence is a common occurrence in patients receiving pergolide mesylate and many clinical experts believe that falling asleep while engaged in activities of daily living only occurs in the context of pre-existing somnolence, many patients who have fallen asleep have perceived no warning.

Pharmacists should be alerted to the potentially serious risks associated with the events and should carefully evaluate patients for the presence of somnolence, and should have a discussion with them. ▼

COMING IN FUTURE MONTHS

- Palonosetron (Aloxi) formulary evaluation
- Pilot program offers pharmacists for paid medicine reviews
- Multitasking in pharmacy practice
- Imatinib mesylate (Gleevec) shows promise in Alzheimer's treatment
- Rosevastatin (Crestor) drug evaluation

IN THE PIPELINE

• ViaCell will begin to enroll patients in a Phase I/II clinical trial of CB001, a highly purified population of stem cells that has been isolated from umbilical cord blood and multiplied using the company's patented Selective Amplification technology. The objective of the trial is to assess the safety of CB001 and the rate and durability of blood and immune system reconstitution using CB001 in the treatment of adult patients with **advanced stages of hematologic cancers** who have undergone high-dose chemotherapy and radiation treatment.

• Stressgen Biotechnologies Corp. has announced today that the U.S. Food and Drug Administration (FDA) has designated HspE7, the company's lead immunotherapeutic for human papillomavirus-related diseases, as a fast-track product development program for the treatment of patients suffering from **recurrent respiratory papillomatosis**.

• Millennium Pharmaceuticals has announced that the FDA has granted its investigational cancer therapy, MLN2704, fast-track designation. MLN2704 currently is being evaluated in a Phase I/II clinical trial at Memorial Sloan-Kettering Cancer Center and New York-Presbyterian Hospital/Weill Cornell Medical Center for the treatment of patients with **metastatic androgen-independent prostate cancer**. ■

New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• ***Regular approval for another indication of imatinib mesylate (Gleevec) by Novartis Pharmaceuticals Corp.*** The FDA has granted imatinib mesylate (Gleevec) regular approval as a second-line treatment for refractory chronic myeloid leukemia (CML).

Regular approval means that the FDA has determined that imatinib mesylate has demonstrated a long-term clinical benefit for refractory CML patients. When imatinib mesylate was originally approved under the accelerated approval program in May of 2001, available evidence indicated that a long-term clinical benefit was highly likely but further studies were necessary to confirm it. Imatinib mesylate's promising effects included a normalization of blood cell counts and a reduction in the percent of abnormal chromosomes in bone marrow white blood cells.

As part of the original approval, Novartis Pharmaceuticals was required to continue to follow patients in their initial studies to confirm long-term benefit for this particular indication. Data presented to the FDA showed that 95% of patients achieved normal blood cell counts. Further, favorable treatment responses were sustained. An estimated 88% of patients who achieved a reduction in the percent of abnormal chromosomes in bone marrow white blood cells maintained that response for at least two years. After two years of treatment, an estimated 85% of patients were free of disease worsening. The estimated overall survival was 91%. As a result of these additional data, the FDA granted regular approval to imatinib mesylate in this particular treatment setting.

Since May 2001, imatinib mesylate has been approved for use in the first-line treatment CML, for use in pediatric leukemia, and for a gastrointestinal stromal cancer. ■

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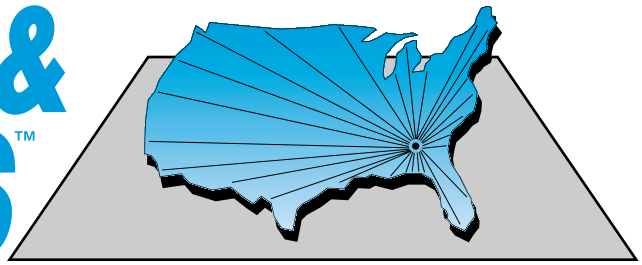

Alefacept (Amevive) Formulary Review

By **Miranda B. Chambers**, PharmD candidate
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Alefacept (Amevive), produced by Biogen, represents a new drug class for patients with chronic plaque psoriasis. The drug was approved by the U.S. Food and Drug Administration (FDA) on Jan. 31, 2003, and became available on Feb. 3, 2003.

