

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 20, 2012. 4 products were added in the *Formulary*, 2 products were designated high-priority nonformulary drugs, and no drugs were deleted from the *Formulary*. 3 products were designated nonformulary and not available. Criteria for use changes were approved for 3 drugs.

◆ ADDED

Boceprevir (Victrelis[®])

Imipenem-Cilastatin (Generic)*

**Restricted: ID, mycobacteria physicians, & Antimicrobial Management Program approval required*

Telaprevir (Incivek[®])

Tenofovir Powder (Viread[®])

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

C-1 Esterase Inhibitor, Human (Berinert[®])

Ecallantide (Kalbitor[®])

Icatibant (Firazyr[®])

Ingenol mebutate (Picato[®])

◆ HIGH PRIORITY NONFORMULARY DRUG

Brentuximab vedotin (Adcetris[®])

Glucarpidase (Voraxaze[®])[†]

†Available via an investigational protocol

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NEWS

Update on Drug Shortages

Drug shortages are an increasing problem. In 2010, the number of new drug shortages reported was 211 and rose to 267 in 2011. To put this in perspective, there were only 58 drug shortages reported in 2004.^{1,2} A drug shortage has been officially defined as a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.¹

There are many causes of drug shortages, but the most common are manufacturing difficulties. If these manufacturing problems pose a risk to public health, a recall may be initiated. This will likely cause a halt in production.³ If the manufacturer cannot obtain the necessary raw materials to prepare the finished drug product, a shortage can occur.

“The Institute for Safe Medication Practices survey showed that 25% of clinicians indicated a [medication] error occurred at their site directly due to a drug shortage.”

Profitability of drugs also plays a major role. If manufacturers do not make enough profit, they will not make generic drugs.⁴ In addition, a product under patent may only have one production facility, so any interruption in manufacturing affects supply. Furthermore, if a drug product has multiple manufacturers, one usually is the dominant product. When a company with dominant market share decreases or stops production, the other companies may have difficulty compensating. Limited production capability by manufacturers is a major contributor towards drug shortages.³

The implications of drug shortages are numerous. The obvious major impact is decreased access to lifesaving drugs. In addition, the cost of those lifesaving drugs may increase as a result. For example, the cost of cancer care has escalated as generic products are in short supply and hospitals are forced to buy the brand name products.⁴ An unexpected impact has been the introduction of more errors. The Institute for Safe Medication Practices performed a survey that showed 25% of clinicians indicated an error occurred at their site directly due to a drug shortage.⁴ This is likely because pharmacies are ordering products that are unfamiliar to hospital staff. In addition, processes for drug use may change as a result of product differences. The increased time and effort put forth by hospital staff managing drug shortages has also been noted. In a recent study in hospitals comparable to the size of Shands, the average number of hours per week spent managing drug shortages was 12 and 13 by pharmacists and pharmacy technicians, respectively.¹ Since 2010, health care labor costs have increased by about \$216 million, which has major implications on hospital budgets.⁴

Resolution of drug shortages at the national level is headed by the Food and Drug Administration's division of the Center for Drug Evaluation and Research (CDER). Their mission is to respond to shortages that have significant impact on public health.³ Drug products that are deemed medically necessary fall into that category and the CDER will work with the manufacturers to resolve the shortage. In some instances, foreign drugs may be made

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◆ INSIDE THIS ISSUE

◆ Is the PDR Obsolete?

◆ INTERCHANGES

Fluticasone (Generic) for **Ciclesonide Aerosol Nasal Spray** (Zetonna®)

Lactobacillus Capsules (Culturelle®) and **Lactobacillus Granules** (Lactinex®)[†]

[†]Based on typical daily doses and what is tolerated

Sitagliptin-Metformin ER (Janumet XR®)[§]

[§]Interchanged to sitagliptin and regular-release metformin

◆ CRITERIA-FOR-USE CHANGES

Axitinib (Inlyta®)*

*Added in the Chemotherapy and Hazardous Drug Policies

Ceftriaxone (Generic)

*Single-dose for gonorrhea prophylaxis in children less than 28 days

Vismodegib (Erivedge®)*

*Added in the Chemotherapy and Hazardous Drug Policies

Boceprevir is an antiviral with a labeled indication for the treatment of hepatitis C virus (HCV) genotype 1 infection in adult patients who are treatment-naïve or who have failed previous interferon and ribavirin therapy. Boceprevir directly and specifically inhibits HCV NS3/4A serine protease, which is responsible for the processing of many viral proteins essential to HCV replication.

