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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met September 15, 2009. 1 product was added in the *Formulary,* and 2 were deleted. 2 products were designated nonformulary and not available. 2 criteria for use were changed.

◆ ADDED

Prednisolone Syrup, Grape
(Generic by Morton Grove)

◆ DELETED

Prednisolone Syrup
(Prelone® by Adamis Laboratories)*

**Nonformulary and not available*

Thalidomide
(Thalomid® by Celgene)†

†Patients must use their own supply

◆ NONFORMULARY AND NOT AVAILABLE

Fentanyl Transmucosal Film
(Onsolis® by Meda Pharmaceuticals)

◆ CRITERIA-FOR-USE CHANGES

Midazolam (Generic)‡

‡IV allowed with efavirenz [Sustiva®] or ritonavir [Norvir®]

Oseltamivir (Tamiflu® by Roche)§

§Adult and Pediatric Oseltamivir Order forms required

Morton Grove's generic, grape-flavored version of **prednisolone syrup** was selected as the liquid dosage form of prednisolone that will be listed in the *Formulary.* **Prelone® syrup** was deleted from the *Formulary* and designated nonformulary and not available. These changes were made because Prelone® syrup does not taste good, and the Morton Grove product was considered more palatable.

(continued on next page)

POLICIES AND PROCEDURES

Update: Automatic dose & route changes

At the September P&T Committee meeting, a comprehensive review of the *Automatic Route and Dosage Changes* policy was approved. This policy permits changing routes from intravenous (IV) to oral or enteral (PO) and dosage standardizations. Dosage standardizations include rounding doses to a measurable dose and rounding doses to prevent wastage (ie, avoiding using an extra vial when it is not needed). These changes improve resource consumption and improve efficiency without affecting patient care. These changes are documented in the chart as "P&T Committee-approved Change."

Incremental doses are based on measurable doses and available container sizes. Ordered doses are changed based on reasonable "increments" to avoid waste (eg, using an extra container for a small amount) and/or to make the dose practical. For example, the current policy states that cytotoxic chemotherapy can be rounded up or down by as much as 5%. If prescribers disagree with roundings, they can write a note stating that the dose should not be standardized (with the exception of erythropoiesis-stimulating agents or electrolytes). Some roundings, like electrolytes, put limits on the maximum dose that can be given at one time to promote patient safety. Some categories of drugs (eg, investigational cytotoxic chemotherapy) are not rounded by policy. A complete list of adult dosage changes is available on the Portal.*

Many pediatric dosages must be rounded. It is preferred that pediatric dosages be written as "milligram-per-kilogram (mg/kg)" doses. Multiplying the patient's weight by the mg/kg dose can result in unmeasurable doses. There is a comprehensive list of pediatric dose changes that addresses this issue on the Portal.†

Changing the route of the drug from IV to PO requires more evaluation than dosage rounding. The dispensing pharmacist assesses the patient to determine if they are eligible for a route change. A complete list of eligible drugs is listed on the Portal.‡

Eligible patients must be receiving oral medications or food; not be NPO; not be a psychiatric patient who refuses oral medication; not have a mechanical obstruction (eg, esophageal sphincter incompetence or severe nausea and vomiting); or, not have a small bowel syndrome, inflammatory bowel disease, malabsorption syndrome, or any condition that prohibits receiving medications by mouth. If it is determined that a patient meets the criteria to be switched from IV to PO medication, the pharmacist documents the route change as an order (ie, P&T Authorized Route Change) as well as a progress note.

The P&T Committee approves all changes to the *Automatic Route and Dosage Changes* policy. Updates to the policy are documented monthly in the *Formulary Update* section of the *Bulletin.* The complete policy is available on the Portal.§

LINKS

*https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Formulary/TherapeuticInterchange/TIs/Dose_Rounding/Standardized-Doses.pdf

†https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pediatrics/Pharmacy/Education/peds%20dose%20standardization_9-22-09%20FINAL.pdf

‡https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Formulary/TherapeuticInterchange/TIs/IVtoPO/IV-to-PO.pdf

§https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Admin_Staff/Policies/06-Satellite_Pharmacy_Operations/58DB74C18597807AE0439FB21E78807A

INSIDE THIS ISSUE

Formulary update, *from page 1*

There are several brands of prednisolone oral solution (Pediapred®, Orapred®) and several generic versions. However, prednisolone syrup is listed in the *Formulary*. Prelone® is marketed by Adamis, but it is made by Teva. Usually for drug products that are deemed bioequivalent by the FDA, we select the product suggested by our group purchasing organization. This product is usually inexpensive and we can reliably get product. However, factors like taste, especially for an oral liquid consumed by children, will be considered. The grape-flavored prednisolone liquid by Morton Grove was recommended by practitioners in the Pediatric Pulmonary Clinic, where it is commonly used.

