

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 15, 2006. 4 drugs or dosage forms were added in the *Formulary* and 3 drugs were deleted. 5 drugs were designated nonformulary and not available. 1 drug was evaluated and designated a high-priority nonformulary drug. There were 5 criteria-for-use changes, and 1 interchange approved.

◆ ADDED

Amyl nitrite (generic)

Dasatinib (Sprycel[®] by Bristol-Myers Squibb)

Intravenous Immune Globulin (Gammagard[®] S/D by Baxter)

Pregabalin (Lyrica[®] by Pfizer)

◆ DELETED

Human Albumin Microspheres (Optison[®] by Amersham Health)*

Intravenous Immune Globulin (Panglobulin[®] by American Red Cross)*

Intravenous Immune Globulin (Polygam[®] S/D by American Red Cross)*

*Discontinued by manufacturers:
Nonformulary and Not Available.

◆ NONFORMULARY AND NOT AVAILABLE

Natalizumab (Tysabri[®] by Elan Pharmaceuticals)

Phenylephrine Oral (eg, Sudafed[®] PE)

◆ EVALUATED BUT NOT ADDED

Lenalidomide (Revlimid[®] by Celgene Corporation)

(continued on next page)

POLICIES AND PROCEDURES

Automatically discontinuing pneumococcal vaccine orders?

In order to comply with national and local quality standards, you ordered a pneumococcal vaccine for a patient recently admitted for a community-acquired pneumonia. A pharmacist follows behind you and cancels the order before it is administered. Why?

At the August P&T Committee meeting, a policy was approved that allows pharmacists to discontinue orders for

are indicated. Although vaccines are usually given in the outpatient setting, the administration of vaccines to hospitalized patients is a method of promoting the use of these vaccines. When followed, these measures can keep patients out of the hospital, decrease morbidity and mortality, and decrease the cost of healthcare.

Unfortunately, it is often difficult to determine a patient's vaccination status. In order to comply with these standards, pneumococcal vaccines are often ordered without regard to a patient's vaccination history. When vaccines are repeated within a short period, it increases the chances a patient will experience an adverse reaction.

Shands at UF's pharmacy computer system will track when patients have previously received a pneumococcal vaccine in the inpatient setting. In order to comply with national quality standards, but not increase the risk of adverse effects, the P&T Committee has established the policy that will allow the order for the repeat vaccination to be discontinued, as long as the date of the previous vaccination is documented in the chart. This can be done without contacting the prescriber and requiring the prescriber to write a new order.

This policy will not track previous vaccinations given in the outpatient clinics or when it was administered at another health system. Thus, a thorough medication history and documentation of previous vaccinations should be done. The goal is to promote appropriate pneumococcal vaccination, but only when it is indicated.

◆ Unfortunately, it is often difficult to determine a patient's vaccination status.

pneumococcal vaccines when there is documentation that the patient has received a previous pneumococcal vaccine within 5 years. A new "P&T-Approved" order will be written discontinuing the order for the vaccine. This action will also be documented in the Progress Notes along with the rationale for the discontinuation. The date the patient previously received the pneumococcal vaccine will be documented in the discontinuation order and in the progress note.

The Center of Medicare and Medicaid Services, the Joint Commission on Accreditation of Healthcare Organizations, and other quality and peer-review organizations have established a Core Measure for Community-acquired Pneumonia (CAP) that promotes the screening of patients in the hospital and/or the administration of pneumococcal vaccination. This quality measure is based on data that recognize the impact pneumonia has on patients and healthcare in general. Several measures are associated with CAP including prompt administration of the first dose of antibiotic, appropriate collection of cultures before initiating antibiotic therapy, and provision of influenza and pneumococcal vaccines, when they

◆ INSIDE THIS ISSUE

- ◆ Re-ordering meds
- ◆ Pediatric IVs standardized

◆ **CRITERIA FOR USE CHANGES**

Clofarabine (Clolar® by Genzyme Corporation)[†]

[†]Use in adults approved.

Leflunomide (generic)[†]

Mercaptopurine (generic)[§]

[§]Must be ordered on a Chemotherapy Order Form.

Podoflox (generic)[†]

Podophyllum Resin (generic)[†]

[†]No longer requires a chemotherapy order form.

◆ **THERAPEUTIC INTERCHANGES**

Senna Liquid for Senna Tablets**

**When patients cannot take oral solids

Amyl nitrite is an inhaled vasodilator. It was re-added in the *Formulary* for use in the Cardiac Catheterization Laboratory and the Echocardiography Laboratory. It was deleted in May when it was thought it was no longer being used. However, the rapid vasodilation and rapid offset is used for diagnostic procedures (eg, for diagnosing structural heart abnormalities).