Boceprevir has been evaluated in two phase III trials. In treatment-naïve patients, regimens containing boceprevir plus peginterferon alfa-2a and ribavirin produced sustained virologic response in 66% of patients, compared to 38% of patients taking only peginterferon alfa-2a and ribavirin [alone].

The most common adverse drug reactions to boceprevir are fatigue, anemia, nausea, headache, and dysgeusia. Boceprevir is expensive, costing approximately \$4500 per month. It was added in the *Formulary* in order to minimize the potential for non-compliance, which could contribute to resistance.

Telaprevir was added in the *Formulary* for the same reason as boceprevir. Its labeled indication and mechanism of action are the same as boceprevir.

Telaprevir has been evaluated in treatment-naïve subjects producing sustained virologic response (SVR) in 75% of patients receiving concomi-

tant interferon and ribavirin, compared with 44% of those taking only peginterferon alfa-2a and ribavirin.

Common adverse drug reactions to telaprevir are rash, anemia, nausea, hemorrhoids, diarrhea, dysgeusia, fatigue, vomiting, and anal pruritus.

The biggest difference between boceprevir and telaprevir is cost. The monthly cost for telaprevir is approximately \$16,740. Boceprevir has to be refrigerated, and telaprevir does not.

Imipenem was the first carbapenem antibiotic. Imipenem is combined with cilastatin (imipenem-cilastatin) to slow the metabolism of imipenem. Carbapenems are broad-spectrum antibiotics that are often streamlined to more narrow-spectrum antibiotics once the organism and its sensitivities are known.

In July 2010, the P&T Committee voted to make imipenem nonformulary and not available. Doripenem [Doribax®] was added in the *Formulary* as the primary carbapenem because it may be less likely to be selected for carbapenem-resistant pseudomonas isolates.

Since that time, interest in imipenem use for the management of non-tuberculosis mycobacterial disease has increased. Most reports about treating non-TB mycobacterial disease are with imipenem. Therefore, the Mycobacteriology Division requested the re-addition of imipenem-cilastatin in the *Formulary*. Imipenem-cilastatin was added in the *Formulary* and restricted to approval by Infectious Diseases, the Antimicrobial Management Program, or mycobacteriology physicians.

Tenofovir is a nucleoside reverse transcriptase inhibitor (NRTI) with a labeled indication for the treatment of HIV as part of highly active antiretroviral therapy (HAART) and for the treatment of chronic hepatitis B in adults. A 40-mg-per-scoop tenofovir powder was recently approved.

The tenofovir dosage in adults for both indications is 300 mg once daily. Pediatric dosing for patients age 2 and above for HIV-1 is 8 mg/kg body weight, up to a maximum of 300 mg daily, administered as oral powder or tablets.

Tenofovir powder was added in the *Formulary* consistent with the philosophy of ensuring availability of HAART to provide continuity of treatment.

C1-esterase inhibitor [Berinert®], **ecallantide**, and **icatibant** are drugs designed to treat acute attacks of hereditary angioedema (HAE) caused by C1-esterase deficiency and dysregulation of complement and coagulation systems. These agents were designated nonformulary and not available after determining that they would not be used at Shands UF. Cinryze® brand of C1-esterase inhibitor was designated a high-priority nonformulary drug in January 2009 because it is only

available by a restricted distribution program. Patients must supply their own drug when used in the hospital for the prevention of HAE attacks.

Berinert® and Cinryze® replace the deficiency of C-1 esterase in patients with HAE. Ecallantide is a kallikrein inhibitor. Icatibant is a bradykinin B2 receptor antagonist.

Berinert® has been shown to be effective in reducing the time to onset of symptom relief for abdominal and facial HAE attacks. Ecallantide was shown to be effective in improvement of symptoms from baseline. Icatibant was shown to be effective in reducing the time to clinically significant relief of symptoms against an active comparator, but there was no difference compared with placebo. Only ecallantide has been used for laryngeal attacks in clinical trials.

The C1-esterase inhibitors and ecallantide are contraindicated in patients with a history of hypersensitivity to the respective products. There are no known contraindications for icatibant. Most of the adverse events for these medications are mild and temporary. The most common adverse events seen in clinical trials include injection site reactions, nausea, dizziness, and headache. Icatibant has been associated with elevated liver enzymes and fever. Subsequent HAE attacks and diarrhea have been reported with Berinert®. There is also a risk of prion or virus transmission with C1-esterase inhibitors because they are derived from pooled human plasma. Adverse reactions with ecallantide include fever and nasopharyngitis.

