UFHealth
SHANDS HOSPITAL

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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 19, 2014. 1 drug was added in the *Formulary* with restrictions, 1 drug had criteria for use changes, 1 drug was designated non-formulary high priority, 2 drugs were designated non-formulary and not available and 1 drug was deleted from the *Formulary*.

◆ ADDED

Fosfomycin (generic)*

**Restricted to approval by the Antimicrobial Management Program for the empiric treatment of uncomplicated urinary tract infections or complicated urinary tract infections in patients with resistant organisms.*

◆ CRITERIA FOR USE CHANGES

Buprenorphine (Subutex®)*

**Criteria for use clarified*

◆ HIGH-PRIORITY NON-FORMULARY

Tacrolimus Extended Release (Astagraf XL™)*

**Restricted to continuation of home therapy only. Initiation of therapy on the inpatient side not allowed at this time.*

◆ NON-FORMULARY AND NOT AVAILABLE

Dapagliflozin (Farxiga®)^

^*Patient may use their own*

Umeclidinium/Vilanterol Inhalation Powder (Anoro Ellipta®)

◆ DELETED

Aminohippurate Sodium 20%

◆ THERAPEUTIC INTERCHANGES

None

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DRUG POLICY

Buprenorphine Ordering at UF Health Shands Hospital

Buprenorphine, a partial mu-agonist and kappa antagonist, is FDA approved for moderate to severe chronic pain in patients requiring continuous opioid analgesia.[1] When combined with naloxone, this agent has been utilized for the treatment of opioid dependence. The combination of naloxone and buprenorphine is advantageous in opioid addicts as the naloxone component is inactive when ingested orally. However, if the pill is crushed and injected, the naloxone will act as a mu-receptor antagonist to inhibit any euphoric effects of the buprenorphine. In August 2013, the Pharmacy and Therapeutics Committee reiterated that the combination product is unnecessary in the inpatient setting and designated this product non-formulary and not available with buprenorphine single agent tablets remaining an available option.

Historically, buprenorphine has been restricted at UF Health for opioid addiction therapy or chronic pain in patients with a history of opioid dependency. In February 2011, these criteria were amended to include use in patients experiencing chronic pain when approved by a physician with pain medicine certification or the Pain Service. Further expansion and clarification of these criteria were requested by the Addiction Medicine Service.

Evaluation of current law indicates neither the Controlled Substances Act (as amended by the Drug Addiction Treatment Act of 2000) nor DEA implementing regulations impose any limitations on a physician or other authorized hospital staff to maintain or detoxify a person with an opioid treatment drug like buprenorphine as an incidental adjunct to medical or surgical conditions other than opioid addiction.[2-3] Thus, a patient with opioid addiction who is admitted to a hospital for a primary medical problem other than opioid addiction, e.g., myocardial infarction, may be administered opioid agonist medications to prevent opioid withdrawal that would complicate the primary medical problem. Neither a DATA 2000 waiver nor a DEA number with an "X" is required for practitioners in order to administer or dispense buprenorphine in this circumstance. However, it is good practice for the admitting physician to consult with the patient's addiction treatment provider, when possible, to obtain treatment history.

In order to clarify the current criteria for buprenorphine use at UF Health Shands Hospital, the following criteria were proposed:

- Continuation of home therapy
- Prevention of withdrawal symptoms in a patient admitted for a primary reason other than opioid addiction (no DATA2000 waiver or "X" DEA number required). Approved by Addiction Medicine Service with provider's name listed in the order.
- Chronic pain therapy in patients as recommended by practitioner with pain management certification or consultation by Pain Service or Addiction Medicine Service with the provider's name listed in the order.

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INSIDE THIS ISSUE

Formulary update, *from page 1*

Fosfomycin, administered orally as fosfomycin tromethamine, was proactively reviewed by the Anti-Infective Subcommittee (AIS) for use in lower urinary tract infections. It is rapidly absorbed and primarily eliminated in the urine. Urinary fosfomycin concentrations remain ≥100 mcg/mL for approximately 24 hours after a 3 gram dose. Fosfomycin demonstrates in vitro activity against commonly encountered gram-negative and gram-positive urinary pathogens (i.e. *Enterobacteriaceae*, *Staphylococcus* sp., and *Enterococcus* sp.). Fosfomycin is well-tolerated with few adverse drug reactions and few drug-drug interactions although agents which increase gastric motility may decrease fosfomycin absorption.