Dasatinib is a small tyrosine kinase molecule similar to imatinib (Gleevec®), which is listed in the *Formulary*. It was evaluated as part of a comprehensive review of oncology drugs.

Dasatinib is a broad-spectrum inhibitor of 5 critical oncogenic tyrosine kinases/kinase families that have been linked to multiple forms of human malignancies. Dasatinib has demonstrated clinical efficacy in patients with chronic myeloid leukemia (CML) in chronic phase, accelerated phase, or blast crisis (myeloid or lymphoid), as well as in Philadelphia chromosome-positive acute lymphocytic leukemia (ALL).

Dasatinib has been evaluated in patients who were resistant to or intolerant to imatinib. Most patients treated with dasatinib had been exposed to at least a year of imatinib and 50% or more were exposed to at least 3 years of imatinib.

In high-risk pre-treated patients, dasatinib produced complete hematologic responses in 90% with CML and a complete cytogenetic response in 33%. As expected, response rates in patients with accelerated phase and blast crisis were lower.

Myelosuppression is a hallmark of CML and is a characteristic adverse

effect of chemotherapy. Therefore, myelosuppression is common in patients receiving dasatinib. It may occasionally result in dosage reductions or interruptions in therapy. CBC monitoring is required. Bleeding from impaired platelet aggregation may also occur.

Other common adverse effects include gastrointestinal disorders (diarrhea, nausea, vomiting), pyrexia, peripheral edema, asthenia, rash, dyspnea, pleural effusion, and headache. Cardiomyopathy occurred in a small number of patients.

Dasatinib therapy costs approximately \$125-\$230 per day, depending on indication and dosage. There is no alternative therapy.

Dasatinib offers an alternative in patients who are refractory to or intolerant to imatinib. Since it is an oral therapy, it maintains quality of life with an outpatient therapy.

Gammagard® S/D is now the low IgA version of **intravenous immune globulin** (IVIG) listed in the *Formulary*. This brand change became necessary when **Polygam® S/D** was discontinued by its manufacturer. Some patients, particularly those requiring chronic replacement IgG therapy (primary immunodeficiency), develop sensitivity to the IgA "contaminant." Because there is a limited supply of Gammagard® S/D, it will be reserved for those patients requiring a low-IgA product.

The American Red Cross no longer markets intravenous immune globulins, which has contributed to the nationwide shortage of IVIGs. **Panglobulin®** is no longer listed in the *Formulary* because it is also no longer being made. Our allocation of Gamunex® has been increased to make up for the loss of Panglobulin®. This is an improvement because Panglobulin® used sucrose as a stabilizer. The high sucrose content in some IVIGs has been associated with renal failure. Gamunex® does not use sucrose as a stabilizer.

Pregabalin is an analogue of gabapentin marketed as the patent for gabapentin expired. Pregabalin has the same mechanism of action as gabapentin, but has more predictable pharmacokinetics. It is well-absorbed with predictable pharmacokinetics over the range of dosages that are used. Dosage titration is simpler with pregabalin than gabapentin.

Pregabalin has labeled indications for the management of neuropathic pain associated with diabetic peripheral neuropathy, management of postherpetic neuralgia, and as adjunctive therapy for adult patients with partial onset seizures. Pregabalin has been used off-label for a variety of disorders. Like gabapentin, the potential for additional off-label uses is great.

Although the dosage regimen varies based on indication, doses are generally given 2 or 3 times per day. Starting dosages are 150 mg per day with usual dosages of 300 mg per day. The maximum dosage is 600 mg per day. Dosages must be decreased for impaired renal function. When stopped, pregabalin must be tapered to avoid withdrawal symptoms.

Because there is negligible metabolism of pregabalin, there is no dosage reduction with impaired liver function. There are also no known metabolic drug interactions. Pregabalin causes sedation, and additive sedation with other CNS depressants has been noted.

Placebo-controlled, clinical trials show that pregabalin is effective for its labeled indications. There are no published trials comparing pregabalin with gabapentin, nor any other active treatment for any of its labeled indications. Thus there are no data showing that the improved pharmacokinetic profile results in better outcomes.

Pregabalin is 5-6 times more expensive than gabapentin. Whether this increased cost can be justified is not known at this time. If twice-daily dosing can be used, compliance may be better. Because pregabalin is a controlled substance, storage and handling is more difficult and expensive than with other drugs.

The main adverse effects of pregabalin are dose-related dizziness, somnolence, dry mouth, blurred vision, peripheral edema, weight gain, and abnormal thinking. Newly developed myoclonus has been reported in patients with epilepsy taking pregabalin. Pregabalin was designated a Schedule V controlled substance because it caused euphoria in patients with a history of drug abuse.

