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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met September 19, 2005. 5 drugs or dosage forms were added in the *Formulary* and 1 dosage form was deleted. 1 drug was evaluated and designated nonformulary and not available. Criteria for use were modified for 2 drugs.

◆ ADDED

Atovaquone Suspension
(Mepron® by GlaxoSmithKline)

Emtricitabine + Tenofovir (Truvada® by Gilead Sciences)

Sildenafil (Revatio® by Pfizer)

Sodium Tetradecyl Sulfate
(Sotradecol® by Bioniche Pharma)

Ziprasidone Tablets
(Geodon® by Pfizer)

◆ DELETED

Aluminum Hydroxide Capsules
(Alu-Caps® by 3M)

◆ NONFORMULARY AND NOT AVAILABLE

Telithromycin
(Ketek® by Aventis)

◆ CRITERIA FOR USE CHANGED

Intravenous Immune Globulin
(various)*

**Requires prior authorization after November 1, 2005*

Rasburicase
(Elitek® by Sanofi Synthelabo)**

***Restricted to children or as a fixed dose (3 mg) for adults*

Atovaquone is an analog of ubiquinone with antipneumocystis activity, although the exact mechanism of action is not understood. It is used as a second-line agent for the treatment and prevention of

(continued on next page)

PRESCRIBING

"Phos" confusion

K-Phos Neutral® is the only oral solid **phosphorus supplement** listed in the *Formulary*. Each K-Phos Neutral® tablet provides 8 mmoles of phosphorus (see Table). It should be administered with a full glass of water with meals and at bedtime.

Sodium phosphate oral liquid (eg, Fleet's Phospho Soda®) is also listed in the *Formulary* as a liquid phosphorus supplement. In low doses, sodium phosphate liquid is a phosphorus supplement; higher doses of sodium phosphate liquid are used for its laxative effect. Even low, phosphorus-supplementing doses of sodium phosphate tablets or liquid can cause diarrhea when therapy is first started.

Neutra-Phos® and Neutra-Phos® K are nonformulary and not available. If you order one of these products, expect a page to clarify the order.

The Institute for Safe Medication Practices has warned healthcare professionals of the potential for confusion between K-Phos Neutral® and Neutra-Phos® K. Confusion could lead to hyperkalemia or under-treatment of a potassium deficiency.

Neutra-Phos K® contains 14.25 mEq of potassium per 8 mmoles of phosphorus, while K-Phos Neutral® only has 1.1 mEq of potassium per 8 mmoles of phosphorus. The names may be confusing, but K-Phos Neutral® in NOT a good potassium supplement; it is a good oral solid phosphorus supplement. Think of K-Phos Neutral® as an oral solid dosage form of sodium phosphate (ie, the small amount of potassium in this product is usually not significant).

Neutra-Phos® and Neutra-Phos® K are designated nonformulary and not available to prevent patients from receiving excess potassium. Some prescribers may not appreciate the amount of potassium in these supplements. There are better potassium supplements, when they are needed (eg, potassium chloride).

In each milliliter of sodium phosphate oral liquid (eg, Fleet® Phospho Soda), there is 4.1 mmoles of phosphorus and 4.8 mEq of sodium. The high sodium content (ie, 492 mEq in 120 mL) of sodium phosphate oral liquid must be considered, especially if it is used as laxative (eg, a bowel prep). Polyethylene glycol-electrolyte solution (eg, Colyte®) is the current bowel prep listed in the *Formulary*. It contains only 125 mEq of sodium per liter.

Please remember to order K-Phos® Neutral or Sodium Phosphate liquid as an oral phosphorus replacement. Order an additional supplement, like potassium chloride, if your goal is to supplement both phosphorus and potassium.