Taste preferences of children do not always match those of adults. When there are products that are problematic (ie, patients refuse them because of an intolerable taste), alternate vendors will be considered.

Thalidomide is probably best known for its teratogenic effects when it was used as a sedative and to treat morning sickness in other countries in the 1950s and 60s. In 1998, thalidomide was marketed in the US for the treatment of leprosy. It was serendipitously found to be effective decades earlier in patients with leprosy who used it as a sedative. The concerns about teratogenic effects limited its use to a restricted distribution program that requires strict patient registration and monitoring in the *System for Thalidomide Education and Prescribing Safety,* or *S.T.E.P.S.,* program.

Thalidomide has a variety of pharmacologic effects including altering cytokine levels. In addition to the treatment of leprosy, it has a labeled indication for multiple myeloma. Also, it has been used for a variety of off-labeled uses (eg, graft-versus-host disease).

Lenalidomide (Revlimid®), a thalidomide analog with a labeled indication for multiple myeloma, was evaluated by the P&T Committee in 2006. It is also only available via a restricted distribution system (ie, RevAssist) but could not be stocked. Thus, it was not eligible for addition in the *Formulary.* Patients must use their own supply of lenalidomide from home.

Although thalidomide was listed in the *Formulary*, it was not dispensed for nearly 2 years. Patients used their own supply that they obtained via the *S.T.E.P.S.* program. Thalidomide prescriptions are filled in registered community pharmacies.

Thalidomide was deleted from the *Formulary* and designated a high-priority nonformulary agent. This requires patients to use their home supply or to obtain an outpatient prescription for inpatient use. Shands' outpatient pharmacies are registered pharmacies and can be used to obtain a supply when patients are hospitalized without their supply from home.

Onsolis® is a buccal transmucosal form of fentanyl approved by the FDA July 16, 2009, for the labeled indication of the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying, persistent cancer pain. The product on the market that is closest to this new dosage form is fentanyl transmucosal "lollipops" [Actiq®]. Actiq® is listed in the *Formulary* but restricted to burn patients who lack IV access. Actiq® is used at Shands for procedural pain, not breakthrough cancer pain.

Because Onsolis® is a controlled substance, patients cannot use their own supply from home. The P&T Committee determined that there is no need for this dosage form and designated it nonformulary and not available.

Midazolam is very short-acting benzodiazepine used for sedation, anxiolysis, and amnesia during short procedures or as an aid in the induction of anesthesia. It is usually given intravenously, and the dose is given slowly in small increments to monitor the patient's level of sedation. Oral administration is used when IV access is not available or to facilitate a more invasive procedure in children.

Patient response to midazolam (including respiratory status) is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients. Sedative doses should be individually titrated, taking into account a patient's age, clinical status, and concomitant use of other central nervous system depressants (and other interacting medications that could increase the effects of midazolam). Continuous monitoring of respiratory and cardiac function is required (eg, pulse oximetry). The midazolam label warns, **BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION, AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAM HCl INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS.**

Midazolam is converted to inactive metabolites via CYP3A4 metabolism. Therefore, agents that inhibit CYP3A4 metabolism can increase the sedative and respiratory depression associated with midazolam use. Usually this is considered a warning. Although no drugs are listed in the *CONTRAINDICATIONS* section of midazolam's label, midazolam is listed in the *CONTRAINDICATIONS* sections of other drugs' labels.

Atazanavir [Reyataz®], **efavirenz** [Sustiva®], and **ritonavir** [Norvir®] are drugs used to treat patients infected with HIV. Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI), and atazanavir and ritonavir are protease inhibitors (PIs). These antiretroviral agents are potent inhibitors of CYP3A4. Ritonavir is frequently used in HIV regimens as a booster to increase patients' exposures to HIV drugs metabolized by CYP3A4.

