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Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 19, 2002. 4 drugs were added in the *Formulary* and 1 drug was deleted. 4 drugs were designated not available.

◆ **ADDED**

Donepezil
(Aricept® by Pfizer)

Galantamine
(Reminyl® by Janssen Pharmaceutica)

Nadolol
(generic & Corgard®)

Rasburicase
(Elitek® by Sanofi-Synthelabo)*

*Restricted to oncology prescribers

◆ **DELETED**

Omeprazole Suspension
(compounded)

◆ **NONFORMULARY AND NOT AVAILABLE**

Omeprazole (Prisolec® by Astra Zeneca and generic)

Pegfilgrastim
(Neulasta® by Amgen)

Risedronate (Actonel® by Proctor & Gamble Pharmaceuticals)

Tacrine (Cognex® by First Horizon Pharmaceutical Corp)

Donepezil and **galantamine** are cholinesterase inhibitors with labeled indications for the treatment of mild to moderate dementia of the Alzheimer's type. They were evaluated for formulary addition because both are in the top 10 nonformulary drugs based on doses dispensed. These are both popular drugs in the ambulatory

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POLICIES AND PROCEDURES

"I need to read this verbal order back to you…"

Effective January 1, 2003, all verbal orders must immediately be written down, signed and dated, and then repeated back to the prescriber. This change will help Shands meet part of Goal 2 of The 2003 National Patient Safety Goals and Recommendations of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

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Effective January 1, 2003, all verbal orders must be immediately written down, signed and dated, and then repeated back to the prescriber. This procedure should decrease medication errors.

Goal 2 is to "improve the effectiveness of communications among caregivers." This goal explicitly requires the implementation of a process for taking verbal or telephone orders that requires a verification "read-back" of the complete order by the person receiving the order. This procedure should decrease medication errors.

This change will apply to all verbal orders — not just orders for medications. Nurses, pharmacists, or any receiver of a verbal order will have to follow this procedure. Prescribers should expect that it will take a little longer for the person receiving the order to write it down, then repeat it back. Please be patient with this new procedure. The "read-back" of the order should include the patient's name, the order, and the prescriber. The order should be explicit and use numerals and the number (eg, "0.1 mg …that is zero point one milligram" or "five hundred…that is five zero zero"). If you are not asked to read back the order, please remind the receiver to read the order back.

The receiver of the verbal order will immediately be writing the order in the chart or, alternatively, on a sticker that will be placed in the orders section of the chart. Repeating a verbal order is not good enough; it must be read from a written order. Like all verbal orders, this order will have to be authenticated in a timely manner.

Verbal orders have long been associated with medication errors. It is best to avoid verbal orders, if at all possible. However, there are situations where verbal orders cannot be avoided. When verbal orders are given, steps must be taken to avoid misinterpretations. Accents, dialects, pronunciation, and poor telephone connections all can cause mistakes. Background noise, interruptions, and unfamiliar terminology cause problems. Sound-alike drug names can also be a problem. It is always a good idea to include the indication in any order, but especially for a verbal order. For example, is the order for Celebrex® for chronic pain or Cerebyx® for a seizure disorder? Using these safeguards, plus the receiver repeating back the order, minimizes the risks of medications errors.

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setting and patients are often admitted on these medications. The addition of these drugs in the *Formulary* will decrease the workload associated with these agents.

Tacrine and rivastigmine (Exelon®) are also cholinesterase inhibitors used to treat Alzheimer's disease. These drugs were not added in the *Formulary*. Tacrine was designated nonformulary and not available. Rivastigmine is rarely requested through the nonformulary system and will remain nonformulary.

Cholinesterase inhibitors are the only drugs with labeled indications for Alzheimer's disease on the US market. Previous research has shown that the brains of patients with Alzheimer's disease have insufficient acetylcholine. Cholinergic agents were designed to overcome this deficit by slowing the breakdown of acetylcholine. Intact neurons must be available for this strategy to work. Since fewer intact neurons exist over time in Alzheimer's disease, the effectiveness of these agents wanes.

Several evidence-based medicine reviews have been done for this category of drugs. The most authoritative and current review was done by the American Academy of Neurology. These guidelines recommend that cholinesterase inhibitors should be considered in patients with mild to moderate Alzheimer's disease, although studies suggest a small degree of benefit. Small changes in cognition, behavior, and functioning have been detected in studies by caregivers and physicians. These differences have not translated into major improvements in outcomes like decreased institutionalization. There are no head-to-head trials comparing any of the products on the market.

The common adverse effects associated with cholinesterase inhibitors are as expected for cholinergic agents: nausea, vomiting, anorexia, diarrhea, insomnia, muscle cramps, and fatigue. Anorexia may manifest as weight loss. Bradycardia can occur. These effects can decrease with continued use, but many patients stop therapy before the reactions subside. Titrating doses slowly, reducing dosages, or holding a few doses may be helpful.

Tacrine is associated uniquely with serious hepatotoxicity. Tacrine also must be given 4 times a day and is more expensive than the other 3 agents. Therefore, tacrine was designated nonformulary and not available.