TABLE. PHOSPHORUS REPLACEMENT PRODUCTS

	Potassium (mEq)[a]	Sodium (mEq)[a]	Phosphorus (mmole)[b]
PRODUCTS LISTED IN THE *FORMULARY*			
K-Phos® Neutral tablet	1.1	12.6	8
Fleet's Phospho-Soda (per mL)	0	4.8	4.1
Potassium Phosphate IV (per mL)	4.4	0	3
Sodium Phosphate IV (per mL)	0	4	3
PRODUCTS NOT AVAILABLE			
Neutra-Phos® capsules/powder	7.1	7.1	8
Neutra-Phos® K capsules/packets	14.3	0	8

[a] mmole equals mEq because the valence is +1
[b] 1 mmole of phosphorus weighs 31 mg (ie, 8 mmole = 250 mg)

INSIDE THIS ISSUE

Formulary update, *from page 1*

Pneumocystis jiroveci (formerly *Pneumocystis carinii)* pneumonia (PJP). It was evaluated for formulary addition because, as an anti-infective, it is a high-priority nonformulary drug.

Sulfamethoxazole-trimethoprim (co-trimoxazole) is the first-line agent for PJP according to CDC guidelines for the treatment and prevention of opportunistic infections in HIV infected adults and adolescents. It is inexpensive and effective. The CDC guidelines recommend the use of atovaquone when patients cannot tolerate co-trimoxazole. Atovaquone has the advantage of being available as an oral suspension, which is useful when patients cannot swallow solid oral dosage forms (eg, patients with feeding tubes).

Atovaquone is considerably more expensive than dapsone, but it is often preferred due to tolerability based on a more favorable adverse effect profile. Gastrointestinal adverse effects including diarrhea, constipation, nausea, vomiting, dysguesia, and dyspepsia are common with atovaquone. Although not common, hemolytic anemia is a potential adverse effect.

Atovaquone suspension is an alternative to pentamidine and dapsone in patients with PJP who cannot be treated with co-trimoxazole.

Truvada® is a combination of 2 reverse transcriptase inhibitors, **emtricitabine** and **tenofovir**, used to treat patients with HIV**.** The combination decreases the pill burden in HIV patients with the goal of improving patient compliance (and hopefully therapeutic response). The individual agents in Truvada® are listed in the *Formulary*; however, the combination product was added to improve continuity of care for HIV patients and avoid medication errors.

Revatio® is a new brand of **sildenafil** with a labeled indication for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. Viagra® was already listed in the *Formulary* specifically for the treatment of pulmonary hypertension.

Revatio® was added in the *Formulary* as a line extension. Revatio® is available as white, 20-mg tablets that do not look like blue Viagra® tablets, which come in 25-, 50-, and 100-mg tablets. The 20-mg tablets were added for patients who may be admitted on this strength. This will also prevent medication errors upon discharge, when patients could be discharged on Viagra® and mistakenly resume their Revatio®.

There should, however, be no therapeutic difference between a 20-mg and 25-mg dose of sildenafil for the treatment of pulmonary hypertension. Revatio® tablets are approximately 5% more expensive than Viagra® tablets.

A recently approved commercial form of **sodium tetradecyl sulfate** was added in the *Formulary*, which replaces the compounded product. Until Sotradecol® was marketed, there was no commercial source of this sclerosing agent used to treat varicose veins.

Before a commercial product became available, the only source came from compounding pharmacies. If the compounded product was used, patients would have had to give informed consent, which discouraged its use. The commercially available product will improve access to this procedure.

Ziprasidone is an atypical or second-generation antipsychotic agent. It was considered for addition in the *Formulary* because it continues to be one of the most frequently prescribed nonformulary drugs, although usage remains modest.

The P&T Committee first reviewed ziprasidone 4 years ago, but it was not added because of lack of data. Injectable ziprasidone was added in the *Formulary* in January 2003 because it was the first injectable atypical antipsychotic. At that time, there still was insufficient evidence to add oral ziprasidone in the *Formulary*.

