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What does DUR mean to you? Definitions and purposes abound

Ultimately, it should provide a path

The phrase drug utilization review, or DUR, takes several different shapes and meanings, depending on the situation and whom you're talking to. Its purpose varies too, often swaying with current issues and problems in pharmacy.

DUR first appeared with the Omnibus Budget Reconciliation Act of 1990 (OBRA '90). Its goals: Reduce Medicaid fraud and ensure that patients receive appropriate medications. DUR has been used in various practice settings to cut costs in hospital pharmacies. Some pharmacies turn to DUR to help reduce medication errors.

The Pharmaceutical Care Management Association (PCMA) says DUR is a "structured, ongoing program that interprets patterns of drug use in relation to predetermined criteria and attempts to prevent or minimize inappropriate prescribing. DUR may be conducted retrospectively or prospectively, and OBRA '90 mandated both types."[1]

OBRA '90 did indeed mandate both prospective and retrospective DUR. As a result of OBRA '90, every state is to offer patient drug counseling to all Medicaid patients and provide a DUR program for covered outpatient prescriptions "in order to assure that prescriptions (i) are appropriate, (ii) are medically necessary, and (iii) are not likely to cause adverse medical results. The program shall be designed to educate physicians and pharmacists to identify and reduce the frequency of patterns of fraud, abuse, gross overuse, or inappropriate or medically unnecessary care as well as potential and actual severe adverse reactions to drugs including education on therapeutic appropriateness, over-utilization and under-utilization, appropriate use of generic products, therapeutic duplication, drug disease, contraindications, drug interactions, incorrect drug dosage or duration of drug treatment, drug allergy interactions, and clinical abuse/misuse."[2] Additionally, DUR must "provide for a review of drug therapy before each prescription is filled or delivered to an individual."[2]

The terminology can be confusing. Some refer to DUR but use DUE, or drug use evaluation, to mean the same thing. Others say DUE evolved from, not into, DUR. Patrick Malone and colleagues in their

book *Drug Information, a Guide for Pharmacists*,[3] hold to this latter evolution of terms and add that the prime difference between DUE and DUR is that DUR is more retrospective. They add that OBRA '90 refers to this function as DUR, which can be more confusing. Here is their generally accepted differentiation of the terms: "In some cases, authors have distinguished the two by stating that DUR uses pharmacy claims data, whereas DUE includes use of patient chart data."[3]

MUE

"There are two very distinctive types of retrospective drug evaluation," **Barry Browne**, PharmD, coordinator of drug information at Scott and White Hospital and Health Plan in Temple, TX, tells *Drug Utilization Review*. "There is the MUE, or medication use evaluation, which many used to call DUE. An MUE is truly a medication use evaluation. It can be conducted prospectively, although that's difficult to do, concurrently, or retrospectively. Most of our MUEs are done concurrently. That is, the patient is still in the hospital, but the evaluation is performed typically one day after the drug order is written and filled. For example, we might double-check today for appropriate use and dosing of gentamicin in a patient with elevated serum creatinine for an order that was written yesterday. Unfortunately, this type of check can't always be done prospectively, or before the order is filled and dispensed."

MUEs meet the requirements of the Joint Commission on Accreditation of Healthcare Organizations, says Browne. At Scott and White, MUEs also go through the pharmacy and therapeutics (P&T) committee. "We choose the drug or drug class to evaluate based on three criteria. The target drug or drug class will be one that either has high volume, high risk, or is problem-prone.

"Although the MUE subcommittee is composed of medical staff, most of the work associated with MUEs is performed by the pharmacy department. At any given time, our institution will have six to seven ongoing MUEs. We'll do an initial review of the drug. If there's no problem, that's the end of it."

If a review finds a problem, the data are used to perform an intervention, Browne says. "An intervention can be in the form of education, a change in the way an order is to be written, or a change in policy. We'll wait an appropriate amount of time for the change to be implemented, typically one to six months, then perform a second evaluation. If, at that time the problem has been solved, that's the end of the process. If the problem still exists, we do another intervention. Most MUEs require just one round of evaluation and intervention. Others require as many as three."

Browne cites proton pump inhibitors as an example, saying that in a three-year period he and his staff performed three evaluations of the drug class, with subsequent interventions.

The education efforts are typically interdisciplinary, involving prescribers, nurses, and pharmacists, he notes.

"It's difficult to make an effective change if the entire team isn't aware of and supportive of the change," he says. "Besides which, Joint Commission started requiring multidisciplinary work a number of years ago."

These educational venues can be in the form of nursing inservices, a description of the change published in the quarterly P&T newsletter, order clarification, or a change in preprinted orders, for a change in doses, for example.

Browne says there is no specific form his team uses for MUE or DUR. "It's more a matter of using a data collection form, and that form and its components vary from one evaluation to the next."

DUR

"When I think of DUR," Browne says, "I think of a retrospective review of pharmacy trends in overuse of a particular drug or drug class. These trends often appear as a result of direct-to-consumer advertising campaigns or from heavy detailing from pharmaceutical reps. I think of dredging through pharmacy claims

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data. DUR involves more patient care and cost issues than does MUE. We can identify prescribing trends and work on cost containment with DUR."

Although DUR extends beyond Medicaid recipients, many health care professionals associate DUR with Medicaid. "It's a valid association," says Browne. "Many people had not heard of DUR until they learned about the components of OBRA '90."

The DUR Board for the State of Kansas describes the DUR for Medicaid recipients on its Web site at www.pharm.ukans.edu/dur/. Retrospective DUR occurs after the medication has been dispensed. "The computer software compares and analyzes varying drug use criteria with both pharmacy and medical claims to identify potential drug therapy problems."[4] Problem areas analyzed include:[4]

- drug-allergy contraindications;
- drug-disease contraindications;
- drug-drug interactions;
- therapeutic duplication;
- incorrect dosage or duration of therapy;
- overutilization;
- underutilization;
- clinical abuse or misuse.

