Pharmacy News

UNIVERSITY HOSPITAL
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Special Points of Interest:

- P&T Update-Formulary Additions/ Deletions
- Policy and Procedure Update
- Uloric® (febuxostat): Black Box Warning Added
- Drug-Induced Lupus Erythematosus
- Use of Herbal Supplements in Liver Transplant Recipients
- Welcome to our New Pharmacist

P&T Update

Formulary Additions

- **Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)**
  Biktarvy is a combination tablet that is indicated as a complete regimen for the treatment of HIV-1 infection in adults. It contains a new integrase inhibitor, bictegravir, to which no patients exhibited resistance in clinical studies. – Formulary addition approved

- **Mifepristone (Mifeprex)**
  Mifepristone is a progestin antagonist indicated, in combination with misopristol, for the medical termination of intrauterine pregnancy through 70 days gestation – Formulary addition approved; restricted to OB/GYN providers credentialed to prescribe mifepristone

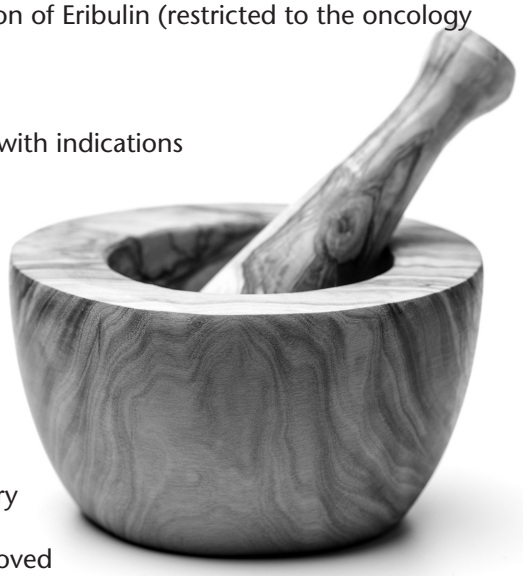
- **Bupivacaine Liposome Injectable Suspension (Exparel®)**
  Formulary addition denied

- **Rasburicase (Elitek®)**
  Rasburicase is indicated for hyperuricemia associated with malignancy and is more efficacious than allopurinol in high risk population. It is also less expensive than IV allopurinol when dosed at 3 or 6mg which is non inferior to the high package insert dosing. A protocol is being developed by oncology subcommittee to ensure proper usage of rasburicase and proposal is to restrict the prescribing to approval by Nephrology and Oncology. Formulary addition of Rasburicase restricted to approval by Nephrology/Oncology service – Approved

- **Eribulin (Halaven®)**
  Eribulin is indicated as per the NCCN guidelines as one of the options for managing metastatic breast cancer. Formulary addition of Eribulin (restricted to the oncology service) – Approved

- **Pembrolizumab (Keytruda®)**
  Pembrolizumab is a monoclonal antibody with indications in multiple organ carcinomas and is recommended as first line in some cases. Formulary addition of pembrolizumab (restricted to the oncology service) – Approved

- **Ado-Trastuzumab Emtansine (Kadcyla®)**
  Ado-Trastuzumab is indicated for HER 2+ metastatic breast cancer for patients who have progressed on trastuzumab. Formulary addition of Ado-Trastuzumab Emtansine (restricted to the oncology service) – Approved



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P&T Updates

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Formulary Deletions

- **Fluconazole D5W IV soln**
  Medication discontinued by manufacturer – Formulary deletion approved. We have Fluconazole in NS 200mg/100mL and 400mg/200mL IV solution

- **Tetracaine ophthalmic soln. 0.5% 0.6 mL** Medication discontinued by manufacturer – Formulary deletion approved
  We have Tetracaine 0.5% 4 mL
- **Prednisolone ophthalmic susp. 1% 1 mL**
  Medication discontinued by manufacturer – Formulary deletion approved. We have Prednisolone susp. 1% 5 mL

- **Erythromycin 500 mg tablets**
  Request for removal due to low usage, have 250 mg tablets – Formulary deletion approved, have 250 mg tablets

- **Propranthelin 15 mg tablets**
  Request for removal due to low usage – Formulary deletion approved

- **Glimepiride 1mg and 4mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

- **Atorvastatin 80mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

- **Glipizide ER 5mg and 10mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

- **Niacin 500mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

- **Paroxetine 30mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

- **Nadolol 40mg and 80mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

- **Medroxyprogesterone 10mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

- **Haloperidol 20mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

- **Premarin 1.25mg tablets**
  Medication discontinued due to low usage / availability of multiple strengths. Formulary deletion approved

Policies & Procedures/Floorstocks

- **UH Timely Medication Administration Policy:**
  Under the critical medication administration policy, insulin may not be administered at the right time with regards to meals as the timing could vary depending on patient preference, delivery of the meals, etc. Rapid acting insulin was removed from the time critical medication list to give the nurse flexibility in administration depending on the actual time of the meals instead of within 30 minutes of the scheduled EPIC time.
  – Policy update approved