These products are expensive. Berinert® costs more than \$4000 per dose for a 70-kg patient. Ecallantide costs over \$8000 per dose, while a dose of icatibant costs nearly \$7000 per dose.

These agents were considered for nonformulary not available designation because HAE is a rare disease (ie, 6,000 to 10,000 people in the US), the self-limiting nature of most acute attacks, and the high acquisition costs of these drugs.

Patients are rarely admitted to Shands UF with acute HAE. It is unlikely that patients would be diagnosed quickly enough to benefit from these agents. These drugs would likely expire before being used.

Ingenol mebutate is a topical gel for the treatment of actinic keratosis, a cutaneous neoplasm that develops on sun-damaged skin. The likelihood of progression of an individual actinic keratosis to squamous cell carcinoma is varied but usually low. Estimates of annual rates of transformation have ranged from 0.03% to 20%. Multiple modalities have been used for the management of these lesions, including physical or chemical destruction,

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Formulary Update, from page 2

topical medication, and photodynamic therapy.

Ingenol mebutate is applied once daily for three consecutive days. Because this is not an acute clinical condition and treatment can be administered on an outpatient basis, it was designated nonformulary and not available.

Brentuximab vedotin is a CD30-directed antibody-drug conjugate with labeled indications for the treatment of patients with Hodgkin's lymphoma after failure of autologous stem cell transplant or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not stem cell transplant candidates and for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. The approved dose for both indications is 1.8 mg/kg/dose (max of 100 kg) IV given every three weeks for up to 16 cycles, or until disease progression or treatment toxicity. Dose adjustments are needed for both neutropenia and peripheral neuropathy.

Patients should be monitored for infusion-related reactions and tumor lysis syndrome, however, inpatient administration is not necessary. It is given as a 30-minute infusion and generally does not require pre-medication. Pertinent drug interactions may occur with potent CYP3A4 and CYP3A5 inhibitors and inducers, as brentuximab vedotin is both a substrate and an inhibitor of CYP3A4 and CYP3A5.

Post-market drug safety information was recently issued by the FDA on brentuximab vedotin. The report warns healthcare professionals of new cases of progressive multifocal leukoencephalopathy (PML), a brain infection, which has been associated with brentuximab vedotin use. Though rare, PML can result in death, thus prompting the FDA to add a new Boxed Warning of this risk to the drug label. The FDA has also added a warning against combined brentuximab vedotin and bleomycin use due to the increased risk for pulmonary toxicity; combined use is considered contraindicated.

A full treatment course of brentuximab for a 70-kg patient receiving 16 cycles of therapy is estimated at \$168,000.

Brentuximab vedotin was designated a high-priority nonformulary drug for use in inpatients, although use should be rare. If needed, there is sufficient time to acquire drug before its administration would be needed. This designation would allow for screening when a patient's routine dose occurs during a hospitalization and prevents use of repeated doses that should be administered in the

outpatient setting.

Glucarpidase is a recombinant bacterial enzyme used as a rescue therapy to inactivate methotrexate, thus providing an alternate route of elimination to renal excretion. In January 2012, FDA approved glucarpidase injection with a labeled indication for the treatment of toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function. It is not a substitute for and must be used in conjunction with leucovorin.

A proactive review of glucarpidase was completed and it was designated a high-priority nonformulary drug. The EPIC entry for this drug will include instructions on the process needed to obtain this drug to facilitate timely acquisition. Currently it is only available as part of an investigational drug protocol. Once it becomes commercially available, this designation will be re-evaluated.

Zetonna® is an aerosol version of **ciclesonide nasal spray** with a labeled indication for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. Its dosage is one 37-mcg actuation per nostril once daily, differing from the other ciclesonide nasal dosage form in its concentration per actuation. **Omnaaris**® nasal spray is available as 50-mcg per actuation.

Omnaaris® was designated nonformulary and not available in August 2009, and an interchange was approved to generic fluticasone one or two sprays per nostril daily.

Consistent with the previously approved interchange, **Zetonna**® was designated nonformulary and not available with an interchange to generic fluticasone nasal spray. Fluticasone spray will be given as one spray per nostril daily. Patients are permitted to use their own supply of **Zetonna**®.

Lactobacillus is an acid-producing probiotic bacterium that is a normal bowel inhabitant. It is used to attempt to reestablish the normal physiologic and bacterial flora of the intestinal tract, and has been used to treat antibiotic-associated diarrhea.