Since 2003, there have been 2 published randomized, controlled trials that have compared ziprasidone to olanzapine or risperidone. These studies concluded that there was no difference in effectiveness among these agents. An unpublished study included in a meta-analysis concluded that olanzapine was superior to ziprasidone.

In September, a third study comparing ziprasidone with other atypical antipsychotics was published. This was the first publication from a National Institutes of Mental Health sponsored study that compared the safety and efficacy of olanzapine, risperidone, quetiapine, and ziprasidone (ie, Clinical Antipsychotic Trials of Intervention Effectiveness or CATIE). Although olanzapine was found to be slightly superior to the other drugs in terms of efficacy, ziprasidone was found to be as effective as risperidone and quetiapine, which are listed in the *Formulary*.

Olanzapine use was also found to have a greater incidence of weight gain and diabetes. Ziprasidone and aripiprazole are atypical antipsychotics associated with less weight gain than the other agents.

CATIE findings that will receive considerable discussion are that the typical antipsychotic, perphenazine, was found to be equally effective as the atypical agents and that none of the agents were very effective. There was a 75% discontinuation rate within 18 months for all agents used, which was the primary response variable.

Aluminum hydroxide capsules were deleted from the *Formulary* because they are no longer being manufactured. Aluminum hydroxide suspension remains listed in the *Formulary*. However, aluminum is rarely used as a phosphate binder today; and, thus, aluminum hydroxide is rarely used.

Telithromycin is the first drug approved in a new class of antibiotics called ketolides. Ketolides are structurally similar to macrolides, but have been modified to bind to 2 sites on the bacterial ribosome, which results in an increased binding affinity. This results in increased antimicrobial activity against multi-drug resistant gram-positive cocci in the laboratory.

Telithromycin has labeled indications for the treatment of infections caused by susceptible strains of organisms causing acute exacerbation of chronic bronchitis, acute bacterial sinusitis, and community-acquired pneumonia. Telithromycin is active against *Streptococcus pneumoniae* (including multi-drug resistant species), *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella cattarhalis*, *Chlamydophilia pneumoniae,* and *Mycoplasma pneumoniae*.

Clinical trials have shown that telithromycin is equal to macrolides, beta-lactams, and respiratory fluoroquinolones for its labeled indications. There is no study that demonstrates the superiority of telithromycin over any agent. Further, telithromycin is used for mild to moderate infections versus moderate to severe infections, which are most common in the hospital setting.

Common adverse effects are similar to other antibiotics including diarrhea, nausea, headache, and dizziness. Emergent visual disturbances (blurred vision, difficulty focusing) have been reported in about 1% of patients. Since telithromycin is a potent inhibitor of CYP 3A4, there are many potential drug interactions.

Since telithromycin is considerably more expensive than equally effective alternative antibiotics, it was designated nonformulary and not available.

Intravenous immune globulins (IVIGs) are immune globulins (primarily IgG) pooled from blood donors. They are used for many indications ranging from immune deficiencies (eg, agammaglobulinemia) to autoimmune diseases (eg, idiopathic thrombocytopenia purpura [ITP]).

(continued on next page)

Formulary update, *from page 2*

There continues to be a severe nationwide shortage of IVIGs. Based on market changes (ie, consolidation of manufacturers, increasing demand for off-labeled uses), it is anticipated that the shortage of IVIGs will become more acute.

Dr. Richard Lottenberg has agreed to provide oversight for adult patients, and Dr. Suzanne Skoda-Smith has agreed to fill this role for pediatric patients. Use of IVIG will be prioritized based on our limited supply. As supply gets tighter, higher priority uses will be approved for use based on patient need.

Before each dose of IVIG is dispensed, it will need to have prior authorization after November 1, 2005. October will be a transition month. In October, prescribers will be notified of the upcoming prior-approval process when each dose is prescribed.

Rasburicase is a recombinant form of urate oxidase with an FDA-labeled indication for the intravenous management of hyperuricemia associated with tumor lysis syndrome in pediatric patients.

