Volume 18, Number 1

SHANDS at the University of Florida

January 2004

Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met on November 18, 2003. 3 drugs were added in the *Formulary* and 1 drug was deleted. 1 dosage form was designated not available and automatic interchange was approved.

◆ ADDED

Capecitabine
(Xeloda® by Roche)

Fenofibrate Tablets
(Tricor® by Abbott Laboratories)

Tegaserod
(Zelnorm® by Novartis)

◆ DELETED

Arsenic trioxide
(Trisenox® by Cell Laboratories)

◆ NONFORMULARY AND NOT AVAILABLE

Fenofibrate capsules (eg, Lofibra® by Gate Pharmaceuticals)*

*Automatically interchanged to fenofibrate tablets

Capecitabine is an oral prodrug of the intravenous antineoplastic agent 5-fluorouracil (5-FU). It is preferentially converted to the active form of the drug at the site of tumor, allowing for high tumor exposure to drug (mimicking continuous infusion 5-FU) without high systemic exposure. Capecitabine has a labeled indication for treatment of metastatic breast cancer in patients who have failed therapy with prior anthracycline or paclitaxel-containing regimens and as a first-line agent for the treatment of metastatic colorectal cancer.

Recently, phase II studies have been conducted and have demon-

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DRUG INFORMATION FORUM

Identifying tablets & capsules by imprint codes

Every prescription and over-the-counter (OTC) oral solid dosage form (ie, tablets and capsules) must have a unique imprint code according to federal law. These imprint codes are sometimes referred to as a "marking" or "inscription" and are usually a combination of letters and numbers, although they can be a company logo or the name of the drug. Usually imprints are cryptic codes that mean something only if you know where to go to break the code.

Interestingly, although federal law mandates that all prescription dosage forms have the unique imprint, there is no official list to look up the codes. Therefore, healthcare professionals must use commercial references to determine what a product is based on the imprint.

Drug identification is important in overdoses. If a patient presents with a half-consumed bottle of tablets or capsules, the identity of the potential toxin must be known in order to appropriately treat the patient.

Being able to identify drugs based on imprint codes is also important when patients bring their medications into the hospital, when patients bring all their medications into your office all mixed in one container, or when a patients thinks a prescription has been misfilled. For these reasons, it is important to know which references can be used to identify tablets and capsules based on imprint codes.

We are fortunate to have several references available from any computer terminal at Shands at UF that will identify imprint codes. IDENTIDEX®, which is marketed by Micromedex, is available through the Health Center Library's databases page at http://healthcare. micromedex.com/. Under the "Find Drugs and Substances" section of this page, select Toxicology, then select INDENTIDEX®. You can simply put the imprint code in the search field, which will lead you to a list of products.

Clinical Pharmacology (http://cpip.gsm.com/) can also be used to identify products. Select the "Drug Products" tab at the top of the page, then the "Product Identification" link. Follow the directions for use in the middle frame, which are a little more difficult than IDENTIDEX®. Our own research suggests that IDENTIDEX® is easier to use than Clinical Pharmacology.

Another reference that is free and can be used from any computer with Internet access is RxList (www.rxlist.com). Select the "RXLIST ADVANCED SEARCH" link, the scroll down to the "RxList-ID Imprint Code Identification" search field.

Our own research has found that IDENTIDEX® is the best reference used to look up imprint codes.[1] IDENTIDEX® identified the most tablets and capsules based on imprint codes. However, RxList is pretty good—considering that it is available to anyone free of charge. Our research also found that drugs on the market for less than a year, generic drugs, and OTC drugs are the most difficult to identify using imprint codes. Even using the best references, there will be drugs that cannot be identified.

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◆ Ipecac not recommended

◆ Who is P&T?

Formulary update, *from page 1*
strated efficacy of capecitabine in the treatment of metastatic pancreatic and gastric cancers. The most common adverse effects occurring in patients receiving therapy with capecitabine include diarrhea, nausea, vomiting, hand-and-foot syndrome, and stomatitis. However, there is a lower incidence of alopecia and myelosuppression observed with capecitabine therapy compared to therapy with 5-FU.