Pharmacists often receive requests from nursing to interchange **lactobacillus capsule** and **powder formulations** when a patient's ability to tolerate one changes. This is consistent with the policy for many other medications available as solid and liquid oral dosage forms. **Lactobacillus** introduces confusion because there is no standard interchange between capsule and powder for liquid administration.

The "conversion" is to switch from the recommended daily dose of one product to that of the other. The "standard" dosage of **Culturelle**® is one capsule twice a day. The "standard" dosage of **Lactinex**® is one packet three

times a day.

Janumet XR® is a dipeptidyl-peptidase-IV (DPP-IV) inhibitor [sitagliptin] and biguanide antidiabetic agent [extended-release metformin] combination product with a labeled indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. It differs from **Janumet**® by its inclusion of extended-release rather than regular-release metformin.

Janumet® was designated nonformulary and not available in March 2008 and interchanged to its individual ingredients. Additionally, in July 2010, extended-release metformin was designated nonformulary and not available, with an interchange approved between 850-mg dose increments of regular release metformin and 750-mg increments of the extended release.

Metformin ER Dosage	Metformin IR Dosage
1000 mg daily	500 mg twice a day
1500 mg daily	500 mg in the AM & 850 mg in the evening
2000 mg daily	1000 mg twice a day

Janumet XR® was designated nonformulary and not available and will be interchanged to an equivalent sitagliptin dosage and regular-release metformin, consistent with previously approved interchanges. (see chart on page 6)

Axitinib and **vismodegib** are new chemotherapy drugs that were added in the *Chemotherapy and Hazardous Drug Policies*. These agents were not added in the *Formulary*, but are included in these policies to assure safe handling in case of nonformulary use.

Axitinib is an oral kinase inhibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy. Progression-free survival was significantly improved with axitinib compared with sorafenib in a multicenter, randomized, phase III study in patients with progressive renal cell carcinoma after one first-line therapy including a sunitinib-, temsirolimus-, or cytokine-based regimen or bevacizumab plus interferon alfa. Patients will usually use their own supply of this drug.

Vismodegib is an oral hedgehog pathway inhibitor indicated for basal cell carcinoma (BCC), a common skin cancer with low metastatic potential. It is also indicated for use in patients with metastatic BCC or in patients with locally advanced BCC that has recurred following surgery. **Vismodegib** is also indicated for patients with locally advanced BCC who are

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available when they meet FDA standards.

On a local level, there are many processes in place at Shands to lessen the impact of drug shortages for our patients. The Pharmacy Department tracks all current shortages likely to impact Shands. When a shortage has been identified, staff looks for product at other manufacturers to try and keep our supply stable. If there are no other supply options, product will be moved to key areas in the hospital. For example, during an etomidate shortage, product was removed from all crash carts and redistributed to areas of high use. If there are therapeutic equivalents or different route options available, staff will be encouraged to increase the use of alternatives. In the case of the intravenous lorazepam shortage, orders were changed to oral lorazepam, when appropriate. Restrictions may also help maintain supply of certain products. Intravenous pantoprazole supply was preserved due to efforts to uphold the criteria for use set in place by the P&T Committee, restricting it for nonvariceal upper gastrointestinal bleeds and patients under strict NPO orders.

Hospital staff notifications of drug shortages usually occur shortly before a change is implemented. Some prescribers ask why they do not receive advance notice when changes are necessary. If all possible shortages were passed on to physician and nursing staff, they would be overwhelmed with the amount of shortages that are reported. Frequently, shortages are resolved at the last minute, so it is difficult to determine when to sound the alarm and implement contingency plans. For instance, our supply of ondansetron injection was previously declining but the manufacturer was able to resume supply before a critical low was hit. Therefore, the medical staff are only notified of a shortage when the situation is critical.

Drug shortages will likely increase and continue to have a major impact on patient care. With new laws being introduced such as the *Preserving Access to Life-Saving Medications Act*, the FDA will hopefully gain the necessary tools to regulate shortages on a national level. This law would make it a requirement for manufacturers to report actual or potential interruptions in supply, develop criteria to identify drugs vulnerable to shortage, revisit the FDA definition of "medically necessary," and improve communication among FDA, manufacturers, and health systems.¹ Necessary resources will continue to be utilized at Shands to effectively manage these shortages.

By Brianna Franklin, PharmD

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Is the PDR Obsolete?

For decades, the *Physician's Desk Reference* or *PDR* has been perceived as the “go-to” reference for “official” drug information. In other words, a manufacturer’s official prescribing information (labeling) could readily be found in the *PDR*. With changes in drug use and the availability of alternative sources of the same information, the future of this reference, which is now in its 66th edition, has to be in doubt.