The Infectious Diseases Society of America recommends fosfomycin as a first line agent for uncomplicated cystitis due to limited resistance and a low propensity to promote colonization/infection with multidrug-resistant organisms. Additionally, data are emerging to suggest fosfomycin is a reasonable treatment choice for complicated cystitis when options are limited due to antibiotic resistance. Fosfomycin should not be used when pyelonephritis is suspected. Other agents available in the *Formulary* for the treatment of lower urinary tract infection include trimethoprim/sulfamethoxazole (TMP/SMX) and nitrofurantoin. However, multi-drug resistance may necessitate the use of more broad-spectrum agents (cefepime, piperacillin/tazobactam, or carbapenems).

Based upon these data, the Pharmacy and Therapeutics Committee recommended the addition of fosfomycin in the *Formulary*. This agent will be restricted to approval by the Antimicrobial Management Program for the empiric treatment of uncomplicated cystitis as an alternative to TMP/SMX or nitrofurantoin or the definitive treatment of complicated cystitis in patients with resistance to other agents.

Extended Release Tacrolimus (Astagraf XL™) is a once daily extended-release oral formulation of tacrolimus, currently approved for the prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction. It has been available in Europe since 2007 under the trade name Advagraf®, and in Japan since 2008 under the trade name Graceptor®. Of note, there is no information regarding conversion from immediate-release tacrolimus to its once daily counterpart. This agent was proactively reviewed in conjunction with input from the Solid Organ Transplant physicians.

One of the major preventable causes of graft failure following kidney transplants is medication non-adherence. Theoretically, a simplified medication regimen involving less frequent drug dosing may improve adherence. However, the literature to support this is not conclusive. The intent of marketing this drug is that it will improve adherence, yet no study has clearly demonstrated better clinical outcomes for patients associated with this dosing schedule. Conversely, one study which evaluated compliance showed that missing one dose of extended-release tacrolimus is in fact more consequential than missing one dose of immediate-release tacrolimus.

A systematic review of all randomized controlled trials and observational studies published between 1948 and mid-2011 that comparing the outcomes of daily versus twice-daily tacrolimus in kidney transplant recipients concluded that there were no significant differences in biopsy proven acute rejection, patient survival, and graft survival at 12 months between the two therapies. This systematic review included over 5,000 patients enrolled from six randomized controlled trials and 15 observational studies, including the two trials that led to the approval of extended-release tacrolimus in the United States.

Currently, UF Health Shands Hospital has immediate release tacrolimus (Prograf®) in the *Formulary* in the following formulations: oral capsules, oral liquid and intravenous solution. On average, the daily cost of therapy with the extended release tacrolimus is twice that of immediate release tacrolimus. Astellas has altered their patient assistance program to allow for Astagraf XL™ assistance only and not Prograf®. However, immediate-release tacrolimus is a covered medication under Medicare Part B at a 20% coinsurance and is also available on the UF Health Charity Care Formulary which decreases the patient's out-of-pocket expenditures.

The Formulary Subcommittee recommended designating this agent non-formulary high-priority limited to use in patients who are already receiving the medication as an outpatient. Initiation of this medication in inpatients was not recommended at this time. A recommendation was made to evaluate the use of this agent at 6 months to determine whether further investigation of formulary status is necessary. The Pharmacy and Therapeutics Committee agreed with this recommendation.

Dapagliflozin (Farxiga®) is the 2nd approved agent in the sodium-glucose co-transporter 2 inhibitor class. This agent is approved as an adjunct to diet and exercise to improve glycemic control. In August 2013, canagliflozin, a similar agent in this class, was designated non-formulary and not available with patients able to take their own medication. The Department of Endocrinology was contacted to determine if this agent could be treated in the same manner, to which they agreed.

The P&T Committee approved the designation of this agent as non-formulary and not available with patients able to take their own medication. In addition, it was recommended that a 6 month review of use occur in order to evaluate the potential for adverse events including urinary tract infection and hemodynamic instability which may be caused secondary to the glucosuria induced with this medication class.

Umeclidinium and Vilanterol Inhalation Powder (Anora Ellipta®) is a combination product which contains an anticholinergic agent (umeclidinium) and long-acting beta$_2$ agonist (vilanterol). It is dosed once daily for the treatment of chronic obstructive pulmonary disease and is the first combination product of its kind.