The use of oral midazolam (not IV midazolam) is specifically contraindicated with atazanavir, yet the pharmacy's computer system alerted this interaction as a contraindication, regardless of route. This has been changed, and the alert now only fires when oral midazolam is ordered.

Efavirenz's and ritonavir's labels list the use of midazolam as contraindicated regardless of route (ie, IV or oral). Even though the labelings differ from atazanavir, these interactions are also most serious when midazolam is given orally, since the oral form is metabolized by the liver via a first-pass effect. Larger midazolam doses are used orally compared with IV in order to compensate for the first-pass elimination. Although administration of IV midazolam with these drugs may result in higher midazolam concentrations, midazolam administration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation (see previous warnings).

Therefore, the P&T Committee determined that IV midazolam use with efavirenz and ritonavir should be considered a warning and not a contraindication. There will be an effort to educate midazolam users about these important interactions.

Oseltamivir is an antiviral with activity against both influenza A and B. It has labeled indications for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days and for influenza prophylaxis in patients 1 year and older. Because of its activity against type-A influenza viruses, oseltamivir is used for the treatment of the current H1N1-swine

(continued on next page)

Formulary update, *from page 2*
virus that is causing swine-originated influenza (or the "swine flu").

In May, the P&T Committee restricted inpatient oseltamivir use to patients approved by an infectious diseases physician. This action was recommended by the Resistant Pathogen Task Force near the beginning of the swine flu outbreak. The goal was to ration supplies so that oseltamivir would be available for the neediest patients.

As the summer progressed, most of the influenza cases diagnosed were swine flu. This was not surprising since seasonal flu is not prevalent during the summer months and the swine flu persisted. As the year progresses and seasonal influenza increases, this will change.

The H1N1 Task Force recommended that the restriction of oseltamivir be changed. Oseltamivir no longer requires Infectious Diseases approval. It must be ordered with a *Pediatric* or *Adult Oseltamivir Order* Form. These forms will collect information on the reasons for oseltamivir use and provide guidelines for appropriate use and dosages. The forms help maintain our stockpile of oseltamivir, potentially decrease resistance, and decrease the chances of medication errors.

These forms are available on the Portal.*† The forms contain the most recent CDC-recommended criteria for oseltamivir use, which are continuously updated at the CDC website.‡. The P&T Committee will evaluate the continued need for oseltamivir forms after 6 months (at the most).

LINKS

*Pediatric Oseltamivir form: https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Forms/UF/PEDS-GENERALMED/95150.pdf

†Adult Oseltamivir Form: https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Forms/UF/Tab12/94768.pdf

‡http://www.cdc.gov/h1n1flu/recommendations.htm

MEDICATION SAFETY

Don't use midazolam with what?

According to the FDA, contraindicated drug-drug combinations should ***never*** be used together because the risk of using the drugs together ***always*** outweighs the benefit. The P&T Committee has established a policy that contraindicated drug-drug combinations should not be used together unless the committee has reviewed the evidence and determined that the benefits outweigh the risk in specific circumstances.[1]

Several exceptions to labeled contraindicated drug-drug combinations have been approved over the last 2 years. The use of the antifungal voriconazole (Vfend®) with sirolimus (Rapamune®) can be used safely if the sirolimus dose is drastically reduced and sirolimus levels are closely monitored.[1] Sildenafil (Revatio®) can be used with nitroglycerin in a monitored unit, where the risk of hypotension can be detected.[2] Anticholinergic drugs can be used with extended-release potassium tablets, since all oral solid doses of extended-release potassium are given with at least 100 mL of fluid and that the bed is elevated to at least 45 degrees.[3] This should prevent esophageal ulcerations because by the time extended-release potassium reaches the stomach, it should be dissolved and the concerns about an oral solid should be moot (ie, lower GI ulceration is not a concern). Finally, the use of the antibiotic linezolid (Zyvox®) is permitted with sympathomimetics in units (where the risk of increased blood pressure can be monitored) and with antidepressants when a progress note is placed in the chart explaining the potential symptoms of serotonin syndrome and to consider these in the patient's monitoring.