Capecitabine offers the advantage of being orally administered and, therefore, does not pose the same complication risks associated with intravenous therapy (ie, the need for central venous access, risk of thrombosis, bleeding, and infection). Capecitabine also facilitates outpatient administration of chemotherapy, thus allowing patients an improved quality of life versus those receiving chemotherapy in the hospital.

While the cost of capecitabine is more expensive than intravenous 5-FU, most patients would be able to receive therapy as an outpatient. Patients most likely requiring capecitabine therapy as an inpatient would be those patients suffering from complications of their disease (such as severe uncontrolled pain associated with progressive pancreatic cancer).

Like all cytotoxic chemotherapy, only credentialed prescribers can prescribe capecitabine. There is a potential for a medication error when the brand name is used. Xeloda® and Xenical® (orlistat) may be confused. Although the doses used are vastly different, both drugs begin in "Xe" and caution is recommended.

Fenofibrate is a fibric acid derivative used for the treatment of dyslipidemia. Fenofibrate was evaluated for formulary addition based on its high nonformulary use.

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults does not differentiate among the fibrates in their recommendations. Fibrates are recommended for persons with very high triglycerides to reduce the risk for pancreatitis. They are also recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL). Fibrates should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia. They should also be considered in combination with statin therapy in people who have elevated LDL cholesterol and atherogenic dyslipidemia.

Few studies have compared the fibrates to each other. Further definitive trials are needed before firm comparisons of effectiveness between these medications can be made. Thus far, studies have shown gemfibrozil to be similarly effective as fenofibrate in reducing triglyceride levels. However, there is some data that suggests that patients who cannot tolerate or who do not respond to gemfibrozil will benefit from fenofibrate.

Most patients should respond satisfactorily to gemfibrozil; however, fenofibrate may offer an alternative in some patients who do not response to gemfibrozil.

Micronized **fenofibrate tablets** and **capsules** are not bioequivalent. The bioavailability of micronized fenofibrate in the tablet formulation is significantly greater than the bioavailability for the capsule formulation. The 200-mg capsule is considered comparable to the 160-mg tablet; and the 67-mg capsule is considered equivalent to the 54-mg tablet (ie, the tablets are approximately 25% more bioavailable).

Fenofibrate tablets were added in the *Formulary* while fenofibrate capsules were designated nonformulary and not available. When an order for fenofibrate capsules is received, a P&T authorized interchange will be done using the following guidelines: 200-mg capsule = 160-mg tablet and the 67 - mg capsule = 54 mg-tablet. Fenofibrate will not be available in the *Charity Care Formulary.*

Tegaserod is used in the treatment of irritable bowel syndrome. It was originally considered by the P&T Committee in September 2002 and tabled based on a lack of data to support its addition in the *Formulary.* Since 12 months have passed, tegaserod was reconsidered for formulary addition. Tegaserod has been the number 1 nonformulary drug in terms of doses dispensed.

Tegaserod has a labeled indication for the short-term treatment of constipation-predominant irritable bowel syndrome (IBS) in women. Tegaserod is the only drug in the US with a labeled indication for constipation-predominant IBS.

Research suggests neurotransmitters are involved in the pathogenesis of IBS. Tegaserod stimulates serotonin Type-4 receptors, which are thought to trigger the release of other neurotransmitters that stimulate intestinal peristalsis and secretion.

The labeled dosage of tegaserod is 6 mg twice a day before meals for 4 to 6 weeks. Responders may receive an additional 4 to 6 weeks. The safety and efficacy of tegaserod in children has not been established; however, research in adolescents is being planned.

The quality of the published evidence for the treatment of IBS is not good. Defining and measuring the appropriate response variables for IBS is difficult. However, several studies have now been published that support the use of tegaserod for the short-term treatment of IBS in women. Available studies suggest tegaserod may not be as beneficial in men; however, these studies are underpowered to detect sex-based differences in efficacy. Also, there still is no long-term efficacy data for IBS.

There is some concern about the use of tegaserod. The limited available published data suggest the treatment effect in IBS is small and may decrease with time. Since IBS is a chronic condition, this could be a problem. Considering the level of evidence, modest benefit, and cost, tegaserod should be reserved for patients with constipation-predominant IBS who have no response to fiber or laxatives and antispasmodics.

