FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 20, 2001. 2 drugs were added in the Formulary and 1 drug was deleted. 1 drug that was added was restricted. 1 drug was designated not available.

◆ ADDED
Drotrecogin* (Xigris® by Eli Lilly)
Insulin glargine (Lantus® by Aventis)

*Restricted to ICUs and order form.

◆ DELETED
Levonorgestrel implants (Norplant® by Wyeth-Ayerst)

◆ NONFORMULARY, NOT AVAILABLE
Darbepoetin (Aranesp® by Amgen)

Drotrecogin alfa activated is recombinant human activated protein C. The inflammatory and procoagulant host responses to infection are closely related. Proinflammatory cytokines, such as tumor necrosis factor (alpha), interleukin-1 (beta), and interleukin-6, are capable of activating coagulation and inhibiting fibrinolysis. Also, the procoagulant thrombin can stimulate multiple inflammatory pathways. The activation of coagulation, followed by intravascular deposition of fibrin, has been implicated in the development of multiorgan dysfunction and death. Activated protein C is an important modulator of the coagulation and inflammation associated with severe sepsis. Drotrecogin inhibits the coagulation cascade and (possibly) improves outcomes in patients who have severe sepsis.

Drotrecogin was evaluated proactively by the P&T Committee before Food and Drug Administration (continued on next page)

DRUG INFORMATION FORUM

Acetylcysteine: Not just an antidote anymore

Acetylcysteine (Mucomyst®) possesses activity as a mucolytic, an antioxidant, and an antidote. Historically, acetylcysteine has been most often used as an antidote after acute ingestion of acetaminophen. Acetylcysteine prevents hepatotoxicity associated with high doses of acetaminophen by acting as a substrate for the toxic acetaminophen metabolite.

Today, acetylcysteine is being used in several unique areas of medicine. Acetylcysteine has gained popularity as an antioxidant and a free radical scavenger in the prophylaxis of radiocontrast-induced nephrotoxicity (RCIN). The Drug Information Center has received several questions concerning the use of acetylcysteine in patients who are undergoing procedures requiring radiocontrast agents.

There is some confusion about why these patients are receiving acetylcysteine. Health care professionals have asked if acetylcysteine possesses any cardioprotective effect because it was given to patients undergoing cardiac catheterization. Acetylcysteine does not have any direct cardioprotective effect in these patients. The benefit seen from using acetylcysteine is its ability to prevent reductions in renal function. Acetylcysteine has also been found to have vasodilatory properties in animal models.

A study by Tepel and colleagues compared to hydration alone in a randomized trial by Solomon and colleagues. Oxygen-free radicals may play a role in the mechanism of nephrotoxicity caused by radiocontrast media. Acetylcysteine has been hypothesized to act as an antioxidant to scavenge the free radicals and help prevent reductions in renal function. Acetylcysteine has also been found to have vasodilatory properties in animal models.

Preventative strategies are recommended for any patient at risk of developing RCIN. Agents that have been previously studied in humans for prophylaxis of RCIN include those that might mitigate the effects of the radiocontrast media on the tubules or alter the local hemodynamics in the kidney. Drugs that have shown either marginal or no benefit in studies with small sample sizes include mannitol, furosemide, low-dose dopamine, theophylline, atrial natriuretic peptide, and calcium-channel blockers. The addition of mannitol or furosemide to hydration before radiocontrast media administration showed no additional benefit compared to hydration alone in a randomized trial by Solomon and colleagues.

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A study by Tepel and colleagues found that administration of acetylcysteine and hydration before the administration of radiocontrast agents could prevent radiocontrast media-induced nephrotoxicity. In this prospective, placebo-controlled, randomized (continued on page 4)
Formulary update, from page 1
approval because the committee
determined that it could represent
an advantage over existing therapi-
es. Drotrecogin was “tentatively
added” in the Formulary with stu-
pulations that follow. The evaluation
of drotrecogin will continue at the
January P&T Committee meeting.
The FDA approved drotrecogin
November 21, 2001—the day after
the P&T Committee met. It has a
labeled indication for the reduction
of mortality in adult patients with
severe sepsis (sepsis associated
with acute organ dysfunction) who
have a high risk of death (eg,
determined by APACHE II).
An expert ad hoc group of ICU
and infectious disease physicians
and pharmacists was established to
determine appropriate criteria for
use. A draft of a Drotrecogin Order
Form was developed to promote
appropriate prescribing and to
facilitate collecting information that
will allow the monitoring of the use
of this drug. The Drotrecogin Order
Form can be found on the Shands

Drotrecogin should be admin-
istered intravenously at an infusion
rate of 24 mcg/kg/hr for a total
duration of infusion of 96 hours. A
96-hour course of drotrecogin costs
approximately $7000—more for
larger patients. Therefore, the
impact of drotrecogin on pharma-
caceutical expenditure could be great. The
Resource Utilization Committee (RUC)
have required that quarterly reports
on use and cost of drotrecogin be
presented.

