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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met January 16, 2001. 5 drugs or dosage forms were added in the *Formulary* and 3 were deleted. 2 drugs and 1 dosage form were reviewed and designated not available.

◆ ADDED

Antihemophilic factor, recombinant [formulated with sucrose] (Helixate® FS by Baxter)

Argatroban (Argatroban by SmithKline Beecham)

Didanosine (Videx® EC by Bristol-Myers Squibb)

Lopinavir & Ritonavir (Kaletra® by Abbott)

Rifabutin (Mycobutin® by Pharmacia Upjohn)

Tretinoin (Vesanoid® by Roche)

◆ DELETED

Antihemophilic factor, recombinant (Helixate® by Baxter)

Phenylpropanolamine (eg, Dimetapp® by Robins)

Triple sulfa vaginal cream (Sultrin® by Ortho)

◆ NONFORMULARY, NOT AVAILABLE

Diazepam rectal gel (Diastat® by Elan)

Dolasetron (Anzemet® by Aventis)

Granisetron (Kytril® by SmithKline Beecham)

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NEWS

Researchers can no longer purchase drugs from Pharmacy Stores

Effective February 5, 2001, Pharmacy Stores will no longer be able to sell drugs to researchers for use in their laboratories. In order to be in compliance with state regulations, researchers who can prescribe will have to obtain these products from a pharmacy with a retail pharmacy wholesaler permit. The only Shands outpatient pharmacy meeting this stipulation is the Plaza Pharmacy across from Shands at AGH. They can be contacted by calling 338-2147.

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Researchers who are licensed to prescribe (eg, MD, DO, DDS, DVM) can contact the Plaza Pharmacy or any other retail pharmacy with the appropriate permit.

Researchers who are licensed to prescribe (eg, MD, DO, DDS, DVM) can contact the Plaza Pharmacy or any other retail pharmacy with the appropriate permit. After providing the appropriate documentation of licensure for prescribing and your DEA permit, you can obtain the prescription medications that you need for your research.

Researchers who are not licensed to prescribe must meet additional regulations. Before you can obtain prescription medications for research, teaching, testing, etc., you must contact the Bureau of Pharmacy Services of the Florida Department of Health. The bureau's Tallahassee telephone number is (850) 487-1257. Sample letters are available from the University of Florida's Environmental Health & Safety website (http://www.ehs.ufl.edu/lab/pdrugs.htm). These letters must explicitly list all the prescription drugs that you require for your research.

If your request is approved, you will be provided with an authorization number and an expiration date. A copy of this letter must be provided to a wholesaler when you set up an account to purchase prescription medications.

Unlike researchers who can prescribe, nonprescribing researchers must get their medications from a licensed wholesaler—not a pharmacy with a retail pharmacy wholesaler permit. There are several licensed wholesalers that service the Gainesville area and a list is available from the Environmental Health & Safety website.

Pharmacy Stores will continue to provide medications to hospital locations under common control or management of Shands based on the guidelines provided by the Florida Bureau of Pharmacy Services. Research coordinated through the Investigational Drug Service (IDS) is **not** impacted by these changes. If the IDS can help with your research, they can be contacted by calling 265-0680 extension 4-4237. The Director of Pharmacy Services can also be contacted with any additional questions at 265-0404.

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INSIDE THIS ISSUE

Formulary, *from page 1*

Recombinant antihemophilic factor formulated with sucrose (thus the "FS" in the brand name) was added in the *Formulary,* and the same product, **recombinant antihemophilic factor**, formulated with albumin was deleted. This product is marketed under the brand names, Helixate® FS and Kogenate® FS. 2 different manufacturers distribute the same product under a licensing agreement.

Recombinant clotting factors were developed to avoid viral transmission that occurred with pooled-plasma products. However, the recombinant clotting factors still contained small amounts of albumin, which is derived from pooled-plasma, to stabilize the product. The product formulated with sucrose uses 1000 times less human plasma protein than the product stabilized with albumin. No albumin is used in the purification or formulation processes of Helixate® FS. Like Helixate®, Helixate® FS does use albumin in the fermentation process. An additional solvent-detergent viral inactivation step has been added to the "FS" product.

There have been no reported cases of viral transmission from Helixate® after the infusion of 2 billion units. However, the theoretical risk of viral transmission is still a concern.

Argatroban is a selective direct thrombin inhibitor with a labeled indication for the prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). This intravenous anticoagulant reversibly inhibits the catalytic site of thrombin, neutralizing the actions of thrombin. Because all thrombin-dependent coagulation assays are affected, thrombin times (eg, aPTT and ACT) are helpful in monitoring argatroban therapy.