Mechanism of action

Alefacept interferes with lymphocyte activation, via binding to CD2, the lymphocyte antigen, and inhibiting the interaction between CD2 and LFA-3, the leukocyte-associated function antigen, which promotes cell-cell interaction. LFA-3 on the antigen-presenting cell and CD2 on T-lymphocytes interact in the pathophysiology of chronic plaque psoriasis.

Secondly, alefacept causes a reduction in subsets of CD2+ T-lymphocytes by attaching to the Fc(RIII IgG, which can engulf multivalent complexes, causing apoptosis in those cells expressing high levels of CD2. Because CD2 is higher on memory cells than naïve cells, there is a selective reduction in circulating total CD4+ (helper cells) and CD8+ (suppressor or cytotoxic cells) T-lymphocyte counts. CD4+ helper cells stimulate other cells in the immune response. CD8+ suppressor cells help to down-regulate the immune response once the pathogen is destroyed. CD8+ cytotoxic cells kill cells that are recognized as foreign. However, this effect seems to be dose-dependent.

Pharmacokinetics

In clinical trials, efficacy was correlated with the serum levels of the drug. However, the package insert does not recommend routine monitoring of levels, and a therapeutic range for drug levels has not been established. Bioavailability is 63%.

Monitoring parameters

White blood cell (lymphocyte) count should be monitored weekly during treatment.

Indication

Alefacept is indicated for treatment of adults with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

Dosage

Intramuscular (IM) dosage is 15 mg once weekly for 12 weeks, and can be repeated after a 12-week treatment-free period if CD4+ count is normal.

As of Oct. 3, 2003, Biogen discontinued a 7.5 mg intravenous (IV) dosage form because more dermatologists preferred the IM injection.

Drug interactions

Formal studies are not available for drug interactions with alefacept. Due to the mechanism of action, alefacept may have additive effects when administered concurrently with other drugs that suppress T-cell activation, such as cyclosporine.

Adverse effects

The most serious adverse effects were:

- Lymphopenia (decreased CD4+ and CD8+ counts)
- Malignancies
- Serious infections requiring hospitalization (immunosuppressive properties)
- Hypersensitivity reactions (urticaria, angioedema, anaphylaxis)

Adverse reactions occurring 2% more frequently

in the alefacept group vs. placebo, included: pharyngitis, dizziness, increased cough, nausea, pruritis, myalgia, chills (5), injection site pain, injection site inflammation, and accidental injury.

The most commonly occurring adverse events, which required clinical intervention, were cardiovascular events: coronary artery disease (< 1%) and myocardial infarction (< 1%).

The most common adverse events causing discontinuation of the drug included: decreased CD4+ T-lymphocyte levels (< 250 cells/mcL), headache (0.2%), and nausea (0.2%).

Contraindications

The only contraindication to alefacept at this time is hypersensitivity to alefacept or any component of the drug.

Precautions

- Immunosuppressive effects occurred, so other immunosuppressive agents or phototherapy should not be coadministered.
- Hypersensitivity reactions occurred when alefacept was administered. If anaphylaxis occurs, alefacept should be discontinued.
- Decrease in T-lymphocytes occurred, so weekly monitoring of white blood cells should be done during the treatment periods. If the CD4+ level falls below 250 cells/mcL, the dose should be withheld. If the count stays below 250 cells/mcL for longer than one month, the drug should be discontinued.
- Malignancies may occur, but no definitive data exist.
- Effects on fetal development are unknown, but a large number of the patients with psoriasis are women of childbearing age. Therefore, women who are pregnant and decide to take alefacept are asked to enroll in a Biogen Pregnancy Registry [(866) AMEVIVE]. Studies performed in monkeys showed no abortifacient or teratogenic effects, so it is rated Pregnancy Category B.
- Excretion in breast milk is undetermined.
- Geriatric patients are more susceptible to some malignancies and infections, so caution should be used when treating this population. However, in a study of 1,357 patients, no differences were shown between different age groups using alefacept.
- Safety and efficacy have not been studied in the pediatric population.

To reduce error potential, physician clinics should be educated that alefacept should be administered IM, not IV.

Clinical studies

Study No. 1: Ellis C, Krueger G. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001;345:248-255.

Objective: To evaluate alefacept as a treatment for psoriasis.

Study design/patient population: Multicenter, randomized, placebo-controlled, double-blinded, parallel-group study involving 229 patients. Study included men and women, ages 18-70 with chronic plaque psoriasis involving at least 10% of body surface area for at least 12 months before study.