- **UH Antimicrobial Stewardship Program Policy Update:**
  Verbiage of the policy did not change; change in template using the Patient Care Services template.
  – Policy template revision approved

- **UH Order Entry, Verification, and Provision of Restricted Anti-infectives Policy Update**
  Several changes in formulary status with anti-infectives so a designation was created under Category II.
  – Policy update approved

- **707-400-108 Resuscitation Equipment Checks & Exchanges- Update:**
  Updates to policy to include the revised adult code cart content list developed in collaboration with the Rescue Steering Committee, revised code cart locations, updated ACC emergency box contents developed in collaboration with the ACC QA committee, updated PCS code cart log sheet, and inclusion of the code cart barcoding process. – Approved

Uloric® (febuxostat): Black Box Warning Added

Gout is a form of inflammatory arthritis that develops in people who have high levels of uric acid in the blood. It occurs in about 4% of American adults – about 6 million men and 2 million women. Uric acid can form needle-like crystals in a joint and cause sudden, severe episodes of pain, tenderness, redness, warmth and swelling. Febuxostat is a nonpurine inhibitor of xanthine oxidase. It selectively inhibits xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine to uric acid thereby decreasing uric acid level. Therapy with febuxostat leads to lowering of serum uric acid levels within a few weeks. Chronic therapy has been shown to decrease uric acid levels into target levels of < 6 mg/dL and to decrease acute gouty attacks. Current indications include therapy and prevention of gout, uric acid nephropathy, and the hyperuricemia caused by malignancy and anticancer therapy. However, febuxostat use is usually reserved for patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. In February 2019, the FDA added a new black box warning on febuxostat for cardiovascular death.

Takeda Pharmaceuticals conducted a post-market safety trial in more than 6,000 patients with gout treated with either febuxostat or allopurinol. The primary outcome looked at a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and unstable angina. The results showed that febuxostat had an increased risk of heart-related deaths and death from all causes. In patients treated with febuxostat, 15 deaths from heart-related causes were observed for every 1,000 patients treated for a year compared to 11 deaths from heart-related causes per 1,000 patients treated with allopurinol for a year.

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Uloric® (febuxostat): Black Box Warning Added
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As a consequence, healthcare professionals should educate patients to seek emergency medical attention if they experience chest pain, shortness of breath, rapid or irregular heartbeat, numbness or weakness on one side of your body, dizziness, trouble talking, and sudden severe headache while taking febuxostat.

References:

1. Febuxostat. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed March 5, 2019

2. Febuxostat [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2019. Food and Drug administration. Medwatch. Available at https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm631824.htm.Accessed March, 2019.

3. Arthritis foundation. Gout. Available at https://www.arthritis.org/about-arthritis/types/gout/what-is-gout.php. Accessed March, 2019.

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Drug-Induced Lupus Erythematosus

In the United States, the incidence of drug-induced lupus erythematosus (DILE) has been estimated to be between 15,000 and 30,000 new cases every year. This number forms about 10% to 15% of patients with idiopathic systemic lupus erythematosus (SLE). As patients of advanced age are often prescribed more medications, senior patients are at higher risk for developing DILE. The prevalence has also been shown to be 6-fold higher in white patients than in black patients.

In the setting of chronic drug exposure, DILE may occur with certain medications. The incidence of drug-induced autoimmunity has increased considerably in the last 10 years, and that may be attributable to the introduction and use of newly developed drugs. For instance, biologic agents that block specific phases of the immune response trigger significant changes in the system. Drugs such as hydralazine, procainamide, isoniazid, quinidine, and chlorpromazine are also known to cause DILE. However, not all medications have a high risk of developing DILE. The highest risk is associated with procainamide and hydralazine, and the frequency of DILE caused by these drugs is as high as 15-20% and 7-13%, respectively. DILE resolves after discontinuation of the offending drug and in most cases, it requires weeks to months to be resolved completely.

Characteristic laboratory findings of DILE are serum positivity for antinuclear antibodies (ANA) and anti-histone antibodies (AHA). ANA positivity is considered to be essential for diagnosis of DILE as it has been reported in 90-100% of the cases. Also, depending on the type of inciting drugs, the autoantibody patterns differ. The majority of DILE-causing agents drive the generation of AHA

while some agents such as TNFαinhibitors induce the production of autoantibodies that are more specific for idiopathic SLE which is anti-dsDNA. DILE differs from drug hypersensitivity reactions in several ways. In DILE, no evidence of drug-specific T cells or antibodies has been found, and it can take months or even years for symptoms to appear. The clinical spectrum of DILE ranges from circumscribed cutaneous signs to systemic involvement.

