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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 18, 2010. 4 products were added in the *Formulary,* and 4 products were deleted. 7 products were designated nonformulary and not available. 4 interchanges and 2 restrictions were approved.

◆ ADDED

Budesonide Capsules (Entocort® by Prometheus Laboratories)

Hyaluronidase, Ovine (Vitrase® by ISTA Pharmaceuticals)

Indapamide (eg, Lozol® and Generics)

Pneumococcal 13-Valent Vaccine (Prevnar-13® by Wyeth)

◆ DELETED

Acetaminophen 80 mg Suppositories (Generic)*

**Nonformulary and not available*

Hyaluronidase, Bovine (Amphadase®)*

Pneumococcal 7-Valent Vaccine (Prevnar-7® by Wyeth)*

Simethicone 40 mg Tablets (Generic)*

◆ NONFORMULARY AND NOT AVAILABLE

Antipyrine-Benzocaine 0tic Solution (eg, Auralgan® Otic Solution)

Pramipexole ER (Mirapex® ER)

Terazosin (eg, Hytrin® and Generics)

(continued on next page)

INVESTIGATIONAL DRUG INFORMATION

"Case Reporting"

Clinical experiences are often the genesis of research questions and the design and development of clinical research protocols. In an academic medical center, it is common for unique and interesting clinical cases (eg, adverse drug events or off-labeled uses) to be written up as case reports for publication in medical journals or presentation at medical or scientific meetings. The Institutional Review Board (IRB) provides guidance on when publication/presentation of case report(s) constitutes human-subjects research and requires prospective IRB approval.

The Federal Policy for the Protection of Human Subjects (45 CFR 46.102[d]) defines "research" as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. In general, the review of medical records for publication of "case reports" of typically **three or fewer patients** is NOT considered human-subject research and does NOT typically require IRB review and approval. Case reporting on a small series of patients does not involve the formulation of a research hypothesis that is subsequently investigated prospectively and systematically for publication or presentation. Reporting or publication is not typically envisioned when one interacts clinically with the subject.

When larger series of patients are being reported, investigators usually begin to ask specific research questions and systematic collection of data occurs, moving these activities closer to research. The boundaries between case reporting and formal medical records research may be unclear for a series of one's own patients. Researchers are advised to consult with the IRB or submit larger case series reports for IRB review when uncertainty exists about whether formal and systematic collection of human subjects' research is occurring.

Patient confidentiality should be respected in all clinical situations involving identifiable medical information from patients. Names, dates, social security numbers, medical record numbers, and other "codes" or combinations of identifiers, which might easily allow someone to identify a subject, should never be used in publications or external presentations.

Unique family trees or pedigrees should be masked or disguised when such information could identify individuals or kindreds. Photographs should be appropriately masked to preclude identification of subjects.

It is strongly recommended (and required at Shands HealthCare) that patients provide written consent to allow publication or electronic dissemination of pictures or other information (eg, videos, voice recordings, transcripts) that might, in any way, identify them. Contact the Public Affairs Office at UF or Shands HealthCare for sample non-research consent forms for use of identifiable material. When photographs will be used ONLY in confidential medical records or as part of direct clinical care of the patient (for example, photograph of a characteristic rash which would be retained in a record for documentation or shown to colleagues in the provision of clinical care), it is appropriate and acceptable to obtain and document verbal consent.

Clinicians should be sensitive to the "small-cell problem": the existence of individuals with such unique or unusual diagnoses or illnesses, that it might be possible for others (or patients and families themselves) to identify the individuals in case reports or medical textbooks based upon limited information, such as state or city of residence, age, and diagnosis.

by R. Peter Iafrate, PharmD

INSIDE THIS ISSUE

◆ Therapeutic interchange

Formulary update, *from page 1*

◆ INTERCHANGES

Doxazosin (Generic) for **Terazosin** (Generic)

Pramipexole IR (Generic) for **Pramipexole ER** (Mirapex® ER)†

†Daily dose given in 3 divided doses

Prevnar-13® for **Prevnar-7®**

Simethicone 80 mg (Generic) for **Simethicone 40 mg** (Generic)

◆ CRITERIA-FOR-USE CHANGES

Alteplase (eg, Cathflo®)‡

‡*Restricted to Physician-approved Protocol*

Gadobenate (Multihance®)§

§*Restricted to use for pediatric brain tumor diagnosis*

Entocort® is a specialized oral dosage form of the corticosteroid **budesonide**. It has a labeled indication for the treatment of mild to moderate active Crohn's disease involving the ileum and/or ascending colon and for maintenance of clinical remission of Crohn's disease involving this same gastrointestinal region. Entocort® capsules contain enteric-coated beads. The formulation delays the release of budesonide until present in the lower gastrointestinal tract, where it then slowly releases. Entocort® is used off-label for the treatment and maintenance of collagenous colitis and for use in graft-versus-host disease. The low systemic bioavailability and low potential for mineralocorticoid effects result in a localized effect on the gastrointestinal tract with minimal peripheral adverse reactions.