Inclusion criteria: Previous phototherapy or systemic treatment or candidates for those treatments.

Exclusion criteria

- Serious hepatic or renal disease
- History of cancer (except basal cell carcinoma or less than three squamous cell carcinomas of the skin)
- Weight of 75% or more above ideal body weight
- Serious infection in previous three months
- Women of childbearing age, unless using contraception
- Systemic treatments, phototherapy, or potent topical treatments within previous four weeks (and not until two weeks after treatment)
- Moderate-potency topical corticosteroids, keratolytics, coal tar, or calcipotriene were restricted to use on groin, scalp, palms, and soles

Endpoints: The endpoints for the study included safety and efficacy.

Treatment regimens: Patients were randomly assigned to receive alefacept 0.025 mg/kg, 0.075 mg/kg, or 0.150 mg/kg, or placebo. Alefacept was administered by 30-second IV injection once weekly for 12 weeks.

Results: During the 12-week treatment phase, patients receiving alefacept had significantly better improvement in psoriasis area and severity index (PASI) than those in the placebo group ($P < 0.001$).

- Two weeks after treatment, significantly more patients from the alefacept groups still had at least 50% reduction in PASI.
- Twelve weeks after treatment, still significantly more alefacept patients had greater than 50% reduction ($P = 0.02$). There were no reports of flare or rebound of disease after treatment ended.

This study showed a correlation between serum levels and drug efficacy. There was also a dose-dependent decrease in peripheral-blood CD4+ memory effector cells. Alefacept was well-tolerated. No adverse event was more than 5% greater

in the alefacept group vs. placebo.

Conclusion: The authors concluded that once-weekly alefacept for 12 consecutive weeks was an effective and well-tolerated treatment for chronic plaque psoriasis.

Strengths

- Adequate sample size
- Study design
- P values and percentages stated
- Intention-to-treat method used
- Appropriate statistical tests used

Limitations

- Confidence interval and power were not stated.
- No patient specific data were given.

Study No. 2: Krueger GG, Papp KA, Stough DB, et al. A randomized, double-blind, placebo-controlled Phase III study evaluating efficacy and tolerability of two courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002;47:821-833.

Objective: To evaluate the efficacy and tolerability of two courses of alefacept in a phase III study of patients with chronic plaque psoriasis.

Study design/patient population: Randomized, double-blind, placebo-controlled, parallel-group study involving 553 patients (166 females and 387 males). Patients, ages 16-84, were randomized to three groups, either receiving two courses of alefacept or one course of alefacept and one course of placebo.

Inclusion criteria

- Chronic plaque psoriasis for at least 12 months prior to trial (10% or more of body surface area)
- CD4+ lymphocyte count greater than lower limit of normal

Exclusion criteria

- Systemic or serious local infection within three months prior to study
- History of malignancy
- Pregnant or nursing females
- Some treatments within four months of the study (phototherapy and some drug therapy)
- Some treatments within two weeks of and throughout the study, except on the scalp, palms, groin, soles (moderate-potency topical corticosteroids, vitamin D analogs, keratolytics, and coal tar)
- Therapeutically ineffective low-potency topical corticosteroids and emollients within 12 hours of the endpoint measurements

Endpoints: The primary endpoint was efficacy, which was defined as 75% or greater decrease in PASI at two weeks after course one was completed. The secondary endpoints were safety and therapy duration, especially looking at the second course of alefacept.

Treatment regimens: Most patients (548) received a 7.5 mg dose once weekly for 12 weeks, while five patients (weighing less than 50 kg) received 5 mg once weekly. Each dose was a 30-second IV injection.

Results: Four hundred eighty-two patients completed course one treatment and follow-up and began course two; 401 patients completed course two treatment and follow-up. Results of the study are detailed in **Table 1**.

Duration of response

- Single course of alefacept (cohort 2): Those who achieved 75% or more reduction in PASI maintained 50% or more reduction in PASI for a median duration of more than seven months.