The computer alerts DUR staff to potential problems, which staff then evaluate. One problem that hospital and community pharmacists face with non-Medicaid patients is solved here. The Medicaid claims process allows for analysis of drugs prescribed by different providers and those filled at different pharmacies. By evaluating data for multiple patients from the same providers, trends in prescribing and dispensing habits can be identified. As with other forms of MUE and DUR, intervention occurs when problem areas are identified. The goal of this DUR is to improve "drug therapy, patient outcomes, and quality of care."[4]

Health Information Designs (HID), an organization that handles Medicaid DUR programs to satisfy the requirements of OBRA '90 for several states, performs both patient-specific therapeutic DUR and provider profiling.[5] HID describes the three main steps involved in patient-specific programs:[5]

1) computer-based analysis of patient-specific drug and medical claims histories using therapeutic criteria to identify high-risk drug therapy cases;

2) review of the 12- to 18-month drug medical history profiles by clinicians to confirm the clinical significance of the computer-identified problems;

3) issuance of education alert letters to physicians and pharmacists involved in treating patients at high risk for drug-induced illness.

Prospective DUR

Prospective DUR occurs before a prescription is dispensed. The U.S. Pharmacopeia (USP) and the American Pharmaceutical Association (APhA) have put their heads together to help enhance the effectiveness of prospective DUR. Their effort was born from discussions in 1996 detailing situations, mostly outpatient, in which pharmacists were presented with "test" prescriptions. Pharmacists were given two prescriptions for one patient, for two drugs that interact with one another. In some cases, pharmacists overrode the drug interaction alerts from their computers and still filled the prescriptions.

"We identified four areas where there were issues," says **Thomas Fulda**, USP program director for DUR. "First and foremost is the issue of the criteria used to drive DUR. There is a need to develop evidence-based criteria."

Fulda referred to an article in *Current Therapeutic Research* in which various drug information sources were examined, including the American Hospital Formulary Service Drug Information, United States Pharmacopeia Drug Information, Drug Facts and Comparisons, Goodman and Gilman's Pharmacological Basis of Therapeutics, and Drug Reax from Micromedex. The references were compared to each other by looking at five therapeutic categories, then asking: For any drug-drug or drug-class interaction listed in one reference, what is the likelihood that that same interaction will appear in two of the references? In three? In four? Secondly, for interactions appearing in two or more references, what is the likelihood the references agree on the clinical significance of those interactions?

"The results showed that the likelihood of an interaction appearing in two or more of these references is increasingly infrequent with the greater number of references examined," Fulda says. "That is, it's much more common to find an interaction listed in only one reference and not in two. It's actually rare to find the same interaction listed in three or more of the references. Furthermore, when interactions did appear in two or more references, those references disagreed on the clinical significance of the interaction.

"Several other studies have been reported since then, including one in which results of data of DUR alerts collected from 41 pharmacies showed that pharmacists override 88% of alerts generated by their computers."

Fulda says the reasons pharmacists gave in this study for overriding the alerts included: 1) the pharmacist already knew about the potential danger but didn't believe it to be significant, and 2) the pharmacist didn't believe the alert to be of any clinical significance to a particular patient.

"These studies point out some of the problems associated with DUR," says Fulda. "Based on the drug information evaluation, the quality of data supporting the criteria for DUR alerts is definitely in question."

'Pharmacists override 88% of [drug interaction] alerts generated by their computers.'

The second focus for Fulda and colleagues is the adequacy of prospective DUR.

"DUR system users should be able to query their computers to determine the number of alerts generated by their systems," Fulda says. "For example, they should be able to learn the number of alerts generated for potential interactions between digoxin and quinidine. But if you ask pharmacists in chains or hospitals to do this, or if you ask the PBMs, they can't do it."

The systems aren't collecting the information, Fulda says. "By the time the pharmacist sends the alert back, the claim has already been adjudicated. If the pharmacist intervenes, another prescription and claim transaction must take place."

A third issue is the quality of systems design. "There are discrepancies in the way different systems do things," says Fulda. Based on these differences and the various ways items are flagged, one system may give an alert, but another system may not.

A fourth issue deals with the professional practice environment.

"All the systems use criteria packages from First DataBank," Fulda says. "These packages take a very comprehensive approach and flag situations beyond just those with significant clinical consequences. This becomes a double-edged sword. Pharmacists get too many inconsequential alerts, so they override and ignore alerts. At the same time, pharmacists are afraid to have a system that is too tightly focused as that kind of system might overlook several types of potential problems and not alert the pharmacist to situations that they might otherwise overlook. That side of the sword poses potential liable suits."

Fulda and his colleagues have written a paper based on their evaluation of these four issues, which is pending publication at this time. In this paper, under the lead authorship of Elizabeth Crischilles, the team also presents recommendations based on its evaluation. (*DUR* will report the citation of the article as soon as it is known.)

"The Academy of Managed Care Pharmacy is in the very early stages of a project to solve these problems," Fulda says. "The first step is to identify drug-drug interaction criteria that are evidence-based and have significant clinical outcomes. One possible part of the solution is to prevent a pharmacy claim from being adjudicated in the computer unless the pharmacist has done something in response to any alerts that appeared when the prescription order was entered.

"Our main concern has been the science behind the criteria," Fulda adds. "It's then up to those who use the DUR systems and who are involved in developing them to see that the criteria are correctly implemented and that pharmacists are presented the depth of focus that both protects the patient and helps ensure that pharmacists don't overlook potential medication problems."

While important to patient care, prospective DUR can be difficult to perform in any practice setting, Browne says. "Pharmacists are only as empowered as the information available to them. Comprehensive prospective DUR can be limited to the hospital pharmacist who doesn't yet have lab data. The community pharmacist can be limited by not having full patient medical history or by simply not being aware of other drugs that patients might be taking that they buy from other pharmacies across town."

Still, Browne adds, "Prospective DUR is, or should be, exercised in every pharmacy setting. Each time a drug is dispensed, whether in a community pharmacy, a hospital pharmacy, a home health pharmacy, or a mail-order pharmacy, pharmacists need to perform prospective DUR based on the patient information they have at hand," says Browne.

Goals of DUR

Browne tells *DUR*, "Cost is not part of the equation we use in determining which drugs to evaluate for DUR or MUE. In fact, Joint

Commission said several years ago that it did not want cost entering into the equation at all." As stated by the Kansas Medicaid DUR Board, the goal of DUR for its Medicaid recipients is to improve "drug therapy, patient outcomes, and quality of care."[4] One of the initial goals of DUR, according to OBRA wording, was to reduce Medicaid fraud. Therefore, the goals of DUR, just like the definitions, terminology, and types of DUR, are many and appear to change with trends in pharmacy.