The business model for the *PDR* has been to publish only the official prescribing information for brand name drugs for which there is not generic competition. Manufacturers paid to have their drug listed in the *PDR*. You could consider a listing in the *PDR* as a form of advertising. In the past, the *PDR* was commonly distributed by drug manufacturers’ sales representatives as a promotional item. Some people, including consumers and librarians purchased the *PDR*.

When most drugs prescribed were brand name drugs, the *PDR* contained most of the official prescribing information for the commonly prescribed drugs. However, times have changed. By 2015, it is estimated that 90% of all prescriptions will be for generic drugs. Thus, the *PDR* would only include 10% of the drugs prescribed. As more drug patents expire, fewer drugs are listed in the *PDR*. In the last 3 years, the size of the *PDR* has decreased.

What is the best alternative? Drug labeling information for most prescription and some non-prescription drugs can now be found in a reference called *DailyMed*. It is available at www.dailymed.nlm.nih.gov. As the URL suggests, this is an official governmental publication of the FDA and the National Library of Medicine.

Unlike the *PDR*, *DailyMed* lists the official labeling for brand name and generic drugs. It contains current prescribing information for most drugs, including recently approved drugs and labeling information that has been recently changed.

The information is also presented in a standardized format that makes it easy to find information in the labeling. Do you need dosage information? You can click on the *Dosage & Administration* tab. Other tabs include *Description*, *Clinical Pharmacology*, *Indications & Usage*, *Contraindications*, *Warnings*, *Precautions*, *Adverse Reactions*, *Overdosage*, *How Supplied*, *Patient Counseling Information*, *Boxed Warnings*, and *Medication Guide*. Each label has a permanent link (URL) that can be referenced and will not change.

Best of all, *DailyMed* is available free with no advertising or potential conflicts of interest. It even archives old versions of a product’s labeling, so you can see how a label has recently changed. We will continue to keep old *PDRs* in the Drug Information Center for historical purposes, but there does not appear to be a continued need for print versions of the *PDR*.

Drugs & Therapy

B · U · L · L · E · T · I · N

Volume 26, No. 4 April 2012

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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not candidates for surgery or radiation therapy. It is the first FDA-approved drug for metastatic BCC.

Vismodegib labeling contains a boxed warning concerning the possibility of embryo-fetal death and severe birth defects.

Again, patients will usually use their own supply of this drug.

Ceftriaxone is an injectable third-generation cephalosporin with activity against gram-positive and gram-negative bacteria. Its long half-life allows for once-daily dosing.

Co-administration of calcium-containing intravenous solutions within 48 hours of ceftriaxone is contraindicated. This includes parenteral nutrient preparations. Use of ceftriaxone with calcium can lead to tissue crystallization and potentially patient harm.

Ceftriaxone is contraindicated in neonates age 28 days or younger and

newborn infants at risk for hyperbilirubinemia. Risk for hyperbilirubinemia is defined as the high-intermediate to high risk zone on the algorithm as outlined by the American Academy of Pediatrics.

The Division of Pediatric Infectious Diseases requested one-time doses of ceftriaxone be allowed in children less than 28 days old for the prophylaxis of gonorrhea if they do not have another contraindication. The benefits of ceftriaxone outweighed any possible risk in this group provided the patient is not at risk for hyperbilirubinemia and has not recently received IV calcium within 48 hours. Cefotaxime is used in this age population for other uses or when patients are at risk for hyperbilirubinemia or who have received calcium-containing products.

Janumet® XR Daily Dosage (Sitagliptin/Metformin ER)	Dosages for Interchanged Products (Sitagliptin + Metformin IR)
Sitagliptin 100 mg– Metformin XR 1000 mg	Sitagliptin 100 mg Once Daily + Metformin IR 500 mg Twice Daily
Sitagliptin 50 mg– Metformin XR 1000 mg	Sitagliptin 50 mg Once Daily + Metformin IR 500 mg Twice Daily
Sitagliptin 50 mg– Metformin XR 500 mg	Sitagliptin 50 mg Daily + Metformin IR 250 mg Twice Daily

Drug information questions?

Contact the Drug Information Service



Call 265-0408



Or submit your
question online at
[www.shands.org/
professionals/druginfo/
default.asp](http://www.shands.org/professionals/druginfo/default.asp)

- This service is for referring physicians and other healthcare professionals taking care of Shands patients
- Phones are staffed from 9 am to 4:30 pm, Monday – Friday
- All answers are thoroughly researched and referenced

For emergent questions that do not need thorough research, go to the pharmacy servicing your area.