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, Ovino
(Vitrase® by ISTA Pharmaceuticals)

Indapamide
(eg, Lozol® and Generics)

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

◆ DELETED

Acetaminophen 80 mg Suppositories (Generic)*

Hyaluronidase, Bovine
(Amphadase®)

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

Simethicone 40 mg Tablets
(Generic)*

◆ NONFORMULARY AND NOT AVAILABLE

Antipyrine-Benzocaine Otic 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
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 collogenous 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. 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 indication with generic corticosteroids, which is a barrier to its use.

Ovine hyaluronidase was added in the Formulary, where bovine hyaluronidase was deleted and designated non-formulary 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
cacetaminophen suppository was used
to administer small rectal doses of
cacetaminophen. Remaining options
include dividing (cutting) the 120-mg
suppository or diluting and adminis-
tering of acetaminophen drops rec-
tally. Neither option is ideal, but they
provide possible options when small
rectal doses are needed.

Simethicone 40 mg tablets (1/2
tables) 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 solu-
tion was designated nonformulary
and not available. It has not been
listed in the Formulary and was occa-
sionally used nonformulary.

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

Systemic pain medications (eg,
cacetaminophen or ibuprofen) are rec-
ommended alternatives for the pain
associated with otitis media. Otitis
externa is usually managed with topi-
cal antibiotics, topical anti-inflamma-
tories, and systemic pain medications.
If a local anesthetic is used, lidocaine
can be used instead of benzocaine. In the
Emergency Department, the pa-
tient 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 non-
ergot 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 Commit-
tee 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 inter-
change 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 For-
mulary that is acceptable for an auto-
matic interchange. Since terazosin is
used for both hypertension and benign
prostatic hypertrophy (BPH), tamsulosin
could not be recommended as an alter-
native for all patients. Since terazosin
lowers blood pressure, whether used to
treat BPH or for hypertension, doxazosin
would be a better alternative. Equiva-
 lent 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 plas-
minogen 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 ap-
propriate dose of tPA for IV line clear-
ance 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 impli-
cations (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 Commit-
tee 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 Commit-
tee 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, house-
staff 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 nonformu-

lar drug is not readily available for
use. If a drug is nonformulary, there are

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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 medications and critically deciding 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.

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