Recently, PCMA immediate past president John Thornton, called on members of pharmacy to form a task force to reduce medication errors by developing enhanced DUR systems. During his farewell address in November, Thornton discussed the consequences of medication errors that occur in prescribing and dispensing and said that, "No one in American healthcare is in a better position to take a lead role in addressing this problem than the members of PCMA." He added that the pharmaceutical benefits management companies cannot tackle this task alone. "Designing and implementing the kind of improved drug utilization review systems that will be capable of significantly reducing medication errors will require the cooperation of every segment of American health care."

In addition to PCMA, Thornton anticipates participation in the task force from the American Pharmaceutical Association, the Academy of Managed Care Pharmacy, the National Association of Chain Drug Stores, the National Council on Prescription Drug Programs, and key leaders such as J. Lyle Bootman of the Arizona University School of Pharmacy.

Professional duty

The benefits of DUR are not restricted just to patients. Pharmacist and attorney, Nicholas J. Lynn, writes in a continuing education lesson:

SOURCES

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Components to Include in Patient Counseling[6]

- the name and description of the medication
- the route, dosage form, route of administration, and duration of drug therapy special directions and precautions for the preparation, administration, and use of the drug by the patient
- common, severe or adverse effects or interactions and therapeutic contraindications that may be encountered, including their avoidance, and the acts required if they occur
- techniques for self-monitoring drug therapy
- proper storage of drugs
- prescription refill information
- action to be taken in the event of a misdose

"One of the better known developments in the 1990s that signaled society's recognition and acceptance of the pharmacist as a unique and vital member of the health care team was the enactment of the patient counseling and drug utilization review (DUR) requirements of the Omnibus Budget Reconciliation Act of 1990 (OBRA '90)."[6] Lynn maintains that performance of DUR by pharmacists, both retrospective and prospective, helps ensure their status as professionals. It also holds pharmacists liable, responsible to carry out their professional duty. However, by following guidelines set forth in OBRA '90 for DUR and patient counseling, a pharmacist helps protect himself professionally. Lynn writes, "A pharmacist should view the OBRA '90 requirements as more than rules that must be complied with; they are, in fact, a federally mandated risk management program."[6]

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UHC to implement Zynx Health information tools

University HealthSystem Consortium (UHC) has chosen Zynx Health to provide evidence-based tools on the Internet to all UHC hospitals. Through a suite of clinical data products, Zynx will provide pharmacists, nurses, and physicians with access to up-to-date evidence-based clinical information important in clinical decision making.

Zynx and UHC anticipate improved clinical performance and patient safety as a result of implementation of the information systems. The key to success of the systems lies in their ability to allow the health care team to customize evidence-based approaches to care, using peer-reviewed literature, and to facilitate improvement around the Joint Commission on Accreditation of Healthcare Organizations' (JCAHO's) core performance measures.

"Zynx Health will provide UHC with three different databases," says **Gregory Dorn**, MD, MPH, senior director for marketing and sales with Zynx. "The first of these is the Clinical Pathway Constructor (CPC), which provides continuously updated peer-reviewed literature in a digested format for acute care management of patients with 23 different conditions," Dorn tells *Drug Utilization Review*. "These conditions cover the causes for the majority of hospital admissions. The system then presents information about how to treat populations of patients with these conditions.

"Instead of presenting each article's abstract, we write a separate summary. A physician writes a one paragraph summary that is then edited twice — once for technical content, and once for readability. The summaries are objective. We also indicate the level of rigor of the studies, based on study design. The articles are organized based on topic areas. Each topic area then is summarized into a recommendation. Or, if conclusive data are too ambiguous, no recommendation is made." Dorn adds that the CPC provides aggregate medical literature. It should not be thought of as a drug information source in the traditional sense of the term. Rather, the database presents outcomes and consensus information about disease states and the medications used to treat them, based on the medical literature.

"The second system UHC will have is the Evidence-Based Forecaster. This system addresses the seven conditions that form the focus of the Health Care Financing Administration's Sixth Scope of Work. With this system, hospitals can measure their performance around the quality indicators provided by HCFA, as well as those extracted from the medical literature. There is much overlap in the two, but there are indicators in the literature that HCFA does not address. UHC hospitals can then ascertain their compliance with HCFA's Sixth Scope of Work," says Dorn.

Keep safety on track

"The Safety Optimizer is the third system," says Dorn. "This is a patient safety tool based on 10 patient safety issues, including medication errors, patient falls, patient restrains, and more. Health care providers can use this system to measure and track inpatient safety issues, including adverse events. The system also provides safety implementation strategies obtained from the medical literature. Additionally, Zynx has the permission of JCAHO to include both the sentinel events reporting and root cause analysis forms in the Safety Optimizer system."

"All three systems are updated quarterly and are available to participating institutions on the Internet. Access is secure and compartmentalized, though, so that systems from one hospital cannot be viewed by another."

Dorn expects application of the systems in UHC institutions to decrease work time for pharmacists. "It should decrease time pharmacists would otherwise spend looking up information on Medline and elsewhere," he says. "It will help pharmacists answer questions they could probably answer on a case-by-case basis anyhow, but which would otherwise take longer to research." In addition, Dorn says that consensus of information and recommendations available in the CPC database is not available by performing a Medline search.

"The interface is very intuitive," Dorn tells *DUR*, describing its user-friendliness. "Of course, it still requires the health care giver's

SOURCE

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initiative to carry out the recommendations, but this would not relieve the professional from exercising cognitive efforts. The information in the systems is not overly prescriptive. These tools still need local review of information and customization of the products to protocols at specific institutions. ■

Alosetron tablets removed from market

Glaxo Wellcome is voluntarily withdrawing its alosetron (Lotronex) tablets from the market. The Food and Drug Administration (FDA) is telling patients taking alosetron to discuss other treatment options with their health care providers.