Since anticoagulants are needed in various settings for patients with documented HIT, argatroban may have various uses. Argatroban has been used as an anticoagulant for percutaneous coronary interventions, acute myocardial infarction, patients on hemodialysis, and for patients on extracorporeal circulation (eg, cardiopulmonary bypass). It has also been used in patients with disseminated intravenous coagulation (DIC).

Argatroban is an alternative to 2 other drugs listed in the *Formulary*: danaparoid and lepirudin. Argatroban appears to be easier to monitor and dose than the alternatives. Because argatroban is metabolized in the liver, the dosage does not need to be modified in patients with renal impairment. However, patients with liver disease may require a reduced dosage. Because argatroban has a relatively short duration of effect, holding the dose can reverse the anticoagulant effects.

As expected, bleeding is the most common complication associated with the use of argatroban. Hypotension, fever, diarrhea, cardiac arrest, nausea, vomiting, tachycardia, cough, and abdominal pain have been reported. Allergic reactions have also been reported. Patients with unstable angina have been reported to have a recurrence of rest angina following the discontinuation of infusions of argatroban. Therefore, infusions of argatroban should be gradually tapered in patients with unstable angina following initiation of aspirin or other antiplatelet drugs.

Co-administration of argatroban and warfarin is complex. Both agents affect INR; thus, dosing and monitoring are complicated. Patients started on argatroban may be transitioned to warfarin; therefore, it is important to appreciate the effect that argatroban has on INR. For example, patients on argatroban and warfarin should have the argatroban stopped only when the INR is >4 on combined therapy. The INR needs to be rechecked in 4 to 6 hours. If the INR is too low, argatroban needs to be restarted and the warfarin dosage adjusted appropriately.

Because the diagnosis of HIT is difficult and the dosing and monitoring of argatroban can be challenging, a Hematology Consult is required before the use of argatroban.

Enteric-coated didanosine is a new dosage-form of the antiretroviral agent didanosine (DDI). The non-enteric-coated formulation of didanosine contains magnesium buffer in order to protect didanosine from degradation by stomach acid. This buffer was responsible for many drug interactions. The enteric-coated product avoids many of these interactions. The older buffered product is also large and difficult to take. Videx® EC must still be taken on an empty stomach for adequate absorption.

The combination of **lopinavir and ritonavir** is the most recently approved protease inhibitor with a labeled indication for the treatment of HIV-1 infection in combination with other antiretroviral agents. Ritonavir has been on the market for several years as a single-entity product. It is included in this product for its beneficial drug interaction that improves the absorption of lopinavir. Ritonavir decreases the pre-systemic metabolism of lopinavir in the gut mucosa. Kaletra® is the 6th commercially avail-able protease inhibitor approved in the United States.

Kaletra® is not addressed in the most recent Guidelines for the Use of Antiretroviral Agents from the Department of Human Services, which was published in January 2000. However, Kaletra® is being used in patients who have failed or who are intolerant to other protease inhibitor containing regimens.

Kaletra® is given twice daily with food. No dosage adjustments are needed with impaired renal function, but may need modification based on the other drugs in the patient's regimen.

The most common adverse effect associated with Kaletra® is diarrhea. Other potential adverse effects are abnormal stools, nausea, abdominal pain, asthenia, headache, vomiting, and rash. Kaletra® can also affect serum glucose, uric acid, AST, ALT, total cholesterol, triglycerides, and amylase. Total cholesterol and fasting triglyceride levels should be obtained before and periodically during therapy. Pancreatitis has been reported.

Because Kaletra® is a potent inhibitor of CYP3A isoenzymes in the liver, drug interactions are a major concern. Concomitant administration with other drugs metabolized by this enzyme can result in increased plasma concentrations and potential toxicities. Conversely, drugs that alter CYP3A can alter the metabolism of Kaletra®.

Rifabutin is a rifamycin antibiotic similar to rifampin with a labeled indication for disseminated mycobacterium avium complex (MAC) in patients with advanced HIV infection. It is also used in the prevention of MAC infection in HIV-positive patients and in the treatment of infections caused by *Mycobacterium tuberculosis*. Because rifabutin is a less potent inhibitor of hepatic microsomal enzymes compared with rifampin, it may be preferable when used in combination with antiretroviral agents in HIV patients with tuberculosis. The dosage depends on the indication.

The most common adverse effects associated with rifabutin include rash, gastrointestinal intolerance, and neutropenia. Uveitis, which may be unilateral or bilateral and is characterized by pain, redness, and possible temporary or permanent loss of vision, may occur in patients receiving 300 to 900 mg daily in combination with other agents—particularly with clarithromycin or fluconazole. Uveitis is rare when the dosage is 300 mg per day (ie, the MAC prevention dosage).