Tumor lysis syndrome occurs when intracellular substances are released from cancer cells that are destroyed by chemotherapy. Patients with large tumor burdens that are sensitive to chemotherapy are particularly at risk. The release of intracellular substances leads to various metabolic disturbances including hyperkalemia, hyperphosphatemia, and hyperuricemia. Hyperuricemia is caused by the rapid breakdown of nucleic acids. As the capacity of the kidney is overloaded, uric acid nephropathy may develop with the precipitation of uric acid crystals.

Prevention of hyperuricemia begins with adequate hydration and the maintenance of good urine output. Alkalization of the urine by administering sodium bicarbonate improves the solubility of uric acid and helps prevent precipitation in the renal tubule. In addition, allopurinol, a xanthine oxidase inhibitor, has been used to prevent the conversion of purines to uric acid. This reduces the formation of uric acid, but does not decrease the level of uric acid present before treatment. Thus, it takes 2 to 3 days for a reduction of uric acid to occur.

Rasburicase decreases the level of uric acid by converting uric acid to allantoin, which is a water-soluble degradation product that is excreted without a risk of renal damage. Uric acid levels drop rapidly, which reduces the incidence of tumor lysis syndrome and its associated morbidity (renal failure) and mortality.

Hypersensitivity reactions, including anaphylaxis have been reported with rasburicase. Patients with G6PD deficiency may experience hemolysis.

When rasburicase was added in the *Formulary* in November 2002, it was limited to pediatric patients with a high risk of tumor lysis syndrome. At that time, rasburicase was 9000-times more expensive than allopurinol. Therefore, rasburicase was restricted to use only by oncology prescribers.

There is now published evidence showing efficacy of rasburicase in adults. However, when weight-based dosing is used, it is prohibitively expensive. Recent data suggest that rasburicase in a fixed-dose regimen may have a role in adult patients. After reviewing these data, the rasburicase criteria for use were revised to include 3-mg fixed-doses for adult patients.

OUTPATIENT PHARMACY

Clarifying controlled substance prescription rules

On August 26, 2005 the Drug Enforcement Agency (DEA) published a statement in the *Federal Register* that clarifies some issues surrounding the prescribing of Schedule II controlled substances. This clarification was necessary after confusion was created by previous information published on the DEA's website and some misleading information provided by some DEA field offices.

Schedule II controlled substances (CIIs), by their nature, are the most likely prescription drugs to be abused. However, they still have legitimate and important therapeutic uses. Illicit drugs with high abuse potential and without reasonable therapeutic uses are Schedule I controlled substances. However, Schedule II drugs, like morphine for pain or methylphenidate for attention-deficit disorder, provide important relief for patients with these conditions.

Schedule II prescriptions have specific requirements that were outlined in last month's issue of the *Bulletin.* These prescriptions cannot be refilled. This is particularly a problem for chronic conditions like chronic pain or attention deficit disorder. In last month's issue of the *Bulletin,* we discussed the practice of writing "do not fill until" on Schedule II prescriptions. This issue is controversial. The DEA may interpret this as being illegal. The safest practice is to write a new prescription each month.

Obtaining a written prescription for a new supply of a chronic medication can be problematic. These prescriptions cannot be "phoned in" like other prescription drugs prescriptions. When a new prescription is required each month, the patient must determine how they can reasonably acquire each new prescription.

Some regulators were under the mistaken notion that an office visit and patient exam was necessary for each new prescription. The DEA has clarified this issue. A monthly office visit is not needed for chronic prescriptions for a Schedule II controlled substance to be written. Exams only need to be done at intervals necessary to monitor the effectiveness and safety of the therapy that has been prescribed. Schedule II controlled substance prescriptions can be issued without a physician seeing a patient when an exam is deemed unnecessary.