Although there was insufficient evidence to justify the addition of pregabalin in the *Formulary*, its addition was necessary because it is a controlled substance. Patients cannot use their own supply of controlled substances at Shands at UF. Also, patients with seizure disorders cannot easily be converted to gabapentin.

Optison® was deleted from the *Formulary* because its manufacturer discontinued it. Optison® had not been used in the last year due to a recall and the subsequent removal from the market. Perflutren liquid microspheres (Definity®) is the IV diagnostic contrast agent used for echocardiography listed in the *Formulary*.

Natalizumab is a humanized monoclonal antibody that binds to the alpha-4 subunit of integrin receptors expressed on the surface of

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Formulary update, from page 2 leukocytes (except neutrophils). This binding prevents the attachment of leukocytes to counter-receptors on vascular endothelium, and inhibits the passage of leukocytes across the endothelium and into inflamed tissues. By blocking these receptors on the blood-brain barrier, natalizumab is thought to prevent the passage of inflammatory mediators into the central nervous system (CNS).

Natalizumab has a labeled indication for the treatment of relapsing remitting multiple sclerosis. It was first approved in November 2004, but was withdrawn from the market in February 2005 because 3 patients developed progressive multifocal leukoencephalopathy (PML).

On June 5, 2006, natalizumab was re-marketed with a special restricted distribution program (ie, Tysabri Outreach Unified Commitment for Health [TOUCH] prescribing program). This program includes a risk-minimization program with mandatory patient and outpatient infusion center registration. Patients must undergo periodic follow-ups. Natalizumab was designated nonformulary and not available because it cannot be obtained for inpatient use.

Oral phenylephrine tablets are used as an alternative to pseudoephedrine in the outpatient setting for nasal decongestion. Oral phenylephrine has become prevalent in the outpatient setting because of recent restrictions placed on the availability of pseudoephedrine (ie, behind the counter, requiring proof of identification, and the signing of a log book).

A review of the available data shows there is insufficient evidence that oral phenylephrine 10 mg tablets are effective. Also, the purported duration of action is only 4 hours, which is much shorter than the 12-hour duration for sustained-release pseudoephedrine. Since pseudoephedrine is listed in the *Formulary*, oral phenylephrine was designated nonformulary and not available.

Lenalidomide is a thalidomide analog with immunomodulatory activity. While the exact mechanism of action is not known, it appears to inhibit production of tumor necrosis factor alpha, activate CD4+ and CD8+ cells, enhance the cytotoxicity of natural killer cells, and have direct antitumor activity.

Lenalidomide has labeled indications for myelodysplastic syndromes and multiple myeloma. Use for myelodysplastic syndromes is for the treatment of patients with transfusion-dependent anemia due to low-to-intermediate-risk myelodysplastic

syndromes associated with a deletion of 5q (q31-q33) cytogenetic abnormality with or without additional cytogenetic abnormalities. Lenalidomide is used to treat multiple myeloma in combination with dexamethasone for the treatment of patients who have received at least 1 prior therapy.

Only 1 clinical trial has been published for myelodysplastic syndromes. In this open-label phase 1-2 study, there was a 56% response rate and 63% of patients became transfusion-independent. All responders with 5q minus abnormalities developed cytogenetic responses. Dose-limiting neutropenia and thrombocytopenia were the most significant adverse effects requiring interruption of therapy and subsequent dosage reductions.

A second, phase 2 study published as an abstract found similar results. 63% of patients reached transfusion independence on therapy. A higher rate of transfusion independence was reached with patients with an isolated 5q31.1 del (69% vs 49%). Neutropenia and thrombocytopenia were again the dose-limiting adverse effects.

The indication for multiple myeloma was approved at the end of June 2006. Approval was based on 2 unpublished randomized studies. These multicenter, multinational, double-blind, placebo-controlled studies compared lenalidomide plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone, in patients with multiple myeloma who had received at least 1 prior treatment. The primary efficacy endpoint in both studies was time to progression (TTP). Preplanned interim analyses of both studies showed that the combination of lenalidomide/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination. Complete response, partial response, and total response rates were also higher in lenalidomide-treated patients.

Diarrhea, pruritus, rash, and fatigue have been associated with lenalidomide use. Increased risk of venous thrombosis has been observed in lenalidomide trials for multiple myeloma.

Like thalidomide, lenalidomide is pregnancy category X and is available only via a limited distribution program (RevAssist™). Since lenalidomide is available only from designated specialty pharmacies via a restricted distribution program, it cannot be added in the *Formulary*. Patients will have to use their own supply if treatment is continued during their inpatient stay.