Alosetron received FDA approval in February for treating irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. In August, after approval and launch of the product, the FDA told Glaxo to provide a medication guide for alosetron patients to help ensure they understand the health risks associated with using the drug. **(See *Drug Utilization Review*, October 2000 and August 2000.)** Those risks included complications of constipation and ischemic colitis.

At the same time, information for prescribers included seven reports of serious complications from constipation (resulting in six hospitalizations and three surgeries) and eight reports of ischemic colitis (resulting in four hospitalizations, four endoscopies, and no surgeries).

Glaxo's decision to pull the drug comes after further FDA analysis of post-marketing reports of patients taking alosetron, including 49 cases of ischemic colitis and 21 cases of severe constipation, resulting in 34 hospitalizations without surgery, 10 surgeries, and three deaths. The FDA also received reports of two additional deaths (not resulting from ischemic colitis or constipation). Following the analysis, Glaxo and the FDA met and discussed risk management options. Options included restriction of drug distribution and market withdrawal.

According to the FDA, goals of restricted drug distribution include:

- safer use of alosetron in appropriately informed patients;
- continued access to alosetron by severely debilitated IBS patients under closely monitored conditions;
- continued clinical studies into the benefits and risks and safe use of alosetron.

Volunteering to step aside

Glaxo Wellcome decided to voluntarily withdraw the drug and indicates its plan to recall the drug from pharmacies. In the mean time, alosetron will remain in pharmacies until supplies are returned to Glaxo or are depleted. Pharmacies may choose not to fill further prescriptions of alosetron.

The FDA has been aware of reports of adverse events since the drug's approval in February and has been monitoring reports of adverse events. In June, the FDA held a public advisory committee meeting to discuss management strategies based on post-marketing reports of

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adverse events associated with ischemic colitis and complications of constipation. At that time, no deaths had been reported. Following this meeting, Glaxo was asked to provide a medication guide for alosetron so that both patients and providers could be advised of the serious adverse effects associated with use of the drug. Glaxo Wellcome also mailed "Dear Healthcare Professional" and "Dear Pharmacist" letters at that time.

Pharmacists aware of adverse events associated with the use of alosetron should report those events to the FDA using a MedWatch report by calling (800) FDA-1088 or visiting the FDA Web site at www.fda.gov/medwatch.

For more information, go to the Lotronex information Web page created by the FDA's Center for Drug Evaluation and Research: www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm. ■

More 'supplemental' news: Tiratricol is trouble

The Food and Drug Administration (FDA) is warning consumers of dietary supplements containing tiratricol, also called triiodothyroacetic acid or TRIAC. Tiratricol is a potent thyroid hormone that can result in serious events, including heart attacks and strokes. Despite four recalls in seven months, various products containing tiratricol still may have reached consumers' hands. The FDA asks that all consumers stop using these products immediately.

In November 1999, the FDA warned the public against using Triax Metabolic Accelerator, a dietary supplement used for weight loss, manufactured by Syntrax Innovations. Since then, several other firms have recalled similar products containing tiratricol. Distribution of these products has been primarily through retail sales to health food stores, fitness centers, and gymnasiums. Similar recalls since that time include:

• A recall made in April 2000 by J.N.G. Sports Supplement Distributors of Tricana Metabolic Hormone Analogue, 1 mg capsules, labeled as a fat burner to be used in reducing obesity and cellulite.

• An April 2000 recall by Thermo-Life International of the same Tricana Metabolic Hormone Analogue from nine direct wholesale accounts. This included a request for sub-recalls by wholesalers who reportedly sold the product through the Internet.

• A third April 2000 recall, this one by Gentech LLC of Tria-Cutz, Thyroid Stimulator, Dietary Supplement Capsules containing 1 mg tiratricol per capsule. The product had labeling claims similar to those of Tricana Metabolic Hormone Analogue. Tria-Cutz was distributed to 45 retail units (namely stores and gyms) and to 30 individuals totaling approximately 1,570 bottles.

• A September 2000 recall by ATF Fitness Products Inc. of Sci-Fi-Tri-Cuts Dietary Supplement Capsules. This product contains 1 mg of tiratricol per capsule, but does not have the claims associated with the other products listed above. This product was sold to 135 accounts, namely gyms and health food stores.

The FDA asks that everyone who purchased these or similar products containing tiratricol stop using them immediately and report any adverse events they've experienced. Such side effects include insomnia, nervousness, sweating, and diarrhea. The *FDA Talk Paper* on this subject can be viewed at www.fda.gov/bbs/topics/ANSWERS/ANS01057.html. ■

DRUG CRITERIA & OUTCOMES™

Levetiracetam (Keppra) for treatment of partial seizures

By **John Fowler**, PharmD candidate
Medical University of South Carolina
Charleston

Indication:

Levetiracetam (Keppra), by UCB Pharma, is approved by the Food and Drug Administration (FDA) for supplemental therapy in the treatment of partial seizures in adult patients with epilepsy.[1]

Pharmacology:

The antiepileptic activity of levetiracetam is thought to occur via a novel pathway that does not appear to affect known mechanisms of inhibitory and excitatory neurotransmission.[1] EEG recordings of hippocampal epileptiform activity have shown that levetiracetam appears to prevent seizure propagation by stabilizing neuronal cell membrane potentials without causing hyperpolarization.[1]

Pharmacokinetics:

Absorption: The bioavailability of levetiracetam approaches 100% and is unaffected by food, antacids, or the size of the dose. Peak drug concentrations (Cmax) and area under the curve (AUC) concentrations display linear kinetics in healthy volunteers.[1,2]

Distribution: Plasma protein binding of levetiracetam and its major inactive metabolite is less than 10%. The average volume of distribution in a 70 kg human is between 35 and 49 liters, indicating that levetiracetam is distributed into extracellular fluids.[1,2]

Metabolism: Approximately 35% of each dose of levetiracetam is metabolized via cytochrome P450 independent enzymatic hydrolysis to an inactive carboxylic acid metabolite. Therefore, levetiracetam is not subject to induction or inhibition by other drugs. Two other inactive metabolites account for less than 3% of the administered dose. Neither the primary metabolite of levetiracetam nor levetiracetam undergoes enantiomeric interconversion.[1,2]