What are the best methods for prescribers to provide ongoing prescriptions for Schedule II controlled substances to their patients? Once a patient's dosage has been stabilized and appropriate monitoring is in place, prescriptions can be mailed to patients, their pharmacy, or patients can pick them up as they are needed. A single prescription for a 3-month supply may be prescribed; however, make sure the patient's third-party payer will allow this. Many prescription benefit plans, including Medicaid, will not cover a 3-month supply. The patient will receive only a partial fill of their prescription (ie, a 1-month supply), and the patient must then get another prescription for the next month.

If Schedule II controlled substance prescriptions are mailed, care must be taken to avoid diversion of the written prescription. Some suggest using certified mail (return receipt requested) to avoid diversion in your office, post office, or from the recipient's mailbox. Requiring patients to pick up their prescriptions each month may be inconvenient, but it does have the advantage of avoiding problems with mailing. If the prescription will be filled at a Shands Outpatient Pharmacy, prescribers can deliver prescriptions to a pharmacist at the pharmacy.

For routine prescriptions that will be picked-up at a pharmacy, faxing is not a reasonable option for Schedule II prescriptions. A prescription can be faxed, but the original must be delivered to the pharmacy before it will be dispensed. This results in little timesavings.

There are 3 exceptions when faxing a Schedule II prescription is permitted. A

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Outpatient pharmacy, *from page 3*
fax may serve as an original prescription when the Schedule II controlled substance is being prescribed for a patient residing in a nursing home, when the patient is receiving hospice care, or when a patient is undergoing home infusion therapy.

A final point that will help avoid confusion with Schedule II controlled substance prescriptions is to make sure that an appropriate quantity is specified. As stated last month, Florida Law now requires that prescribers must write the quantity of all prescription drugs in numerals and words to prevent adulteration (ie, #60 [sixty]). When directions for use are vague, like PRN-orders, a do-not-exceed-per-day quantity should be specified. This number will be compared to the quantity to make sure that the quantity matches the maximum amount that will be allowed for the duration of the prescription (ie, by the patient's prescription benefit plan).

Writing chronic prescriptions for Schedule II controlled substances can be challenging for the prescriber, the pharmacist, and, most importantly, the patient. Understanding limitations placed by the Drug Enforcement Agency and third-party payers can decrease problems that can arise.

NEWS

IVIG shortage triggers prior approval process

As stated in the *Formulary Update* section of the *Bulletin,* intravenous immune globulins (IVIGs) will require approval before each use beginning November 1, 2005. This decision was based on the limited supply of IVIGs that we are able to obtain.

IVIGs are derived from donated blood. There is limited manufacturing capacity to convert blood to IVIG. Supply is an issue. In the early part of this decade, there was an oversupply of IVIGs, which forced some companies out of this market. The American Red Cross, which was a major supplier of a relatively inexpensive lyophilized product, exited the market.

Each month Shands at UF receives an allocation. At the end of each month, we run the risk of having no IVIG to treat patients.

By establishing a prior approval process with medical staff gatekeepers, we can reserve the limited supply for the most critical patients. Alternative therapies will be recommended, whenever reasonable. The difficulty will be determining who is "most needy." Unfortunately, if priorities are not set, there is a real risk of having no product for critical patients.

Each month, our largest allocation of IVIG is for Panglobulin®. Generic orders for "IVIG" will be filled with Panglobulin®. We get a smaller supply of Polygam®, which is a product that has the lowest amount of IgA contaminant and is sucrose-free. A small percentage of patients do not tolerate IgA in IVIG. A portion of our Polygam® supply is being reserved for these patients. Gamunex®, the third IVIG listed in the *Formulary,* is also sucrose-free. Sucrose is a stabilizer in IVIG, but it has been associated with acute renal failure patients in some patients. Sucrose-free products are reserved for patients who are at highest risk from this potential adverse effect.

Drs. Richard Lottenberg and Suzanne Skoda-Smith will use patient need, total supply, and product characteristics to help prescribers during this time of product shortage. Hopefully market demand will ultimately increase the supply of IVIGs.