Nadolol is an oral, nonselective, beta-blocker similar to propranolol. Nadolol does not demonstrate intrinsic sympathomimetic or membrane-stabilizing activities. Nadolol is renally eliminated and dosages may need to be adjusted in patients with renal dysfunction. The usual dosage range is 40 to 80 mg per day. It has a low degree of lipid solubility and has the longest half-life of all beta-blockers. Typical adverse effects are as expected for beta-blockers (eg, bradycardia, hypotension). Nadolol was added in the *Formulary* because it was frequently prescribed nonformulary and it is available as a generic.

The top nonformulary drugs by number of doses dispensed are periodically reviewed to determine whether there are opportunities to add drugs in the *Formulary*. Drugs that are available as generics are good candidates for formulary addition because they are not subject to marketing pressures that can promote inappropriate use.

However, these agents may not have adequate evidence of safety and efficacy, which would be inconsistent with our evidence-based approach to formulary management. Of the top 100 generic drugs by volume 6 are available as generics. The only product recommended for addition at this time was nadolol.

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. Alkalinization 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 more rapidly, which may reduce 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.

Only patients with a high risk of tumor lysis syndrome should receive rasburicase. Hydration, alkalinization, and allopurinol are preferred in most patients. It is difficult to justify the 9000-times increased cost of rasburicase compared with allopurinol in most instances. Therefore, rasburicase was restricted to use only by oncology prescribers.

All dosage forms of **omeprazole** are now nonformulary and not available. In February 2002, lansoprazole suspension was added in the *Formulary*. Omeprazole suspension was kept in the *Formulary* for children less than 3 years old because there were limited data in this age range. Omeprazole capsules were already designated nonformulary and not available. Pantoprazole is the solid oral and injectable proton-pump inhibitor (PPI) listed in the *Formulary*.

Lansoprazole now has a labeled indication for use in children from 1 to 11 years old. For children in this age range who weigh less than or equal to 30 kilograms, the recommended dosage for lansoprazole suspension is 15 mg per day. For children weighing greater than 30 kilograms, the recommended lansoprazole dosage is 30 mg per day. Therefore, lansoprazole suspension is now the only oral "liquid" PPI available.

Pegfilgrastim is a long-acting covalent conjugate of filgrastim (G-CSF). Pegfilgrastim and filgrastim share the same mechanism of action. Pegfilgrastim can be given once per cycle to increase neutrophil counts and prevent the complications of neutropenia (ie, infection) in nonmyeloid cancers. Filgrastim is given daily for 5 to 10 days per cycle.

The published evidence supports equivalent efficacy for filgrastim and

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pegfilgrastim. There were no differences shown in 2 published studies and 4 abstracts based on absolute neutrophil count (ANC) at nadir, peak ANC, incidence of severe neutropenia, mean duration of severe neutropenia, incidence of febrile neutropenia, and time to ANC recovery.

Pegfilgrastim costs over $2100 per dose. Using the recommended dosages for a 70-Kg patient, filgrastim would have to be given for 14 days to equal the cost of pegfilgrastim. If the American Society for Clinical Oncology guidelines for G-CSF are followed, the cost of filgrastim will be as much as 60% less than for pegfilgrastim. Current inpatient reimbursement schemes do not cover the increased costs of pegfilgrastim. Therefore, pegfilgrastim was designated nonformulary and not available for inpatient use. Because of the convenience of once-per-cyle dosing, it is expected that pegfilgrastim will frequently be used in the clinics.

Risedronate is a bisphosphonate similar to alendronate. In June 1999 alendronate was designated nonformulary and not available. Although alendronate is a reasonable therapeutic choice for some patients with osteoporosis in the ambulatory setting, it is difficult to effectively and safely administer this drug in the inpatient setting. If given with food or any other fluid except water, the absorption of alendronate is impaired. In order to avoid esophagitis, patients must take alendronate with 6 to 8 ounces of water. The patient must be sitting up and cannot lie back down for at least 30 minutes.

Since alendronate has such a long half-life, most patients can stop their alendronate while they are hospitalized without any decreased therapeutic effect. If patients are in the hospital more than 14 days and they can follow the recommended administration guidelines, alendronate may be given in the inpatient setting.

Risedronate is used for the same indications and has the same warnings and administration restrictions as alendronate. Therefore, risedronate was designated nonformulary and not available, with the same exception as above for alendronate.

NONFORMULARY DRUG USE

Hear ye, hear ye... The Legend of Auralgan® and Otitis Media

Although Auralgan® has a labeled indication for the relief of pain and to reduce inflammation associated with otitis externa or swimmer's ear, it is often used inappropriately for otitis media. This leads to unnecessary nonformulary requests for Auralgan®. Auralgan®'s effectiveness in relieving pain associated with acute otitis media (AOM) is questionable.

Acute otitis media (inflammation of the middle ear) is characterized by inflammation of and fluid accumulation in the middle ear.[1] The cause of acute otitis media may be viral, bacterial, or both. The presence of otalgia (ear pain), partial deafness (secondary to effusion), fever, and a sudden onset of irritability are symptoms that characterize AOM.