There are limited data available to support the off-labeled use of tegaserod. Only 1 small study is published supporting the use of tegaserod for GERD. There are no published data for other potential off-labeled uses (eg, chronic constipation, gastroparesis). Abstracts on these topics have been presented at GI meetings and publication is expected.

Tegaserod was added in the *Formulary*; however, the volume of use will be monitored. If usage is higher that expected, an audit of its use will be considered. Tegaserod will not be listed in the *Charity Care Formulary.*

Arsenic trioxide is used for the treatment of leukemia. The labeled indication for arsenic trioxide is for the induction of remission and consolidation of acute promyelocytic leukemia (APL) in patients who are refractory to or have relapsed from retinoid and anthracycline chemotherapy and whose APL is characterized by the presence of the t(15;17) translocation of the PML/RAR-alpha gene expression. APL is a subset of acute myelocytic leukemia with this specific chromosomal abnormality.

Current treatment for newly diagnosed APL includes all-trans retinoic acid (ATRA) in combination with anthracyclines for consolidation, then ATRA for maintenance therapy. Although most patients respond to standard therapy, about one-third of patients who achieve remission will relapse. Patients with APL who relapse are treated with stem cell transplantation (SCT), when an HLA-compatible donor is available.

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DRUG INFORMATION FORUM

Misunderstandings about COX-2 inhibitors

"COX-2 inhibitors" are the newest nonsteroidal anti-inflammatory drugs (NSAIDs) on the market (ie, celecoxib [Celebrex®], rofecoxib [Vioxx®], and valdecoxib [Bextra®]). These agents are specific for the second isoform of cyclooxygenase (COX). The COX enzymes catalyze the conversion of arachidonic acid to prostaglandins and thromboxanes, which subsequently regulate physiologic processes throughout the body. When prostaglandins cause inflammation and pain, interruption of the production of prostaglandins results in a favorable therapeutic effect. When beneficial prostaglandins are inhibited (ie, those responsible for protection of the gastrointestinal tract or perfusion of the kidney), adverse effects result.

COX-2 inhibitors were developed because traditional NSAIDs are nonspecific cyclooxygenase inhibitors that inhibit pain and inflammation associated with the COX-2 enzyme as well as normal regulatory effects associated with the COX-1 enzymes. The inhibition of COX-1 in the gastrointestinal tract prevents the protective effects of this enzyme. COX-2 inhibitors have less GI toxicity because these drugs have little effect on the COX-1 enzyme.

Although COX-2 inhibitors have less GI toxicity, they do cause GI toxicity. Because of a selection bias (ie, using COX-2 inhibitors selectively in patients who are risk for NSAID-induced toxicity), GI toxicity with COX-2 inhibitors may be misperceived as being common. There are other misperceptions associated with the COX-2 inhibitors.

Because these are newer agents, some clinicians incorrectly think COX-2 inhibitors are more effective than traditional NSAIDs. COX-2 inhibitors are no more effective than traditional NSAIDs.

There are no published data that show that COX-2 inhibitors are better anti-inflammatory agents or better pain relievers.[1] This is particularly relevant for intermittent and short-term use. The better GI toxicity profile of COX-2 inhibitors is most relevant for long-term use. Since COX-2 inhibitors are no more effective, traditional NSAIDs are the preferred agents for short-term and intermittent use.

When COX-2 inhibitors were developed, it was hoped they would be less nephrotoxic. Unfortunately, COX-2 plays an important role in maintaining renal perfusion in the kidney. Kidney tissue is rich with the COX-2 enzyme. COX-2 inhibitors are just as nephrotoxic as traditional NSAIDs.

Published data show nephrotoxicity rates with COX-2 inhibitors are at least equal to that of traditional NSAIDs.[2–4] Selecting a COX-2 inhibitor over a traditional NSAID in an attempt to avoid nephrotoxicity is irrational. Risk factors for nephrotoxicity are the same for COX-2 inhibitors and traditional NSAIDs. Patients who are at risk for NSAID nephropathy have decreased renal blood flow and include those with volume depletion (eg, vomiting, diarrhea, diuretic therapy), congestive heart failure, cirrhosis, and chronic kidney disease.