How it exits

Elimination: Levetiracetam is primarily eliminated in the urine as the parent drug (~66%) via first-order elimination. Renal and total clearance of levetiracetam and its carboxylic acid metabolite are directly proportional to creatinine clearance and both are readily removed by hemodialysis. Renal elimination of the carboxylic acid metabolite of levetiracetam is decreased by coadministration of probenecid.[1,2] Elimination of levetiracetam and its metabolites in feces is negligible.[2] The half-life of levetiracetam is approximately seven hours in adults who have normal renal function.[1] It is unknown if levetiracetam is excreted in human breast milk.[1]

Selected clinical trials:

Patients were eligible for the three pivotal trials[3,4,5] if they were 16 years of age or older, experienced a minimum of one seizure per week despite a stable regimen of one or two antiepileptic drugs (AEDs), and if they had at least a two-year history of partial seizures. Study exclusion criteria included the following: current use of medications with central nervous system (CNS) activity (concomitant use of one or two antiepileptic drugs was mandatory for study inclusion); a history of drug or alcohol abuse; weight less than 50 kg; clusters of partial seizures during the baseline period; the display of either suicidal tendencies or psychiatric illness that required treatment; or lack of general good health. The only differences among the three studies with regard to inclusion and

exclusion criteria were as follows: in the studies by Cereghino and Ben-Menachem, patients who exhibited clusters of partial seizures three months or five years prior to entry, respectively, were excluded; in the study by Ben-Menachem, the use of only one other concomitant antiepileptic drug was allowed; in the study by Ben-Menachem, the required baseline seizure rate was one-half of the baseline seizure rate in the studies by Cereghino and Shorvon. Therefore, patients in the studies by Cereghino and Shorvon were generally more resistant to current therapy.[3,4,5]

The primary measure of effectiveness in all three studies was the mean or median percent reduction in weekly partial seizure frequency during the titration and maintenance periods. The number of patients with ≥ 50% reduction from their baseline seizure frequency was the secondary endpoint.[3,4,5]

Trials compare levetiracetam to placebo

Cereghino and colleagues[3] conducted a multicenter, parallel-group, double-blind, randomized, controlled trial that was designed to compare the difference in efficacy of levetiracetam to placebo in the treatment of adult patients who had partial seizures that were refractory to the use of one or two other antiepileptic drugs. On average, patients were 38 years old and had had epilepsy for 24.2 years. A total of 294 patients, 62% of whom took two antiepileptic drugs, were randomized to one of three treatment arms after a prospective 12-week baseline period. The treatment arms included the following: levetiracetam, 500 mg, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n = 98); levetiracetam, 1,500 mg, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n = 101); or placebo, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n = 95). A four-week titration period ensued, after which patients were followed for 14 weeks. Both primary and secondary outcome measures included the titration and maintenance periods.[3]

Shorvon and colleagues[4] conducted a randomized, double-blind, multicenter trial with a cross-over design to assess the effectiveness of levetiracetam vs. placebo in the treatment of adult patients who experienced partial seizures that were resistant to the use of one or two other antiepileptic drugs. The average patient age was 37 years, with most patients having had epilepsy for 23.6 years. Three hundred twenty-four patients participated in this trial. Two hundred forty-seven (76%) were also taking two antiepileptic drugs. The patients were randomized to one of three treatment arms after an eight- to 12-week prospective baseline period. The treatment arms were: levetiracetam, 500 mg, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n = 106); levetiracetam, 1,000 mg, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n = 106); or placebo, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n = 112). After a four-week titration period, the patients were followed for 12 weeks. Both primary and secondary outcome measures included the titration and maintenance periods.[4]

Ben-Menachem and colleagues[5] conducted a randomized, double-blind, parallel, multicenter trial that evaluated the efficacy of levetiracetam vs. placebo in the treatment of partial seizures in adult patients that were resistant to the use of one other antiepileptic drug. On average, patients were 36 years old and had had epilepsy for 19 years. A total of 286 patients were randomized to one of two treatments after a prospective 12-week baseline period. The treatment arms were: levetiracetam, 1,500 mg, given orally, twice daily, plus one concomitant antiepileptic drug (n = 181); or placebo, given orally, twice daily, plus one concomitant antiepileptic drug (n = 105). A 4-week titration period ensued after which patients were followed for 12 weeks. Both primary and secondary outcome measures were included in the titration and maintenance periods.[5]

Adverse reactions:

In clinical trials, levetiracetam has been studied in 769 patients as adjunctive therapy for partial seizures. During these trials, patients received either one or two concomitant AEDs. Adverse effects reported at a frequency of ≥ 2% when compared to placebo included somnolence (7%), asthenia (6%), dizziness (5%), infection (5%), ataxia (2%), depression (2%), emotional lability (2%), nervousness (2%), pharyngitis (2%), and vertigo (2%).[1,3,4,5] Asthenia, somnolence, and dizziness appeared to occur predominantly during the first four weeks of treatment. Slow upward titration of the

levetiracetam dose may help decrease the incidence of somnolence. Laboratory changes that occurred during clinical trials at a frequency of ≥ 1% when compared to placebo included the following: leukopenia (1.4%) and neutropenia (1%).[1]

Pregnancy/lactation:

Levetiracetam is rated as a pregnancy category C, based on the presence of teratogenic or embryocidal activity during animal studies.[1,5] Levetiracetam has not been studied in pregnant women and has a pregnancy category C rating based solely on animal data. It is not known whether levetiracetam is excreted in human breast milk. The use of levetiracetam during pregnancy or while nursing should be reserved for the adjunctive treatment of partial seizures only if the potential benefit justifies the potential risk to the fetus or nursing infant.[1]

Contraindications:

Levetiracetam is contraindicated in individuals with a prior history of a hypersensitivity reaction to levetiracetam or any of the inactive ingredients in levetiracetam tablets.[1]

Warnings:

In controlled clinical trials, patients treated with levetiracetam developed psychotic symptoms, psychotic depression, or attempted suicide at an increased frequency of 0.5% over placebo-treated patients. One of these cases resulted in suicide. Levetiracetam-induced psychosis was seen during the first week of treatment and abated following treatment discontinuation.