The main symptoms in systemic DILE are musculoskeletal pain, serositis, and constitutional manifestations such as fever, fatigue, and loss of appetite. Arthritis is usually symmetric and affects small joints and does not cause deformation. This clinical pattern is typically seen with hydralazine-induced cases. Pleuritis, pleural effusion, and pulmonary infiltrates are not uncommon when the culprit drug is procainamide. The etiology and laboratory findings of drug-induced subacute cutaneous lupus erythematosus (DISCLE) are similar with the idiopathic form of subacute cutaneous lupus erythematosus.

Signs of DISCLE include an eruption of papulosquamous lesions in the face, neck and throat, and the outer surface of the arms. For an appropriate management, early recognition is crucial. Also, different drugs may be associated with distinct clinical and serological profiles. As new therapies are developed for a multitude of diseases, the incidence of this autoimmune disorder is expected to rise significantly. Therefore, in patients with lupus-like manifestations, even if signs and symptoms are not specific, a careful observation is mandatory.

References:

1. Vaglio A, Grayson PC, Fenaroli P, et al. Drug-induced lupus: Traditional and new concepts. Autoimmunity Reviews 2018;17:912-918
1. Pretel, M, Marquès L, and Espana A. Drug-Induced Lupus Erythematosus. Actas Dermosifilliogr. 2014;105(1):18-30.
2. Guicciardi F, Atzori L, Marzano AV, et al. Are there distinct clinical and pathological features distinguishing Idiopathic from Drug-Induced Subacute Cutaneous Lupus Erythematosus? A European retrospective multicenter study. J Am Acad Dermatol 2019;0:1-29
4. Laurent Arnaud, Philippe Mertz, Pierre-Edouard Gavand, et al. Drug-induced systemic lupus: revisiting the everchanging spectrum of the disease using the WHO pharmacovigilance database. Ann Rheum Dis Epub 2018;0:1-5 doi:10.1136/annrheumdis-2018-214598

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Use of Herbal Supplements in Liver Transplant Recipients

The use of herbal and dietary supplements is becoming increasingly prevalent in today's society. An estimated 1 in 5 adults utilize dietary or herbal supplements with only 12% seeking care from a physician or licensed complementary and alternative medicine (CAM) provider.[1] Rationale for use of supplements include the common misconception that all-natural products must be safe and may be synergistic when used with other medications. The potential to cut costs with an easily accessible, over-the-counter agent compared to meeting with a healthcare provider has also been reported as an appealing motive. As up to 70% of patients fail to disclose their use of herbal supplements to physicians, it is imperative that providers inquire about herbal supplement use in addition to prescription history.[2]

In 1994, the Dietary Supplement Health and Education Act (DSHEA) separated herbal supplements from the classification of drugs. Thus, manufacturers of herbal supplements are exempt from the pre-marketing drug approval process by the FDA, including clinical trials to support safety and efficacy. With a lack of standard regulations, products may often contain variable quality and content of active ingredient as each product may be manufactured from different parts of the herbal source.[4] Glisson

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Use of Herbal Supplements in Liver Transplant Recipients

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et al demonstrated this by testing 13 products of St. John's Wort preparations; none of the products were within 10% of their label's claim for hypericin, the active chemical in St. John's wort.[5]

In patients who receive a solid organ transplant, the concern regarding use of herbal supplements can be multifactorial, starting as early as the peri-operative course due to potential effects on bleeding and sedation. Table 1 outlines common herbal supplements and their concerns when used in post-transplant patients.[6] As many supplements claim to have immunomodulatory properties and "boost" the immune system, post-transplant patients may be at risk of acute rejection through enhanced T-cell proliferation or activation of the complement pathway.[8]

Additionally, transplant patients commonly require calcineurin inhibitors (CNIs) as the backbone of long-term maintenance immunosuppression. Both CNIs and mTOR inhibitors require routine drug monitoring due to inter and intra-patient variability, mediated by cytochrome P450 metabolism and P-glycoprotein (P-gp) transporter function. The presence of drug-drug interactions affecting CYP3A4 substrates have been reported among several common herbal supplements.[7-15]

Table 1. Common herbal supplements and safety concerns

Herbal supplement	Potential concerns	Drug-Drug Interactions
St Johns wort	• Decreased levels of CNIs and mIQRi → increase risk of rejection	Strong CYP3A inducer
Echinacea	• Stimulate immune system → increase risk of rejection	Inhibit CYP 3A4
Tumeric	• Antiplatelet properties	Inhibit CYP 3A4
Ginkgo Biloba	• Antiplatelet properties	
Feverfew		
Grapefruit	• Risk of CNI toxicity due to accumulation	Inhibits CYP 3A4
Saw Palmetto	• Stimulate immune system → increase risk of rejection	↑Anticoagulants, Oral Contraception
Red Yeast Rice	• Case report of muscle pain/breakdown with concomitant CNI use	↑Statin exposure
Alfalfa	• Stimulate immune system → increase risk of rejection	
Ginseng	• Antiplatelet properties • Stimulate immune system → increase risk of rejection	
Garlic		
Vitamin E		
Milk thistle	• ↓ Blood sugar	
Kava Kava	• Hepatotoxicity • Over sedation	
Valerian		
Black cohosh	• Hepatotoxicity • Visual disturbance	↑anticonvulsant, alcohol benzodiazepine effect and anesthesia effect
Ma huang (ephedra)	• Hepatotoxicity • Nephrotoxicity • Cardiovascular effects	