Clinical evidence has demonstrated that Entocort®, at a dose of 9 mg every morning, has comparable efficacy to systemic corticosteroids in the treatment of active Crohn's disease. Entocort® 6 mg daily for up to 3 months is an efficacious therapy for the maintenance of clinical remission in Crohn's disease. Although only validated against placebo, the use of Entocort® at doses of 9 mg daily for the treatment of active collagenous colitis and 6 mg daily for 3 to 6 months for the maintenance of clinical remission in collagenous colitis has been supported by several studies. Weak retrospective and quasi-experimental studies are the only evidence suggesting a benefit for the use of Entocort® 3 mg three times daily in graft-versus-host disease, but better designed studies are currently in progress.

The lower systemic bioavailability of Entocort® is associated with fewer adverse effects with lower frequencies and less intensity than systemic corticosteroid comparators, but Entocort® is associated with complications. Corticosteroid adverse effects, such as acne, easy bruising, and moon face, can be problematic with Entocort® and has been associated with discontinuation of therapy. These adverse reactions can be amplified by CYP 3A4 inhibitors, like ketoconazole, ritonavir, and erythromycin, which suppress the metabolism of budesonide and increase its systemic bioavailability. Entocort® costs 2.6 times as much as treatment of the same indications with generic corticosteroids, which is a barrier to its use.

Ovine hyaluronidase was added in the *Formulary*, while **bovine hyaluronidase** was deleted and designated nonformulary and not available. Bovine hyaluronidase production has been "suspended" by its manufacturer, Amphastar. This product had been in short supply, reportedly because of insufficient raw materials. There is no alternative source of bovine hyaluronidase. The manufacturer claims that it may re-market this product in mid-2011, but it is difficult to predict this far into the future.

Ovine hyaluronidase and recombinant human hyaluronidase [Hylenex®] were the alternative products to bovine hyaluronidase. Recombinant hyaluronidase costs roughly twice as much as the ovine product. Because of the bovine hyaluronidase shortage, ophthalmologists were already using ovine hyaluronidase. In ophthalmologic surgery, hyaluronidase is used as a dispersing agent with a local anesthetic. Hyaluronidase is also in extravasation kits to promote the resorption of extravasated fluids, and, hopefully, minimize the risks of tissue damage. The extravasation guidelines will be modified to take into consideration the change in source of hyaluronidase.

Indapamide was evaluated for possible addition in the *Formulary* because of high-volume (ie, greater than or equal to 3 patients per month) nonformulary use. Because indapamide is available as a generic from multiple sources, it is inexpensive.

Indapamide is similar to thiazide diuretics like hydrochlorothiazide and chlorthalidone, both of which are already listed in the *Formulary.* Indapamide has labeled indications for the treatment of hypertension (alone or in combination with other antihypertensive drugs) and salt and fluid retention associated with congestive heart failure. Off-labeled uses include isolated systolic hypertension, to reduce cardiovascular risk in type 2 diabetes mellitus, hypercalciuria, and neurohypophyseal diabetes insipidus.

Indapamide has not demonstrated a therapeutic advantage over thiazide-type diuretics; however, some reports suggest it has less detrimental effects on blood lipids. There are other reasons expressed by clinicians as to why they prefer indapamide to thiazide diuretics. These include less effect on low-density lipoprotein (LDL), a beneficial effect on high-density lipoproteins (HDL), less effect on blood glucose, less effect on serum potassium (less lowering), less effect on serum sodium (less lowering), and less effect on uric acid (less increase).

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), lists indapamide with chlorthalidone, hydrochlorothiazide, and metolazone as a "thiazide" diuretic. The usual dose is 1.25 to 2.5 mg given once a day. JNC VII does not state any conditions for preferential use of indapamide over other diuretic options.

Indapamide is not a "thiazide." It is a benzamide-sulfonamide-indole compound without the thiazo-ring. It is sufficiently different from hydrochlorothiazide or chlorthalidone, so a patient with a true allergy to these drugs might tolerate indapamide.

There are few outcome data with indapamide compared with the thiazide diuretics, like chlorthalidone. Indapamide (2.5 mg/day) produces similar diuretic and antihypertensive effects as hydrochlorothiazide (25 to 100 mg/day).