Due to the availability of alternative agents in the *Formulary*, the P&T Committee recommended that this agent be designated non-formulary and not available.

Aminiohippurate Sodium 20% has been listed in the *Formulary* and stocked for a number of years. This product is utilized to measure effective renal plasma flow which estimates the functional capacity of the renal tubular secretory mechanisms primarily in the research setting. There has been zero utilization since 2008. As such, the P&T Committee approved deletion of this agent from the *Formulary*.

MEDICATION SAFETY

FDA Lifts Restrictions on Rosiglitazone (Avandia®)

Rosiglitazone (Avandia®) was approved in 1999 for use as an adjunct to diet and exercise to improve glycemic control in patients with Type II diabetes.[1] In 2010, a meta-analysis (RECORD study) of 42 trials was published which raised concerns about possible increased cardiovascular risk associated with the use of rosiglitazone.[2] The study reviewed and analyzed the outcome data for myocardial infarction and death from cardiovascular causes in patients with type 2 diabetes showing an odds ratio of 1.43 for the risk of myocardial infarction in patients receiving rosiglitazone compared to control groups. This meta-analysis in conjunction with additional analyses conducted by the 2010 joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee prompted the Food and Drug Administration (FDA) to institute a Risk Evaluation and Mitigation Strategy (REMS) program.[3]

The REMS program mandated that patients receive a medication guide detailing the increased cardiovascular risks associated with the medication. In addition healthcare providers were required to enroll in the rosiglitazone REMS program, attest that they would document initiation of rosiglitazone in the medical record along with the rationale for use, and enroll the patient in the REMS program. Pharmacies dispensing rosiglitazone were also required to enroll in the REMS program and attest that they would verify prescriber enrollment as well as patient enrollment in the program.[3]

Rosiglitazone was removed from the *Formulary* at UF Health Shands Hospital in response to this initial restriction in April 2010. An automatic therapeutic interchange was approved by the P&T Committee for the conversion of rosiglitazone to pioglitazone. The conversion is as follows: pioglitazone 15 mg for rosiglitazone 2 mg; pioglitazone 30 mg for rosiglitazone 4 mg; and pioglitazone 45 mg for rosiglitazone 8 mg at the same dosing interval for all doses.

In June 2013, an FDA Advisory Committee reviewed available data, including a re-adjudicated RECORD trial. The RECORD trial initially evaluated over 4,000 patients with Type II Diabetes who received either rosiglitazone or combination therapy with metformin or a sulfonylurea.[3] The 2013 Advisory Committee noted that the trial was not an independent review as it was funded by GlaxoSmithKline, and there were accusations of "extreme mishandling" of the data in addition to methodological flaws. Readjudication of over 2000 patients revealed no statistically significant differences in the two treatment arms.[4]

◆

"On November 25, 2013, the FDA lifted restrictions on the use of rosiglitazone…no longer required to enroll in the REMS program…"

On November 25, 2013, the FDA lifted restrictions on the use of rosiglitazone on the basis of this re-evaluation of data.[5] This means that the prescribers, pharmacies, and patients are no longer required to enroll in the Risk Evaluation and Mitigation Strategy (REMS) program to prescribe, dispense, or receive the medication and patients will be able to receive rosiglitazone through regular pharmacies.

While thiazolidinediones (TZDs) are not considered first-line agents, in certain clinical settings, such as especially high risk for hypoglycemia or intolerance of or contraindication to metformin or sulfonylurea, a TZD may be useful. With the changes in the rosiglitazone label, an increased number of prescriptions for rosiglitazone in the community are anticipated – therefore, more patients on rosiglitazone will likely be seen at our institution. Rosiglitazone remains non-formulary and not available at UF Health Shands Hospital with patients able to use their own supply if available as outlined in the Patient's Own Medication Policy. The prescriber or pharmacist may also interchange the agent to pioglitazone as per P&T approval.

–Jimin Lee, Pharm D

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Buprenorphine, *from page 1*

- Opioid addiction as primary reason for admission (UF Health Psychiatric Hospital only) – DATA2000 waiver or "X" DEA number required with provider's name and DEA number listed in the order.

Based upon the review of the legal language and data for appropriate use, the Pharmacy and Therapeutics Committee agreed to the amended criteria as proposed.

–Carrie Lagasse, Pharm D, BCPS

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