CNIs: Cajcmemin inhibitors (tacrolimus, cydosporine); **mTQRi: mTOR** inhibitors (everolimus, sirolimus)

Limited regulation of herbal/dietary supplements has also led to post-marketing reports of severe hepatotoxicity. Wong et al analyzed registry data for 2,408 adults who underwent urgent liver transplantation for acute liver failure between 2003 and 2015, 625 of whom were recorded as having drug-induced liver injury. A majority of cases were due to acetaminophen toxicity (N=300); however, the fourth leading cause was determined to be herbal/dietary supplements (N=21).[16] This number may be an underestimation as many patients are not forthcoming in regards to their use of supplements and these products are readily available for use.

Given the lack of standardization and limited data regarding safety and efficacy, herbal and dietary supplements are typically not recommended after transplant. The risks of unknown side effects, including hepatotoxicity, drug-drug interactions and acute rejection are among many reasons why all liver transplant recipients should be counseled on avoiding herbal supplements. Thorough medication reconciliations addressing use or interest in herbal/dietary supplement is essential for physicians and pharmacists.

References:

1. Wheaton AG, Blanck HM, Gizlice Z, Reyes M. Medicinal herb use in a population-based survey of adults: prevalence and frequency of use, reasons for use, and use among their children. Ann. Epidemiol. 2005;15:678–685.
2. Tickerhoof L, Wagener MM, Cacciarelli TV, Singh N. Alternative therapy use in liver transplant recipients. Prog Transplant. 2006 Sep;16(3):226-31.
3. Herbal supplements. Food and Drug Administration. 2014. www.fda.gov.
4. Ruparel P, Lockwood B. The Quality of Commercially Available Herbal Products. Natural Product Communications. 2011;6:733–744
5. Glisson JK, Rogers HE, Abourashed EA, Ogletree R, Hufford CD, Khan I. Clinic at the health food store? Employee recommendations and product analysis. Pharmacotherapy 2003;23:64–72.
6. National Center for Complementary and Alternative Medicine. National Institutes of Health. A quick guide to herbal supplements. www.nih.gov. 2012.
7. Ehrlich SD. Botanical Medicine. University of Maryland Medical Center. 2011. www.umm.edu.

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8. Christians U, Jacobsen W, Benet L, et al. Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet. 2002;41(11):813-51
9. Foroncewicz, B., et al. Dietary supplements and herbal preparations in renal and liver transplant recipients. Transplantation proceedings. Vol. 43. No. 8. Elsevier, 2011.
10. Bolley R, Zulke C, Kammerl M, et al. Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort. Transplantation. 2002 Mar 27;73(6):1009.
11. Hebert MF, Park JM, Chen Y, et al. Effects of St. John's Wort (Hypericum perforatum) on Tacrolimus Pharmacokinetics in Healthy Volunteers. J Clin Pharmacol. 2004;44:89-94.
12. Barone GW, Gurley BJ, Ketel BL, et al. Herbal supplements: a potential for drug interactions in transplant recipients. Transplantation. 2001 Jan 27;71(2):239-41.
13. Prasad GV, Wong T, Meliton G, et al. Rhabdomyolysis due to red yeast rice in a renal transplant recipient. Transplantation. 2002 Oct 27;74(8):1200-1.
14. Tirona RG, Bailey DG. Herbal product-drug interactions mediated by induction. Br J Clin Pharmacol. 2006 Jun;61(6):677-81.
15. Corey, Rebecca L., and Jorge Rakela. Complementary and Alternative Medicine Risks and Special Considerations in Pretransplant and Posttransplant Patients. Nutrition in Clinical Practice 29.3 (2014): 322-331.
16. Wong LL, Lacar L, Roytman M, Orloff SL. Urgent Liver transplantation for dietary supplements; An Under-recognized Problem. Transplant Proc. 2017 Mar;49(2):322-325.

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Welcome Our New Pharmacy Technician

Mohammed Elghannam is a licensed pharmacy technician with six years of retail experience. He worked for Rite Aid Pharmacy for five years in Jersey City, New Jersey. He is excited to be a part of the University Hospital and is looking forward to learning from the University Hospital team. When time permits, he loves to read and listen to music.