Hemorrhage is a major concern
with drotrecogin. When drotrecogin
is used in a wider patient population
than in the published clinical trials,
a higher rate of bleeding should be
anticipated. Drotrecogin is contrain-
dicated in patients who have active
internal bleeding, or who are more
likely to bleed because of certain
medical conditions including recent
stroke, recent head or spinal injury,
or severe head trauma. In the event
of clinically important bleeding, the
infusion of drotrecogin should be
stopped immediately.

Also, the efficacy of drotrecogin
may not be as impressive in practice
as it was in the clinical trials since it
will probably be used in a wider
population of patients (eg, trans-
plant recipients). Therefore, patient
selection will be very important to
balance safety and efficacy.

Drotrecogin orders must be
written by attending physicians
from the BICU, CICU, MICU, PICU,
and SICU using the Drotrecogin Order
Form. Since a decision to use drotre-
cogin can be delayed as much as 24
hours, requiring an attending to
complete the order form should not
result in adverse consequences.

Insulin glargine is a long-acting
recombinant analogue of human
insulin with a labeled indication for
both type 1 and type 2 diabetes in
patients greater than 6 years of age.
It is only used in patients with type
2 diabetes who require insulin.
Insulin glargine is a chemically
modified analog of human insulin
that is not water-soluble at a neutral pH.
When administered subcutaneously,
insulin glargine precipitates and is
slowly released over 24 hours. Essen-
tially, it is a sustained-release form
of insulin.

The Drotrecogin Order Form

The Drotrecogin Order Form can be
found on the Shands intranet at http://
intranet.shands.org/pharm/xigrisform.pdf and
orders must be written by attending physicians from the BICU, CICU, MICU, PICU, and SICU using the Drotrecogin Order Form.

Insulin glargine is given once a day
at bedtime as a subcutaneous injec-
tion. It is not intended for intravenous
administration and should not be
mixed with any other insulin. Al-
though there are no current recom-
mendations as to the reductions
needed in insulin glargine dosing in
renal and hepatic impairment, it
should be used cautiously and moni-
tored carefully in these patients. A
review of drug-induced hypoglycemia
published in the New England Journal
of Medicine concluded that patients
should have their maintenance doses
of daily insulin reduced upon admis-
sion to avoid the occurrence of hypo-
glycemia due to fasting and decreased
caloric intake. These recommendations
should be considered for insulin glar-
gine, although these recommendations
were based on older forms of insulin.
Clinical trials show that insulin glar-
gine is at least as effective at lowering
fasting plasma glucose levels compared
with NPH insulin. Insulin glargine has
been associated with less nocturnal
hypoglycemia compared with NPH
insulin.
Insulin glargine costs 3-times as
much as NPH or Lente insulin, but
use should be relatively low. Patients
started on insulin glargine in the
hospital will not be able to take this
drug home. Unlike other forms of
insulin, insulin glargine is a prescrip-
tion product and must have an ap-
propriate prescription label. There
is no mechanism for this labeling
at this time, and the prior authorization
that is required until the patient
is using as an inpatient cannot legally be sent home with
the patient.

There is a medication safety
hazard associated with Lantus®
insulin. Reports at other hospitals
have shown confusion between
Lantus® and Lente insulin when
orders are not written clearly.
Pharmacy and nursing education
efforts have already been instituted.
An article was also placed in
the October issue of the Drugs &
Therapy Bulletin to alert the medical
staff about this possible problem.

Levonorgestrel implants are
case-controlled studies that are
implanted in a superficial plane
of the upper arm and that slowly
releases the progesterin, levonorges-
trel, over up to a 5-year period
providing a constant method of
contraception. This method is
reversible upon removal of the
implants.