Prevnar-13® was added in the *Formulary* and will automatically be substituted for **Prevnar-7®**. Prevnar-13®, which is a 13-valent conjugated pneumococcal vaccine, was recently approved for use in infants and young children through 5 years old to prevent invasive pneumococcal disease and otitis media. This agent replaces the 7-valent vaccine, which was listed in the *Formulary*. The Advisory Committee on Immunizations Practices (ACIP) now recommends the 13-valent vaccine instead of the 7-valent vaccine (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5909a2.htm). ACIP recommends Prevnar-13® for all children 2 to 59 months and for children 60 to 71 months with medical conditions that increase their risk for pneumococcal disease or complications. The ACIP provides complete guidelines for previously unvaccinated patients and patients who have already received Prevnar-7®.

Acetaminophen 80-mg suppositories were deleted from the *Formulary* because they are no longer

(continued on next page)

Formulary update, *from page 2*
commercially available. The 80-mg acetaminophen suppository was used to administer small rectal doses of acetaminophen. Remaining options include dividing [cutting] the 120-mg suppository or diluting and administering of acetaminophen drops rectally. Neither option is ideal, but they provide possible options when small rectal doses are needed.

Simethicone 40 mg tablets (1/2 tablets) were listed in the *Formulary*, but these tablets will no longer be pre-split and will be automatically interchanged to the 80-mg tablet. The 80-mg tablets are difficult to split in half without crumbling because they are too friable. There is little risk from receiving too much simethicone. There is a 66.6 mg/mL drop available in the *Formulary* for low doses of simethicone.

Antipyrine-benzocaine otic solution was designated nonformulary and not available. It has not been listed in the *Formulary* and was occasionally used nonformulary.

Auralgan® Otic Solution is very expensive [~$150 per bottle]. There is a generic solution that has antipyrine with benzocaine in slightly different concentrations that is 1/20th the cost, which was considered for addition in the *Formulary* with a therapeutic interchange.

Systemic pain medications (eg, acetaminophen or ibuprofen) are recommended alternatives for the pain associated with otitis media. Otitis externa is usually managed with topical antibiotics, topical anti-inflammatories, and systemic pain medications. If a local anesthetic is used, lidocaine can be used instead of benzocaine. In the Emergency Department, the patient could be given a prescription for a generic version of Auralgan®. The cost of brand name Auralgan® may prevent some patients from filling the prescription.

Mirapex® ER is a once-daily version of pramipexole. Pramipexole is a nonergot dopamine agonist with a labeled indication for the signs and symptoms of Parkinson's disease. The immediate-release (IR) version of pramipexole is given 3 times a day. The P&T Committee approved an automatic interchange from Mirapex® ER to the immediate release version using the same daily dose divided into 3 doses.

Terazosin is an alpha-blocker that was evaluated for possible addition in the *Formulary* or therapeutic interchange based on frequent nonformulary use.

Because this product is available as a multi-source generic and is inexpensive, it was considered for addition in the *Formulary*. However, it was determined **doxazosin** is an alternative in the *Formulary* that is acceptable for an automatic interchange. Since terazosin is used for both hypertension and benign prostatic hypertrophy (BPH), tamsulosin could not be recommended as an alternative for all patients. Since terazosin lowers blood pressure, whether used to treat BPH or for hypertension, doxazosin would be a better alternative. Equivalent doxazosin doses for terazosin are 1 mg for 1 mg, 2 mg for 2 mg, 4 mg for 5 mg, and 8 mg for 10 mg.

Alteplase is tissue plasminogen activator or tPA. Alteplase converts plasminogen to plasmin. Plasmin degrades fibrin and fibrinogen, and is not active without fibrin present. Alteplase has labeled indications for the treatment of systemic thromboses in large doses and for occluded intravenous (IV) catheters in small doses.

An evidence-based review of the appropriate dose of tPA for IV line clearance supports the use of lower dosages (eg, 0.5 mg or 1 mg) as long as proper administration technique is used. This issue could have significant cost implications (ie, if 2-mg dosages are used instead of a lower dose).

In addition to the appropriate doses, other clinical issues evaluated included the volume to instill (topping off to fill the catheter), administration technique, dwell time, and patient safety (impact of losing an IV line). Administrative issues include waste, convenience to pharmacy and nursing (commercial product vs frozen), labor to prepare, and potential cost savings.

A standardized protocol was developed for all "TPA to clear line" orders. The *Alteplase Order Form for Central Venous Line De-Clotting* will now be initiated by nursing staff per a Physician-approved Protocol (PAP) for the use of alteplase to clear occluded catheters. The order form provides the specifics for dose, dwell time, and specific considerations for each type of catheter. The PAP procedure will not be implemented by June 1st.