Clofarabine is a purine nucleoside

antimetabolite that has been shown to have activity against refractory or relapsed ALL in both children and adults. It has been shown to have a favorable toxicity profile with the primary dose-limiting toxicity being reversible elevations in liver enzymes. Long-term studies assessing effects of therapy on survival are currently lacking.

In March 2005, clofarabine was added in the *Formulary* for use in pediatric patients with acute leukemia who failed at least 2 prior regimens. At this time, adult patients were excluded because of insufficient evidence. Based on recent evidence, the criteria for use were expanded to include adult patients with acute lymphoblastic leukemia (ALL) who have failed at least 2 prior regimens and adult patients with AML.

Leflunomide, podofilox, and podophyllum resin no longer have to be ordered on a Chemotherapy Order Form. The P&T Committee reviewed the list of agents that require ordering on a Chemotherapy Order Form and determined that these agents can safely be removed from the list.

Mercaptopurine was added in the list of agents that must be ordered with a Chemotherapy Order Form. The limited use for non-oncology indications and the risk of bone marrow suppression with an overdose led to its addition in the list.

Senna liquid can now be automatically interchanged for **senna tablets** in patients who cannot swallow solid oral dosage forms. Senna is a plant derivative used as a nonprescription stimulant laxative. It is commonly used to treat constipation associated with opioid use. The typical oral dosage is 1 or 2 tablets once or twice a day.

The official dose of senna is based on the sennoside content. The amount of sennoside in a typical senna tablet (eg, Senokot®) is about 8.6 mg of sennoside, but the amount varies from manufacturer to manufacturer. The amounts of sennoside in liquids are slightly different and also varies among manufacturers; thus, direct interchange was not possible without a P&T-approved interchange.

Since the typical tablet senna dose is 1 or 2 tablets and the typical liquid dose is 10 mL or 15 mL, an interchange of 1-tablet-equals-10 mL and 2-tablets-equal-15 mL was approved. This allows nurses to use the tablets or liquid, depending on whether the patient can tolerate an oral solid dosage form, without obtaining a new order. This dosage form change will be documented in the chart as a "P&T-Authorized" interchange.

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POLICIES AND PROCEDURES

Automatic stop orders

Many hospitals use automatic stop orders to require prescribers to reconsider whether certain drugs need to be continued. This has been common for medications like pain medications and antibiotics. For several years, the Shands at UF P&T Committee has tried to decrease the use of Automatic Stop Orders.

Although review and reordering is a good concept, the chance that an order would be inadvertently stopped is always a concern (ie, an error of omission). When antibiotics are still needed or a patient is still in pain, the last thing needed is therapy to be prematurely stopped.

Our current Automatic Stop Order Policy only has 2 situations requiring the re-writing of orders to prevent them from being stopped. Any time a patient is transferred from 1 level of care to another (eg, from a critical care unit to a general ward or from the OR to a critical care unit) their medication orders have to be re-written.

Respiratory medications administered by a respiratory therapist also have to be rewritten after 72 hours (ie, a 72-hour stop order). This is designed to prevent the unnecessary continu-

ation of medications (eg, nebulized albuterol) when they are no longer needed. The respiratory medication stop-order policy explicitly excludes patients with chronic respiratory diseases (eg, COPD, asthma, lung transplant patients). An automatic stop order will not be applied to these pa-

tients in order to avoid an error of omission. Before the respiratory medication is stopped, reminders will be placed in the chart (ie, stickers) requesting that the order be rewritten. This policy will not apply to respiratory medications administered by nurses or patients (eg, metered-dose inhalers).

POLICIES AND PROCEDURES

Standardized IV concentrations in pediatrics

Shands Children's Hospital at UF is transitioning to standard concentrations for intravenous products to comply with Joint Commission-mandated medication safety standards. Pediatric clinical pharmacists and anesthesiology attendings developed the list, which was reviewed by the various pediatric specialties. At the August P&T Committee meeting, a policy was approved that requires the use of these standard concentrations.

There are 2 lists of standard IV concentrations. There is a list specific to the Neonatal Intensive Care Unit and a list for the rest of the pediatric patients. These standard concentrations are based upon the weight of the

patient in order to control the amount of fluid needed to deliver the appropriate amount of medication. Concentrations that will be used in children will also be used in most adult patients. A list of adult standard concentrations is still being developed.

Shands Children's Hospital is using a computerized order entry process for pediatric intravenous medications that helps prescribers choose the appropriate standard concentration and manage the amount of fluid that is delivered to the patient from the intravenous medications prescribed (ie, Accupedia®). A complete list of these standard concentrations is available from the Department of Pharmacy Services.