Approximately 1 year ago, Nor-
plant® implants were removed from
the market because of quality control
issues. They remain unavailable at
this time. The OB-GYN department
used Norplant® as a birth control
method for noncompliant patients
before their discharge. Depot
medroxyprogesterone is now used,
but it must be administered every 3
months. Women who had Norplant®
implanted before it was removed
from the market last year were
advised to use a back-up, barrier
or other nonhormonal method of
contraception, such as a condom,
spermicide, a diaphragm, or IUD. No
new implants have been placed since
this warning.

Because of lack of availability and
the need to re-evaluate this product
should it become available again,
Norplant® was deleted from the
Formulary. Its formulary status can
be reconsidered if it is re-released to
the market.

Darbepoetin is a hyperglycosylated
analogue of recombinant human
erthropoietin. The extra carbohydrate
chains result in amino acid
substitutions, giving darbepoetin
an increased circulating half-life
compared with epoetin. Darbepoetin’s
half-life is 2 to 3 times longer than that of epoetin.

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Formulary update, from page 2

Instead of 3-times a week administration, darbepoetin can be given weekly. Instead of weekly administration, darbepoetin can be given every other week. This could result in less nursing and pharmacy time and, potentially, fewer patient office visits in the outpatient setting.

Clinical trial data show that darbepoetin has similar effectiveness and adverse effects compared to epoetin. Thus, the main advantage of darbepoetin is that it can be given less frequently than epoetin.

Darbepoetin is less expensive than epoetin for large dosages, but more expensive for lower dosages. Therefore, adding it in the Formulary should not increase pharmaceutical expenditures, but it is difficult to estimate the actual effect.

Reimbursement is a critical issue with darbepoetin. Currently, there is no Medicare reimbursement code for darbepoetin when it is used in a hospital-based clinic. If darbepoetin is administered in a physician-owned clinic, it can be billed on an HCFA 1500 Form (superbill) using a miscellaneous code (ie, code J-3490), which is used for all new drugs, provided that it is used only for an approved indication and that additional explanatory text is provided. Very specific explanatory text is required to justify the use of a drug when a miscellaneous code is used. If not done correctly, the clinic will not receive any reimbursement. Poor reimbursement could be financially devastating.

Darbepoetin cannot be billed in a hospital-based clinic. If it were used, there would be no reimbursement for this expensive agent.

When the temporary C-code is assigned, darbepoetin can be billed in a hospital-based clinic, but only for the approved indications. In other words, if someone used it in the Shands Infusion Center or the BMT outpatient clinic for a cancer-related indication, there would be no reimbursement.

Darbepoetin is not available in the Shands Outpatient Pharmacy at this time. Once the reimbursement issues have been clarified, the formulary status of darbepoetin will be reconsidered. Until that time, it has been designated not available in the inpatient setting as well.

PHARMACOTRIVIA

Making sense out of “MAbs”

Does it seem like generic names are getting more difficult to remember—and pronounce? There is a method to this madness, and this article will try to explain the generic names of monoclonal antibodies or “MAbs.”

A drug company can request that a generic name be assigned to a drug after an investigational new drug application (IND) has been submitted to the Food and Drug Administration (FDA). The United States Adopted Name (USAN) Council assigns generic names. Since generic names are nonproprietary, they are not subject to proprietary trademark rights and are entirely in the public domain. Generic names are selected using principles that are designed to be logical and assure safety and consistency.

Although generic names are supposed to be brief, easy to pronounce, and easy to remember, that is not the general perception—particularly for monoclonal antibodies. Most generic names have few syllables. Monoclonal antibodies’ generic names often have 4 or more syllables. Once you understand the principles used to establish the generic names of monoclonal antibodies, each syllable provides information about these biological agents.

The rules for naming monoclonal antibodies were established by the USAN Council in conjunction with the FDA, the US FDA Center for Biologics Evaluation and Research (CBER), and the World Health Organization’s (WHO) International Nonproprietary Names (INN) Committee. The first guideline is easy to remember: all monoclonal antibodies end in mab.

By working backward from the “mab” suffix to the prefix of the generic name, you can determine how the MAbs are created and what they are used for. In front of “mab” is the animal source used to create the antibodies. The following letters are approved as product source identifiers.