The reported cases of hallucination, psychotic depression, or attempted suicide either resolved or were not attempted again despite continued treatment. All of these cases occurred within the first six months of therapy.[1]

Dosage and administration:

A definitive dose-response relationship has not been established in clinical trials. The recommended dose of levetiracetam as adjunctive therapy for partial seizures in adults is 1,000 mg, by mouth, per day, given as two divided doses. If an incomplete response is seen after two weeks, the daily dose can be increased by 1,000 mg at two-week intervals until the maximum daily dose of 3,000 mg is obtained.

Levetiracetam is only available as a tablet for

Causes of Seizures

- High fevers in children, also known as a fever fit. A temperature higher than 102° F can set off a fever fit. High fevers are the most common cause of seizures in children ages 6 months to 4 years. These seizures are generally harmless.
- Epilepsy; seizure is the most common symptom of epilepsy
- Brain injury, tumor, or stroke
- Electric shock
- Heat stroke
- Poisons
- Infections
- Reactions or overdoses to medicines or drugs
- Reye's syndrome
- Snakebites
- Vaccinations
- Breath-holding
- Sometimes the cause is unknown

Source: The American Institute for Preventive Medicine at www.healthy.net/asp/templates/book.asp?PageType=Book&ID=815.

Drugs Commonly Used for Epilepsy Prevention

- Carbamazepine (Tegretol, Tegretol XR, Carbatrol)
- Clonazepam (Klonopin)
- Ethosuximide (Zarontin)
- Phenobarbital
- Phenytoin (Dilantin)
- Primidone (Mysoline)
- Valproic acid (Depakene)
- Divalproex sodium (Depakote)
- Felbamate (Felbatol)
- Gabapentin (Neurontin)
- Lamotrigine (Lamictal)
- Levetiracetam (Keppra)
- Oxcarbazepine (Trileptal)
- Tiagabine (Gabitril)
- Topiramate (Topamax)
- Zonisamide (Zonagran)
- Others in development

Source: The Epilepsy Foundation of America, www.efa.org/answerplace/treatment/treatment.html

Useful Web Sites

- Epilepsy Foundation of America at www.efa.org/
- Epilepsy USA, the Epilepsy Foundation's magazine at www.efa.org/epusa/index.html

oral administration. The dose of levetiracetam should be adjusted in patients with renal dysfunction according to the product labeling and is adjusted according to patient creatinine clearance (ClCr). Patients with normal renal function (ClCr > 80 mL / min) should be dosed 500 to 1,500 mg every 12 hours. Those with mild renal impairment (ClCr 50 to 80 mL / min) may be dosed 500 to 1,000 mg every 12 hours. Moderate renal dysfunction (ClCr 30 to 50 mL / min) requires an adjustment down to 250 to 750 mg every 12 hours. For severe renal impairment (ClCr < 30 mL / min), the recommended dose is 250 to 500 mg every 12 hours, and for patients with end stage renal disease requiring dialysis, the recommended dose is 500 to 1,000 mg every 24 hours. Approximately 50% of the total body stores of levetiracetam are removed during a four-hour hemodialysis session. Therefore, a 250 mg to 500 mg supplemental dose should be given at the end of each dialysis session. There is no need to adjust the dose of levetiracetam in patients with hepatic dysfunction.[1]

Drug interactions:

The pharmacokinetics of levetiracetam were studied in humans when levetiracetam was coadministered with digoxin, warfarin, oral contraceptives, probenecid, and other antiepileptic drugs, including the following: carbamazepine; gabapentin; lamotrigine; phenobarbital; phenytoin; primidone; and valproic acid. No interactions of clinical significance were reported.[1,2]

Drug-food interactions:

Administration of levetiracetam with food decreases peak serum concentrations but not the bioavailability. Levetiracetam can be administered without regard to food.[1]

Dosage forms available:

Levetiracetam is supplied as 250 mg, 500 mg and 750 mg tablets.[1]

Potential for medication errors:

Levetiracetam 250 mg and 500 mg tablets could be confused for Levaquin 250 mg and 500 mg tablets. However, Levaquin is dosed once daily and levetiracetam is dosed twice daily.

Discussion:

Levetiracetam is FDA-approved for the adjunctive treatment of partial seizures in adults and has been studied in 769 patients at daily doses ranging from 1,000 mg to 3,000 mg administered orally in two divided doses.[1] The most frequently reported adverse effects were somnolence (7%), asthenia (6%), dizziness (5%), infection (5%), ataxia (2%), depression (2%), emotional lability (2%), nervousness (2%), pharyngitis (2%), and vertigo (2%).[1] During these trials, patients treated with levetiracetam experienced either psychotic symptoms, psychotic depression, or attempted suicide at an increased frequency of 0.5% over placebo-treated patients. Four of these patients attempted suicide, whereas, no placebo-treated patients attempted suicide. One of these cases resulted in death.[1] Patients were excluded from these trials if they were taking drugs with CNS activity (with the exception of other antiepileptic drugs) or displayed either suicidal tendencies or psychiatric illness that required treatment.[3,4,5]

Drug interaction unlikely

Levetiracetam has a low potential for drug interactions because it is not a cytochrome P450 substrate or inhibitor and is < 10 % bound to plasma proteins.[1,2] The primary route of levetiracetam elimination is via the kidneys and it exhibits predictable first-order kinetics.[1,2] Levetiracetam has a FDA pregnancy category C rating.[1] Because the safety and efficacy of levetiracetam has not been compared to other antiepileptic drugs in the adjunctive treatment of partial seizures, direct comparisons cannot be made.