Depending on the cause of AOM, treatment may include antibiotics (ie, amoxicillin, ampicillin) and/or analgesics (systemic and topical). Otalgia (ear pain) is usually the most troublesome symptom of AOM. Therefore, the role of systemic analgesics in the treatment of AOM is apparent. However, the role of topical analgesics is not clear.

Auralgan® is a product that been on the market for more than 40 years. It contains antipyrine (phenazone) and benzocaine. Antipyrine is an anti-inflammatory/analgesic agent that works by inhibiting the production of prostaglandins and does not directly affect hyperalgesia or the pain threshold. Benzocaine is a local anesthetic that works by causing a reversible blockade of nerve conduction. To achieve effective anesthesia, benzocaine must be applied directly to the area to be anesthetized.

Auralgan® is designed for instillation into the external auditory canal. In order for the pain relief to occur, Auralgan® must come in direct contact with the pain source. The source of pain in otitis media is the middle ear, ***not*** the external auditory canal.

There are limited published data regarding the use of Auralgan® in AOM. There have not been any published studies comparing Auralgan® to systemic analgesics. An unpublished study by Matz and colleagues that is widely cited on the Internet claims that Auralgan® is as effective as antibiotics at reducing pain. However, these press releases do not discuss the use of systemic analgesics.

Hoberman and colleagues conducted a double-blind study comparing the efficacy of Auralgan® to an olive oil placebo in the management of AOM at the Children's Hospital of Pittsburgh.[2] There was no statistically significant difference in reduction of ear pain between Auralgan®- or olive oil-treated patients. Results showed that Auralgan® provided analgesia within 30 minutes. However, all the children in the study were also treated with acetaminophen 15 mg/kg in a single dose. Acetaminophen is completely absorbed within 60 minutes of administration. Therefore, acetaminophen's analgesic and antipyretic effects occur within 1 hour of administration. Based on this, it is possible that the proposed analgesic effects of Auralgan® may be attributed to the use of acetaminophen in this study. There are still unanswered questions about the usefulness of a topical analgesic in the place of (or in addition to) a systemic analgesic.

Analgesics that may be used for AOM include ibuprofen and acetaminophen. The usual daily dosage of ibuprofen is 40 to 50 mg/kg/day orally divided into 3 to 4 daily doses. The maximum daily dose of ibuprofen is 3200 mg/day. The usual dose of acetaminophen is 10 to 15 mg/kg/dose orally given every 4 to 6 hours as needed for pain.

Auralgan®'s effectiveness in the treatment of pain associated with AOM is questionable. There is no evidence supporting its use in the place of systemic analgesics, which effectively alleviate pain and fever associated with AOM. Therefore, Auralgan® is classified as a low-priority nonformulary drug and its use in the hospital setting is discouraged.

By Gina Soliman, PharmD

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POLICIES AND PROCEDURES

5 Unacceptable abbreviations and dosage designations

Effective January 15, 2003, there will be 5 unacceptable abbreviations or dosage abbreviations that will make an order invalid. This new policy requires that prescribers be contacted for order clarifications. The 5 unacceptable abbreviations are listed below.

INAPPROPRIATE ABBREVIATION	APPROPRIATE ABBREVIATION
U	Spell "Units" instead
IU	Spell "International Units" instead
μ (Greek mu symbol)	Use "mcg" for micrograms
doses < 1 unit	Use leading zero (eg, 0.1 mg)
doses > 1 unit	Do not use trailing zero (eg, 1.0)

The word "units" should always be spelled out because a "u" may be interpreted as a zero and lead to a 10-fold overdose. The handwritten "mu" symbol (μ) can look like an "m," which could be misunderstood as milligram. If a microgram dose is misinterpreted as a milligram dose, it could result in a 1000-fold overdose. The safest abbreviation to use for a microgram dose is mcg. A leading zero should always precede a decimal expression of less than 1 (ie, 0.5 not .5), and a terminal zero should never be used after a decimal (ie, 5 not 5.0). Decimal points may not be readable and lead to 10-fold overdoses.

The Joint Commission's mandated 2003 National Patient Safety Goals and Recommendations stimulated this new policy. In order to improve the effectiveness of communications among caregivers, institutions are required to have a list of abbreviations, acronyms, and symbols that cannot be used. The 5 problem abbreviations have long been associated with patient overdoses and harm.

These changes are going to require some effort. A recent audit showed that 1.6% of medication orders used 1 of these inappropriate abbreviations or dosage designations. The inappropriate use of "u" was the biggest problem, accounting for 80% of the inappropriate orders. Since approximately 3000 medication orders are processed daily at Shands at UF, about 50 orders a day have 1 of these 5 problems. These problems are found in 18,000 orders a year! This could mean a lot of pages, phone calls, and order clarifications — if the new policy is not followed. Avoiding these inappropriate abbreviations will make everyone's job easier — and protect patients from potentially unnecessary medication errors.