Table 1: Efficacy in Krueger GG, Papp KA, Stough DB, et al study

	Course 1, # (%)		Course 2, # (%)		Both Courses, # (%)
Endpoint	Placebo (n = 186)	Alefacept (n = 367)	Placebo (n = 142)	Alefacept (n = 154)	Alefacept/alefacept (n = 183)
75% or more PASI reduction two weeks after treatment	7 (4)	53 (14)	10 (7)	36 (23)	47 (26)
Overall response rate	15 (8)	102 (28)	27 (19)	57 (37)	73 (40)
50% or more PASI reduction two weeks after treatment	18 (10)	139 (38)	35 (25)	74 (48)	100 (55)
Overall response rate	44 (24)	204 (56)	70 (49)	99 (64)	130 (71)
PGA of "clear/almost clear" two weeks after treatment	7 (4)	42 (11)	8 (6)	31 (20)	39 (21)
Overall response rate	11 (6)	83 (23)	25 (18)	46 (30)	58 (32)

The P values for all efficacy endpoints were $P < 0.001$.

- Single course of alefacept (cohort 2): Those who achieved PGA of "clear/almost clear" during or after treatment maintained a 50% or more reduction in PASI for a median duration of about eight months.
- Double courses of alefacept (cohort 1): Those who achieved 75% or more reduction in PASI or physician global assessment (PGA) of "clear/almost clear" maintained a 50% or greater response longer than the final endpoint of the study (one year); no median duration could be determined.

The duration of 50% or greater reduction in PASI was significantly longer in cohort 1 vs. cohort 2 among patients who achieved a 75% or greater reduction in PASI (P = 0.019) or PGA of "clear" or "almost clear" (P = 0.35) at any time during the study. This predicts that two courses produce longer duration than one course.

Tolerability

- Alefacept was well-tolerated.
- Alefacept caused chills, elevation of ALT (cohort 2), and CD4 depletion more than placebo.

Conclusion: In this study, the authors concluded that either one or two courses of IV alefacept produced significant clinical improvements in measures of chronic plaque psoriasis. There was a further increase in efficacy with the second course of treatment. Alefacept was well-tolerated, and the duration of treatment was longer than currently available treatments. Because psoriasis is a chronic disease that fluctuates from remission to disease flare, it is frequently managed with significantly toxic drugs. Alefacept may help meet the need for safe and effective remittive therapy.

Strengths

- Study design
- Large sample size
- Intention-to-treat analysis used
- P values and percentages stated
- Appropriate statistical tests used

Limitations

- Confidence interval not stated
- No long-term data (of more than one year)
- More males than females
- Sample size needed (555) vs. actual (553)

Cost

A cost analysis is provided in **Table 2**. Biogen offers an assistance program to uninsured patients, which is available through an application process.

Storage

Store the dose tray of lyophilized powder at controlled room temperature (15-30° C or 59-86° F). It should be protected from light and remain in the carton until used.

Conclusions and recommendation

Based on currently available literature, alefacept is a novel drug therapy for chronic plaque psoriasis. It is different from currently available treatments in that it targets specific lymphocytes involved in the immune response and has a longer duration of action. It has proven safe and effective in clinical trials, with two treatment courses being even more effective than one course.

Due to the dosage form and administration, it generally will be administered in physician offices or clinics **(see Table 3 for a criteria for use tool)**. For this reason, the drug is recommended to be non-formulary status, and not stocked in the hospital. If an inpatient on alefacept therapy requires a dose while in the hospital, the prearranged home supply should be used. Initiation of therapy should be deferred to the outpatient setting.

Additional resources

- Biogen Amevive package insert. Cambridge, MA; 2003.
- Anonymous. Alefacept (Amevive) for treatment of psoriasis. *Med Lett Drugs Ther* 2003;45:31-32.
- Krueger GG, Callis KP. Development and use of alefacept to treat psoriasis. *J Am Acad Dermatol* 2003;49:87-97.
- Pham DQ, Bandy V, Song JC. Alefacept: A T-cell-specific immunosuppressant to treat moderate to severe plaque psoriasis. *Formulary* 2002;37:346-353. ■

Table 2: Cost analysis

Size	15 mg IM
Four-dose package	$ 3,230.93
One-dose package	$ 807.74

Table 3: Criteria for use

Chronic plaque psoriasis (diagnosis for at least 12 months)	*Yes / No*
Greater than 16 years of age	*Yes / No*
Previous systemic therapy, phototherapy, or a candidate for these treatments	*Yes / No*
CD4+ lymphocyte count greater than the lower limit of normal (250 cells/mcL)	*Yes / No*
If pregnant, enrolled in Biogen Pregnancy Registry (1-866-AMEVIVE)	*Yes / No*
No history of malignancy	*Yes / No*