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Calfactant (Infasurf) for respiratory distress

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Indications:

Calfactant (Infasurf), manufactured by Forest Pharmaceuticals, is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants (less than 29 weeks gestational age) that are at high risk for developing RDS, and for the treatment of premature infants ((72 hours of age) who develop RDS and require endotracheal (ET) intubation.[1,2]

Pharmacology:

Calfactant is a calf-lung surfactant that contains phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C).[1,2] It rapidly adsorbs to the surface of the air:liquid interface resulting in decreased surface tension and stabilization of the alveoli, thereby increasing lung compliance and decreasing the work of breathing.[1,2]

Pharmacokinetics:

Absorption and metabolism of calfactant in humans is unknown, because pharmacokinetic studies have not been performed. In one study, radiolabeled calfactant was administered to adult rabbits. After 24 hours, 50% of the radioactivity persisted in the lung alveolar lining, 25% persisted in the lung tissue, and less than 5% was found in other organs.[1]

Selected clinical trials:

Bloom and colleagues[3] conducted a randomized, double-blind clinical trial comparing the safety and efficacy of calfactant and beractant in the prevention and treatment of RDS. The prevention arm enrolled 374 patients (calfactant, n = 180; beractant, n = 194) less than 29 weeks gestation with birth weights less than 1,250 g. The treatment arm enrolled 608 patients (calfactant, n = 303; beractant, n = 305) who were less than 2,000 g birth weight with established RDS. The primary endpoints were a 25% reduction in the need for a second dose in the prevention arm and a 25% reduction in the need for a third dose in the treatment arm. Secondary endpoints included severity of RDS, number of air leaks, complications of surfactant administration, and survival to 36 weeks postmenstrual age without oxygen requirement.[3]

Infants in both arms were randomized to receive either calfactant 4 mL/kg via ET tube or beractant 4 mL/kg via ET tube.[3] Administration of surfactant occurred within 15 minutes of birth in the prevention arm and within two hours of meeting criteria in the treatment arm. In the prevention arm, the patients were stratified into two gestational age groups (less than 27 weeks and 27 to 29 weeks). In the treatment arm, stratification was according to birth weight (less than 750, 751 to 1,250, and 1,251 to 2,000 g). In order to maintain blinding, both the initial and subsequent doses were administered according to the beractant dosing protocol (100 mg/kg of phospholipid). In the first 96 hours, three repeat treatments at least six hours apart were scheduled only if the infant remained intubated for RDS and required at least 30% oxygen.[3]

Comparing doses

The primary endpoint of the number of doses required did not reach statistical significance in the prophylaxis arm.[3] In the treatment arm, the number of patients requiring four or more doses was significantly lower in the calfactant group than in the beractant group (67 vs. 101, respectively). The number of hours between doses reached statistical significance after dose two in the prophylactic arm, and was significantly longer between all doses in the treatment arm.[3]

The secondary endpoints of total number of deaths and deaths related to RDS were statistically significant in the prophylaxis arm.[3] There were 40 total deaths in the calfactant arm and 26 total deaths in the beractant arm ($p = 0.03$). There were 25 RDS-related deaths in the calfactant arm and nine RDS-related deaths in the beractant arm ($p = 0.005$). This was an unexpected finding and is explained by examining the birth-weight subgroups. The calfactant arm had 63% mortality for infants weighing less than 600 g, a rate that would be expected in such low-weight infants. The beractant arm had an unusually low mortality (26%) in this same weight group. The investigators do not have an explanation for this occurrence, and these results have not been seen in other studies.[3]

In the treatment arm, significant reductions in the time-weighted average (0 to 72 hours) for supplemental oxygen and mean airway pressure requirements were seen in the calfactant arm.[3] There was no statistically significant difference in any other secondary endpoints in the prophylaxis or treatment arms.[3]

The authors concluded that a modest improvement in mean airway pressure, need for supplemental oxygen, and duration of surfactant effect can be achieved when calfactant is administered to infants of less than 2,000 g birth weight with established RDS.[3] The lengthening of the duration of surfactant effect is also seen when calfactant is administered to infants less than 29 weeks gestation with birth weights less than 1,250 g.[3]

Adverse reactions:

The most common adverse reactions seen in clinical trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of calfactant into the endotracheal tube (21%), manual ventilation (16%), and reintubation (3%). In general, these events were transient and did not result in serious complications or death.[1,2]

Pregnancy/lactation:

Calfactant has not been assigned a Food and Drug Administration pregnancy category since studies assessing the effect of calfactant in pregnancy have not been performed.[1,2,4] Lung surfactants are sometimes used in the treatment of acute respiratory distress syndrome in adults. If this agent were to be considered for use during pregnancy, the benefit to the mother would need to outweigh the possible risk to the fetus, since studies in women or animals are not available.[1]

Pulmonary Surfactant

- Is a phospholipid bound to a protein
- Is secreted by type II alveolar cells
- Lowers surface tension of the water layer at the alveolar surface, which increases lung compliance (i.e., it makes it easier for the lungs to expand)
- Its concentration decreases when lung volume is small and constant
- Is replenished when type II alveolar cells are stimulated by a deep breath

From Vander AJ, Sherman JH, Luciano DS, eds. *Human Physiology.* 5th ed. New York, NY: McGraw-Hill Publishing Co.; 1990.

Contraindications:

There are no contraindications stated in the product labeling for this agent.[1,2]

Warnings:

The administration of exogenous surfactants rapidly improves oxygenation and lung compliance. Patients should be carefully monitored to allow for modification of oxygen therapy and ventilatory support in response to respiratory status changes.[1] If cyanosis, bradycardia, airway obstruction, or reflux of calfactant into the endotracheal tube occur, therapy should be discontinued, followed by appropriate management of these complications. After resolution of complications, therapy may be reinitiated with appropriate monitoring.[1] There is a theoretical risk of immunologic or allergic reactions due to the foreign proteins in calfactant; however, no cases have been described in humans.[1,2]

Dosage and administration:

Calfactant is intended for intratracheal administration only. The usual dose is 3 mL/kg body weight at birth instilled via an endotracheal tube.[1,2] It may be administered every 12 hours for a total of three doses. The product may settle during storage and should be gently swirled before administration; however, it should not be shaken. It does not require reconstitution or dilution. Calfactant should be refrigerated. Warming prior to administration is not necessary.[1,2]

Drug interactions:

There are no documented drug interactions.[1]

Drug-food interactions:

No drug-food interactions have been reported.[1]

Dosage forms available:

Calfactant is available as a sterile 35 mg/mL suspension for intratracheal use.[1,5]

Samples status:

Inpatient samples of calfactant should not be allowed.

Potential for medication errors:

A medication error could potentially occur with beractant since the name sounds similar and it is used for the same indication.

Filtration requirement:

Since calfactant is not an intravenous preparation, filtration is not required.