Gadobenate was added in the Formulary at the March P&T Committee meeting. The P&T Committee put 2 stipulations on its addition. Explicit criteria (or protocols) for the use of gadobenate over gadodiamide had to be submitted to the P&T Committee within 2 months and a review of relative use statistics (eg, based on purchases) will occur after 6 months.

When gadobenate was added in the *Formulary*, it was noted that for each 10% that gadobenate replaced the use of gadodiamide [Omniscan®], it would add about $25,000 to $30,000 to pharmaceutical expenditures (ie, 100% replacement could cost around $300,000).

Gadobenate use will be limited to pediatric brain tumor patients, especially those being evaluated for drop metastases in the spine. The CSF spread of tumor in these cases can be very subtle, but if present can dramatically alter management. Thus, this use justifies the increased cost.

POLICIES AND PROCEDURES

Therapeutic Interchange: The importance of medication reconciliation

It is estimated that there are at least 20,000 prescription drugs that could be stocked in the hospital. If you add in all the possible nonprescription drugs, there is an unmanageable number of possible drugs that patients admitted to Shands already could be taking.

Like all hospitals, Shands limits the number of drugs readily available for use while the patient is hospitalized. Our *Formulary* has fewer than 3000 items, a small fraction of the drugs that patients could be taking on admission.

When a patient is admitted, housestaff often just write orders for all medications their patient is taking [rather than consulting the *Formulary*] and wait to hear from a pharmacist if there is a problem (ie, a drug is not "stocked"). By definition, a nonformulary drug is not readily available for use. If a drug is nonformulary, there are several possible approaches. If the patient has their own supply from home, an order can be written allowing the patient to use their own supply from home. Homes supplies of controlled substances, injectables, oral solutions, and drugs that are unsafe for use in the hospital (eg, bisphosphonates) cannot be used.

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Policies and procedures, *from page 3*

If the drug is nonformulary and there is not a similar option in the *Formulary*, it can be acquired via the nonformulary process. This requires justification to obtain the drug that is not stocked. The delay needed to acquire the drug may make this impractical.

If a similar drug is listed in the *Formulary*, the patient can be converted from the nonformulary drug to a formulary alternative. For example, a patient admitted on moexepril (Univasc®) could be changed to an equivalent dose of lisinopril or ramipril, which are both listed in the *Formulary*. After being paged, the prescriber must write an order discontinuing moexepril and write an order starting a formulary ace inhibitor (eg, lisinopril).

The problem with this approach is there is no explanation for the switch. At discharge, the patient's current medication includes lisinopril. Often, a prescription for lisinopril would be written at discharge. The prescriber would usually not appreciate that the patient should be switched back to moexepril. This might lead to the patient taking BOTH lisinopril and moexepril after discharge. The patient still has a supply of moexepril. If not specifically instructed to stop taking the moexepril, this could lead to duplicate therapy and an adverse effect.

Therapeutic interchange could result in the same type of adverse effect where a patient after discharge takes 2 drugs in the same category. Therapeutic interchanges are automatic interchanges of similar drugs at similar doses that are approved by the Pharmacy and Therapeutics Committee. A complete list of therapeutic interchanges can be found on the Shands Portal.* Therapeutic interchange has advantages over the ad hoc changing of orders to match what is listed in the *Formulary*. Therapeutic interchange is automatic; no page or phone calls are needed. In addition, there is documentation in the chart that a change was made. In addition to a notice in the *Orders* and *Progress Notes* sections of the chart, the change is noted on the *Transfer Medication Report* and *Medication Administration Record* (*MAR*). This improved documentation should prompt the prescriber writing discharge prescriptions either to convert the patient back to the admission medication or to instruct the patient NOT to take the duplicate medication.

This stresses the importance of medication reconciliation at discharge. Medication reconciliation is the process of comparing a patient's list of medication at each change in level of care (eg, upon admission, transfer from an ICU to a general ward, post-operative, and discharge) to determine what changes, if any, are needed to the patient's regimen. The goal is to improve patient care (eg, avoid omissions, interactions, therapeutic duplications, new contraindications, etc).

No system will replace the cognitive function of comparing the patient's list of medications and critically deciding what changes, if any, need to be made to a patient's list of medications. Medication reconciliation continues to be an emphasis of The Joint Commission because it has the potential, when done correctly, to improve medication safety and the quality of patient care.

When a patient is discharged, it is important to compare the list of medications they were taking upon admission to their discharge medications. If a patient should stop taking a drug at home, make sure that the patient or their caregiver gets this message. If a drug taken in the hospital needs to be switched back to what they take at home, the appropriate discharge prescriptions need to be written.

LINKS

*https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Formulary/TherapeuticInterchange.