Brown-orange discoloration of the urine is common. Patients should anticipate this effect. Brown-orange

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NEWS

New drugs in 2000

The FDA approved 27 new drugs in 2000 (see table). This was a decrease from last year's 35 approvals. Only 8 of these approvals were considered priority reviews. The low number of approvals and the low number of priority reviews suggest that 2000 was a relatively lean year for new drug approvals. 1 approval, alosetron, was removed from the market in November after reports of severe gastrointestinal events. Alosetron may be re-released after the FDA works with the manufacturer to establish an appropriate risk management program.

Only 2 new drugs were approved in December (ie, bivalirudin and nateglinide), which is quite unusual. Traditionally, a disproportionate number of drugs are approved at the end of the year. End-of-the-year approvals have been attributed to the FDA trying to make their numbers look good to show they are meeting their goals of getting drugs to market. However, the advent of user-fees and approval deadlines may have changed this paradigm.

This year there was no category of drugs that dominated the approvals. Only 1 antibiotic (linezolid) and 1 antiviral (lopinavir plus ritonavir) were approved. Approvals ranged from the military's approval of a paste to use with protective gear to prevent or delay the absorption of chemical warfare (ie, SERPACWA or Skin Exposure Reduction Paste Against Chemical Warfare Agents) to the over-the-counter cream for oral-facial herpes, docosanol.

Mifepristone took the longest to get through the FDA's review process. It was under review for over 4.5 years. Also known as RU-486, mifepristone is an abortifacient that is used in combination with another prostaglandin, misoprostol.

6 important biologicals approved in 2000 are also included in the table. ReFacto® is similar to the new formulation of Helixate® FS, which was added in the *Formulary* in January.

Fewer than anticipated biotechnology products were approved in 2000; however, more are anticipated in 2001. 5 biologicals applications have already undergone complete reviews and are poised for approval this year.

NEW DRUGS & SELECTED BIOLOGICS APPROVED BY FDA IN 2000

GENERIC NAME	TRADE NAME	INDICATION
Alosetron*	Lotronex	Irritable bowel syndrome
Antihemophilic factor, recombinant†	ReFacto	Hemophilia A
Argatroban‡	Argatroban	Heparin-induced thrombocytopenia
Arsenic trioxide	Trisenox	Acute promyelocytic leukemia
Articaine; Epinephrine	Septocaine	Dental anesthesia/nerve block
Balsalazide disodium	Colazal	Ulcerative colitis
BCG, live†	Pacis	Bladder cancer
Bivalirudin	Angiomax	Anticoagulant for PTCA
Botulinum toxin type B†	Myobloc	Cervical dystonia
Cetrorelix acetate	Cetrotide	Controlled ovarian stimulation
Cevimeline	Evoxac	Dry mouth in Sjögren's Syndrome
Colesevelam	Welchol	Primary hypercholesterolemia
Crotalide polyvalent immune fab, ovine†‡	CroFab	Rattlesnake envenomations
Docosanol	Abreva	Cold sores and fever blisters
Gemtuzumab Ozogamicin	Mylotarg	Acute myelogenous leukemia
Insulin aspart recombinant	NovoLog	Diabetes mellitus
Insulin glargine	Lantus	Diabetes mellitus
Linezolid‡	Zyvox	Antibiotic
Lopinavir; Ritonavir‡	Kaletra	HIV
Meloxicam	Mobic	Osteoarthritis
Mifepristone	Mifeprex	Medical termination of pregnancy
Nateglinide	Starlix	Type 2 diabetes
Oxcarbazepine‡	Trileptal	Seizures
Perfluoroalkylpolyether; Polytetrafluoroethylene	SERPACWA	Chemical warfare exposure reduction
Pneumococcal 7-valent conjugate vaccine‡†	PrevNar	Vaccine
Pantoprazole	Protonix	GERD
Rivastigmine	Exelon	Alzheimer's disease
Tenecteplase†‡	TNKase	Acute mycardial infarction
Tinzaparin sodium	Innohep	Deep venous thrombosis
Triptorelin pamoate	Trelstar Depot	Prostate cancer
Unoprostone isopropyl	Rescula	Glaucoma
Verteporfin	Visudyne	Macular degeneration
Zonisamide‡	Zonegran	Seizures

* Withdrawn from the market
† Biological
‡ Listed in the Shands UF *Formulary*

Formulary, *from page 2*
discoloration of tears may also occur during rifabutin therapy. In addition, permanent discoloration of soft contact lenses has been reported.

Tretinoin (also known as all-trans-retinoic acid or ATRA) is a retinoid that induces the maturation of acute promyelocytic leukemia (APL) cells. It has a labeled indication for the induction of remission in patients with APL, French-American-British (FAB) classification M3, characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RAR(alpha) gene who are refractory to, or who have relapsed from anthracycline chemotherapy or for whom anthracycline-based chemotherapy is contraindicated. Tretinoin is used for the induction of remission only.