Discussion:

Calfactant is a calf-lung surfactant that contains phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C).[1,2] It is indicated for the prevention of RDS in premature infants (less than 29 weeks gestational age) who are at high risk for developing RDS, and for the treatment of premature infants ((72 hours of age) who develop RDS and require endotracheal intubation.[1,2]

Common adverse reactions seen with calfactant therapy are cyanosis, airway obstruction, bradycardia, reflux of calfactant into the endotracheal tube, need for manual ventilation, and reintubation.[1] Due to the rapid improvement in oxygenation that occurs following administration of calfactant, this agent should not be used in situations where rapid modifications of oxygen therapy and ventilatory support cannot be made (i.e., transport).

The two major categories of exogenous surfactant preparations are synthetic and natural preparations. Many trials have compared natural vs. synthetic surfactants. In general, natural surfactant preparations have a more rapid onset of action and a longer duration of action than the synthetic surfactant preparations.[6]

In a trial conducted by Bloom and colleagues comparing calfactant to beractant, a modest improvement in mean airway pressure, a decreased need for supplemental oxygen, and a longer duration of surfactant effect was seen with calfactant.[3] There was also a statistically significant difference in the number of infants requiring a fourth dose of surfactant therapy (67 vs. 101, respectively).[3] This is approximately a 10% reduction in the need for a fourth dose. Due to the high cost of these agents, the ability to use fewer doses without compromising efficacy should be an important consideration when choosing between surfactant preparations.

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IN THE PIPELINE

Pfizer has received an approvable letter from the Food and Drug Administration (FDA) for oral and intramuscular (IM) formulations of its atypical antipsychotic, ziprasidone (Zeldox), for the treatment of **schizophrenia**. The product is already launched in Sweden, in both oral and IM formulations. This represents the first IM formulation of an atypical antipsychotic.

Novartis says it does not expect any delay in the approval of its new monoclonal antibody **asthma therapy**, omalizumab (Xolair, E25), despite problems in animal trials with E26, a second-generation, more potent version of omalizumab. Omalizumab is the first in a new class of therapies for asthma that target immunoglobulin E, the antibody trigger of allergic reactions. Although some predict blockbuster status for the product, there are concerns about where exactly it will fit into asthma therapy and about its anticipated high cost.

Merck & Co.'s investigational drug etoricoxib (also referred to as MK-663) appears to relieve **moderate to severe pain associated with tooth extraction** to a greater degree and in shorter time than placebo. Results from a dose-ranging study of etoricoxib, ibuprofen, and placebo show that the overall analgesic effect of etoricoxib is not significantly different from that of ibuprofen. Etoricoxib is designed as a cyclooxygenase-2 (COX-2) enzyme inhibitor.

Biomira announces that an independent data

safety monitoring board (DSMB) has completed a second review of safety data from an ongoing phase III pivotal trial of 600 patients. The DSMB has recommended the trial continue without modifications. The trial is designed to study Biomira's Theratope **vaccine for metastatic breast cancer**. The goal for enrollment is 900 patients.

Baxter Healthcare Corp. announces initiation of a phase III clinical trial of its recombinant Factor VIII therapy for the treatment of **hemophilia A**. By eliminating the use of human- or animal-derived materials in producing the agent, the final product should be free from the risk of transmission of related infectious disease.

Aviron and American Home Products Corp. announce that a Biologics License Application for FluMist has been submitted to the FDA. FluMist is an investigational **intranasal influenza vaccine** for use in preventing influenza in children and adults.

IDEC Pharmaceuticals Corp. announces the submission of a BLA to the FDA for ibritumomab tiuxetan (Zevalin). Ibritumomab tiuxetan is submitted as a radioimmunotherapy for the treatment of low-grade or follicular, relapsed or refractory, CD20-positive, B-cell **non-Hodgkin's lymphoma** (NHL) and Rituximab-refractory follicular NHL. The FDA has designated the agent for fast-track review.

Genmab announces positive results from a phase I/II clinical trial of HuMax-CD4, a human antibody used to treat patients with **rheumatoid arthritis**. The study shows a high level of safety and activity in severely diseased patients.

United Therapeutics announces that its New Drug Application for UT-15 has been accepted by the FDA for filing. UT-15 is a prostacyclin analog being developed for subcutaneous treatment for **pulmonary arterial hypertension**. ■

New FDA Approvals

These drugs have received final approval from the Food and Drug Administration (FDA):

Topical agent clobetasol propionate (Olux) foam, 0.05%, by Connetics Corp. The FDA granted approval for this agent in May 2000. It is now available for use as short-term topical treatment of the inflammatory and pruritic manifestations of moderate to severe **corticosteroid-responsive dermatoses of the scalp**.

Bisphosphonate alendronate (Fosamax) by Merck & Co. The FDA has given approval for a new once-weekly formulation of alendronate for the prevention and treatment of **post-menopausal osteoporosis**. The weekly doses are 35 mg for prevention, and 70 mg for treatment.

HIV-1 combination agent abacavir sulfate, lamivudine, zidovudine (Trizivir) by Glaxo Wellcome. The FDA has granted approval for the use of Trizivir in the treatment of **HIV-1 infection**.

In-stent restenosis agent Checkmate System by Cordis Corp. The FDA has granted approval for this intravascular brachytherapy (or radiation) system for **recurrent blockages in coronary arteries** previously treated with coronary artery stents. The system's gamma-radiating Iridium-192 seeds are placed within the blocked stent for 15-20 minutes in order to interrupt the growth of scar tissue into the stent. The seeds are then removed.

Blood glucose monitor Sof-Tact by Abbott. FDA has granted approval for Sof-Tact, a new **diabetes management system** that is the first automated glucose monitor to provide lancing, blood collection, and glucose testing with a single button. The device also allows blood sampling from areas of the skin less sensitive than the fingertip, such as the arm.

Antihypertensive agent telmisartan and hydrochlorothiazide (Micardis HCT) by Boehringer Ingelheim Pharmaceuticals. Telmisartan is an angiotensin II antagonist (on the AT1 receptor type), and hydrochlorothiazide is a diuretic. The FDA has approved the combination for treatment of **hypertension**, alone or with other antihypertensives agents. The drug is available in tablets that are 40/12.5 mg and 80/12.5 mg of telmisartan/hydrochlorothiazide, respectively. ■