- a = rat
- u = human
- e = hamster
- xi = chimera
- i = primate
- zu = humanized
- o = mouse

Currently, all monoclonal antibodies on the US market come from a chimeric or humanized source (see table below). Chimera means the fusion of 2 genetically distinct types of cells. This term comes from Greek mythology where the chimera was a monster with a lion’s head, a goat’s body, and a serpent’s tail. Chimeric antibodies are usually the fusion of mouse and human antibodies. Humanized refers to the manipulation of animal genes (usually mouse) to create antibodies that appear to be human (ie, < 10% mouse).

In front of the source in the name of a monoclonal antibody is the disease or target of that antibody. The current list of diseases or targets includes the following.

- bac = bacterial
- circ = cardiovascular
- col = colon (tumor)
- got = gonad/testis (tumor)
- lim = immune (immunomodulator)
- mar = mammary (tumor)
- mel = melanoma (tumor)
- pro(o) = prostate (tumor)
- tum = tumors (miscellaneous)
- vir = viral

Thus far, the only monoclonal antibodies that have been marketed are targeted at the cardiovascular system, miscellaneous tumors, viruses, or are immunomodulatory. In an attempt to make these generic names pronounceable, often the last consonant of the target syllable is dropped (eg, lim truncated to li).

In order to create a unique name, a distinct compatible syllable is selected as the starting prefix. There is no rule for this selection, although you can guess where these syllables are derived. For example, does the starting prefix in abciximab come from being a Fab fragment (ie, fAB) or from antibody (ie, Ab)?

Using your new understanding of the generic names of monoclonal antibodies, look at the generic names in the table that lists all currently

(continued on page 4)

<table>
<thead>
<tr>
<th>TABLE. MONOCLONAL ANTIBODIES ON THE US MARKET</th>
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<tbody>
<tr>
<td><strong>Generic Name</strong></td>
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<tr>
<td>Abciximab</td>
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<tr>
<td>Alemtuzumab</td>
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<tr>
<td>Basiliximab</td>
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<tr>
<td>Daclizumab</td>
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<td>Palivizumab</td>
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<tr>
<td>Rituximab</td>
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<tr>
<td>Trastuzumab</td>
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</table>
Drug information forum, from page 1


1. Stevens MA, McCullough PA, Tobin KL, et al. A prophylactic administration of acetylcysteine and hydration decreased the incidence of reduced renal function in high-risk patients undergoing procedures that require radiocontrast agents. Comparable adverse effects were experienced in both groups and included gastrointestinal discomfort and dizziness. This clinical trial showed a benefit to patients receiving both acetylcysteine and hydration compared to hydration alone, which is in contrast to earlier trials with other agents that showed no improved benefits for patients.

REFERENCES


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Monoclonal antibodies can be beneficial in treating a variety of medical conditions. Here are five questions to test your knowledge:

1. What is the name of the monoclonal antibody used in the treatment of multiple sclerosis?

2. Which monoclonal antibody is approved for the treatment of non-Hodgkin’s lymphoma?

3. What is the name of the monoclonal antibody used in the treatment of chronic renal insufficiency undergoing a computed tomography (CT) procedure?

4. Which monoclonal antibody is used for the treatment of acute respiratory distress syndrome (ARDS) in neonates?

5. What is the name of the monoclonal antibody used in the treatment of rheumatoid arthritis?

Drug information forum, from page 1


1. Stevens MA, McCullough PA, Tobin KL, et al. A prophylactic administration of acetylcysteine and hydration decreased the incidence of reduced renal function in high-risk patients undergoing procedures that require radiocontrast agents. Comparative adverse effects were experienced in both groups and included gastrointestinal discomfort and dizziness. This clinical trial showed a benefit to patients receiving both acetylcysteine and hydration compared to hydration alone, which is in contrast to earlier trials with other agents that showed no improved benefits for patients. Acetylcysteine is an old drug that has gained some renewed interest because of its antioxidant properties. Despite the small numbers of patients in clinical trials performed in patients receiving radiocontrast agents, acetylcysteine is being used in this patient population. The dose of acetylcysteine for RCIN prophylaxis is 3 mL (600 mg) of a 20% solution. The inhalation solution is given orally undiluted. Unfortunately, acetylcysteine has a very bad taste and smells similar to rotten eggs. The cost of this dose of acetylcysteine is minimal. Knowledge about the current evidence to support the use of acetylcysteine in these patients, the correct dose to be used, and any adverse effects is essential when making evidence-based medicine decisions. by Kalen Porter, PharmD

REFERENCES