APL is a relatively rare disease and only a few patients each year will be treated at Shands at UF. However, the effectiveness of tretinoin has made it a standard of care. APL has become the most curable subtype of acute myelocytic leukemia (AML).

The recommended dosage of tretinoin for APL is 45 mg/m^2/day administered as 2 evenly divided doses until remission is documented. Therapy is stopped 30 days after achievement of complete remission or 90 days of treatment, whichever occurs first. The cost of a typical induction cycle is approximately $2500.

Compared with conventional chemotherapy, tretinoin is relatively safe. Although almost all patients will experience tretinoin-related adverse effects, these effects are seldom permanent and generally do not interrupt therapy. Most frequent adverse effects are typical of the retinoids (eg, headache, skin abnormalities [dry skin, pruritus, chelitis, and xerostomia], bone pain, and arthralgias). Tretinoin is a potent teratogen and should be avoided in pregnant patients, although its use has been reported in the 2nd and 3rd trimesters.

Triple sulfa vaginal cream is a combination of sulfathiazole, sulfacetamide, and sulfabenzamide. The generic versions of this product have been discontinued and only the brand product (Sultrin®) is still available. It is expensive ($31 per tube), it contains peanut oil, and there is no rational indication for it in the *Formulary*. The peanut oil could result in serious allergic reactions in patients with a history of peanut allergy. Because there is no

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EDITOR,
DRUGS & THERAPY BULLETIN
Randy C. Hatton, PharmD

DIRECTOR,
PHARMACY SERVICES
Alan Knudsen, MS, RPh

CHAIRMAN,
PHARMACY & THERAPEUTICS COMMITTEE
Ricardo Gonzalez-Rothi, MD

EDITING, DESIGN, & PRODUCTION
Shands HealthCare's Publication Svcs.

SHANDS
Shands at the University of Florida
DRUG INFORMATION SERVICE
PO Box 100316
Gainesville, FL 32610-0316

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Formulary, *from page 3*
rational inpatient use (and for safety reasons), triple sulfa vaginal cream was deleted from the *Formulary.*

Phenylpropanolamine is an over-the-counter oral decongestant found in many popular cold and weight loss products. The FDA recently issued a public health warning about phenylpropanolamine that recommended its removal from the market. This recommendation, which comes after a recently published epidemiological study, found an increased risk of hemorrhagic strokes associated with phenylpropanolamine use.

There are suitable alternatives to phenylpropanolamine as a decongestant (eg, pseudoephedrine oral or oxymetolazine nasal spray). The only product listed in the *Formulary* that contained phenylpropanolamine was Dimetapp®. This product has been removed from the *Formulary.*

Diazepam rectal gel is a prefilled rectal syringe of diazepam that is intended for the management of selected, refractory patients with epilepsy on stable regimens of antiepileptic agents who require intermittent use of diazepam to control bouts of increased seizure activity. This convenient dosage form is designed for the outpatient setting. Each twin-pack of syringes cost over $70 compared with less than a dollar for an equivalent dosage of an injectable benzodiazepine (eg, diazepam or lorazepam). In the inpatient setting, the injectable dosage form can be given IV or rectally.

Dolasetron and **granisetron** are selective 5-hydroxytryptamine3 (5-HT3) receptor antagonists that are used for chemotherapy-induced and post-operative nausea and vomiting. Ondansetron is the 3rd drug in this category and is the preferred drug listed in the *Formulary.*

There is no evidence of therapeutic superiority among these agents. Also, there is no evidence to support any significant differences in their safety profiles. The American Society of Clinical Oncology Guidelines on the Use of Antiemetics states that these agents have equivalent safety and efficacy and can be used interchangeably based on convenience, availability, and cost.

When ondansetron is used for chemotherapy-induced nausea and vomiting at dosages of 8 mg IV or oral twice a day, it is far less expensive than dolasetron or granisetron. Currently, granisetron is the most expensive agent (ie, IV = $103 and PO = $39), and dolasetron is the 2nd most expensive agent (ie, IV = $67 and PO = $39). When given at the 8-mg-bid dosage, ondansetron costs approximately $32 a day intravenously and $19 a day orally. However, ondansetron is expensive when used at the labeled dosage (ie, 32 mg IV = $64).

In January 2000, ondansetron orally disintegrating tablets (ODT) were added in the *Formulary* for use as an alternative to granisetron for chemotherapy-induced nausea and vomiting. The orally disintegrating tablets were added instead of the regular tablets since they are the same cost and can be used in patients who have difficulty swallowing tablets. Even patients who cannot take most medications by mouth can tolerate these orally disintegrating tablets, resulting in a significant decrease in the cost of therapy.