COX-2 inhibitors have a lower incidence of gastrointestinal adverse effects when used chronically, but there is a limited role for COX-2 inhibitors in the inpatient setting (eg, continuation of outpatient chronic therapy in patients at high risk for gastrointestinal adverse effects). Misperceptions about the efficacy and safety of COX-2 inhibitors have led to overuse in the inpatient setting. Only celecoxib is listed in the Shands at UF *Formulary*. Rofecoxib and valdecoxib are not listed in the *Formulary*. Valdecoxib is nonformulary and not available.

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Formulary update, *from page 2*

Arsenic trioxide offers an alternative to SCT. The response rate depends on the patient's previous treatment status, but more than half of the previously treated patients responded in clinical trials.

Since arsenic trioxide is rarely used, this expensive agent often sits on the shelf, goes out-of-date, and must be wasted. Arsenic trioxide is never needed on short notice; therefore, it was designated nonformulary. It can be obtained through the nonformulary process for use in the rare instance that it is needed. It is a medium-priority nonformulary drug and may be obtained within 48 hours.

NEWS

Ipecac no longer recommended

The American Academy of Pediatrics recommends that the routine use of ipecac syrup in children who have swallowed a poisonous substance be stopped. Because no evidence shows that ipecac helps in the outpatient management of poisoning, it is recommended that home supplies of ipecac syrup be "flushed down the toilet." The presence of ipecac syrup in the home can lead to inappropriate use.

It was initially thought that giving ipecac would reduce ER visits and improve patient outcomes. There is no data to support this contention.[1] In fact, research shows that even when ipecac is used within 30 minutes of an ingestion, as much as 59% or as little as none of the poison is removed.[2] The vomiting induced by ipecac can also interfere with the administration of activated charcoal, which is effective in the prevention of absorption of some poisons.

Because of the misuse of ipecac syrup in patients with eating disorders, some are recommending that it be available only by prescription. Ipecac syrup is now available over-the-counter.

Parents are encouraged to take steps to prevent poisonings in their homes. If a poisoning does occur, a poison control center should be contacted immediately. The national telephone number that will connect the caller with the closest poison control center is 800-222-1222.

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Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 18, No. 1 January 2004

This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

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NEWS

Who is the P&T Committee?

The Pharmacy and Therapeutics Committee is commonly referred to as "the P&T Committee." Many physicians have misconceptions about the make-up and nature of this medical staff committee.

The name of the committee contributes to the confusion. The term "pharmacy" in the name may mislead a practitioner into thinking this is a pharmacy committee. It is not.

The P&T Committee is a subcommittee of the Medical Operations Committee, which is the formal line of communication between the medical staff and the hospital on all drug-related matters. Being a medical staff committee, the P&T Committee is primarily physicians. 14 of 18 (77%) P&T committee members are physicians. The 4 non-physicians on the committee are 2 pharmacists, 1 nurse, and a hospital administrator.

The P&T Committee decides which drugs should be listed in the *Formulary*. The *Formulary* is a list of drugs that are readily available for use. The drugs listed in the *Formulary* reflect the opinions of the medical staff as represented by the P&T Committee. The P&T Committee uses an evidence-based medicine approach to determine which drugs should be listed and whether any limitations are needed. Limitations range from endorsing appropriate criteria for use — which can be used for educational purposes — to formal restrictions to specific uses, areas, or other criteria.

The P&T Committee is a subcommittee of the Medical Operations Committee, which is the formal line of communication between the medical staff and the hospital on all drug-related matters.

The P&T Committee also establishes policies for drug use in the hospital. Again, the P&T Committee uses an evidence-based approach when establishing policies.

A broad range of medical practitioners is useful in establishing these drug-use policies. However, when special input is needed, input is sought from specialty areas or, in some cases, ad hoc committees of physicians with special expertise.

Dr. Ricardo Gonzalez-Rothi chairs the P&T Committee. Dr. Randy Hatton staffs the committee. A list of the P&T members is not generally made available. In the past, this information has been used by drug manufacturers' sales representatives to lobby for their products. This unwanted solicitation has led to a more limited distribution of the membership list.

If you have any questions or comments about the P&T Committee, please contact us. Correspondence about the P&T Committee can be mailed to Secretary, P&T Committee, PO Box 100316, JHMHSC.