The P&T Committee recently determined that the use of intravenous midazolam can be used with caution in patients receiving ritonavir and efavirenz (see *Formulary Update*). This is consistent with the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and* Adolescents which states that protease inhibitors and non-nucleoside reverse transcriptase inhibitors are contraindicated with oral midazolam, but parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.[5] Thus, the most recent governmental guideline for the use of antiretroviral agents is inconsistent with the products' labels.

◆

Users of oral midazolam must be aware of these potentially serious drug-drug interactions.

The table *(see page 4)* shows that oral midazolam is often contraindicated in the labeling of drugs that are potent inhibitors of CYP3A4. Whether intravenous midazolam is contraindicated is inconsistent in the products' labels. Users of oral midazolam must be aware of these potentially serious drug-drug interactions. These interactions are particularly problematic because they are not listed in midazolam's labeling.

Contraindicated drug-drug combinations are relatively rare, and often computer screening programs suggest that combinations are contraindicated, when the labeling does not support that safety limitation. An evaluation of contraindicated drug-drug alerts generated over a 1-year period at Shands at UF showed that 60% of the alerts were inappropriately listed as contraindicated in the Pharmacy Department computer systems' knowledgebase. These interactions were downgraded to decrease the risk of alert fatigue.

Contraindicated midazolam drug-drug interactions pose an additional problem, since they may be used in the Operating Room (OR) or another setting where computer generated alerts may not warn the midazolam user. Thus, knowledge of these potential interactions is important. It also emphasizes the potential unpredictable response to midazolam, particularly oral midazolam, and the need for vigilant monitoring of patients who receive this agent as an adjunct to anesthesia or for sedation-anxiolysis-amnesia during a procedure.

As noted, the drugs listed in the table *(on page 4)* suggest patients infected with HIV receiving midazolam deserve particular attention. Patients undergoing bronchoscopies, endoscopies, or other procedures may be best sedated with other agents. Midazolam is often used concomitantly with other agents (eg, fentanyl), which already causes added sedation and respiratory depression. Patients may rapidly go from an appropriate level of sedation to being over-sedated with risk of insufficient respiration. Increased monitoring and possible lower titrated doses of midazolam and the adjuvant medications may be necessary.

Oral midazolam has the most potential for serious reactions. Because of the high first-pass with oral midazolam, higher doses are often used. When the first-pass metabolism is inhibited, the effective dose is much higher. It is also possible that oral midazolam could be used in a setting where monitoring is not as vigilant. Therefore, if you use oral or intravenous midazolam, please familiarize yourself with these interactions and make the appropriate adjustments in choice of sedative, sedative doses, and monitoring.

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DRUG-DRUG COMBINATIONS "CONTRAINDICATED" WITH MIDAZOLAM

GENERIC	BRAND	CONTRAINDICATED WITH IV	CONTRAINDICATED WITH ORAL
Protease Inhibitors (PIs)			
Atazanavir	Reyataz®	**NO**	YES
Darunavir	Prezista®	**NO**	YES
Fosamprenavir	Lexiva®	YES	YES
Indinavir	Crixivan®	**NO**	YES
Lopinavir + Ritonavir	Kaletra®	YES	YES
Nelfinavir	Viracept®	YES	YES
Ritonavir	Norvir®	YES	YES
Saquinavir	Fortovase®	YES	YES
Saquinavir	Invirase®	YES	YES
Tipranavir	Aptivus®	**NO**	YES
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Delavirdine	Rescriptor®	YES	YES
Efavirenz	Sustiva®	YES	YES
Tenofovir* + Efavirenz* + Emtricitabine†	Atripla®	YES	YES
Antifungals			
Itraconazole	Sporanox®	**NO**	YES

*NNRTI
†NRTI = nucleoside reverse transcriptase inhibitor

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2. Hatton RC. Formulary update: nitroglycerin intravenous and sublingual. *Drugs & Therapy Bulletin* 2009;23(3):1-2.
3. Hatton RC. Formulary update: potassium chloride extended-release. *Drugs & Therapy Bulletin* 2009;23(4):2-3.
4. Hatton RC. Formulary update: linezolid. *Drugs & Therapy Bulletin* 2009;23(6):2-3.
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008;115. Accessed online September 30, 2009 at http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.