Formulary Additions

**Humalog U-200 KwikPen Sample** This sample will only be available in the UMDCare ACC medicine clinic. This sample will be subject to the same storage/labeling requirements as any other formulary insulin product (High alert).

**Ivabradine (Corlanor®)**
FDA approved for use in select heart failure (HF) patients with persistent elevated HR, despite maximally tolerated beta blocker doses but with heart rate > 70 bpm in sinus rhythm, and left ventricular ejection fraction of < 35%. Medication to be restricted to the cardiology service for approval.

**Sacubitril/valsartan (Entresto®)**
A combination medication consisting of ARB (valsartan) and the novel agent, neprilysin inhibitor (sacubitril). This combination has been shown to reduce the rate of hospitalization and mortality from cardiovascular causes in patients with heart failure compared to enalapril alone.

Formulary Deletions

1. **Ferrous Fumarate 50mg ER tab**
   Minimal usage and availability of ferrous sulfate 300mg/5ml

2. **Ferrous Sulfate 220mg/5ml**
   Minimal usage and availability of ferrous sulfate 300mg/5ml

3. **Phenoxybenzamine (Dibenzyline®)**
   Minimal usage

4. **Carmustine in Polifeprosan wafer 7.7mg (Gliadel Wafer®)**
   Minimal usage

Policies & Procedures/Floor Stock Update

1. **707-700-105 Intravenous Medication Administration Guideline Update** reflects ketamine infusion include intensivist restriction.

2. **707-700-101 Administration and Charting of Patient Medications**
   Update reflects the use of barcoding being required in administration and charting of patient medications.

3. **707-800-103 Multi-Dose Vial Policy**
   Update specifies that the sterile water pour bottles are now single use based on manufacturer recommendations.

4. **707-600-128 UH Warmers Policy**
   IV fluid in warmers must be discarded once they are put in the warmers and not used.

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P&T Updates
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Miscellaneous:
Off label and New FDA approved indications for the formulary products
Aerosolized Epoprostenol (Flolan®) for Acute Respiratory Distress Syndrome (ARDS): Literature was presented to the committee in support of using inhaled Epoprostenol as an alternative to inhaled nitric oxide for treatment of ARDS. Use at UH in accordance with approved guideline (Agenda item V. B. 3) via Off Label Route for off label indication – Approved.

Remove PCA meds from Pyxis over-ride list recommendation

Intranasal Fentanyl (Peds ER)

Literature was presented to the committee in support of using intranasal fentanyl for analgesia in the Peds ER. Use in Peds ER via Off Label Route – Approved.

Nursing Pharmacy Steering Subcommittee Meeting
Pharmacy to provide ½ tablet meds except controlled substances – Approved.

Codeine containing products for pediatric inpatients - formulary deletion

The pediatric physician champion, who had requested the deletion of codeine containing products from the formulary for the pediatric patients, presented the house wide education progress on this proposal to the committee. The education is still ongoing and once completed a go live date will be set to execute the proposal.

Pharmacogenomics, the Future of Personalized Medicine

The current way for a healthcare professional to evaluate a patient’s response to a medication is through trial and error. The side effects of certain medications can be tolerated by most patients but specific genetic polymorphisms can cause other patients to have intolerable ADRs that lead to significant injury or death. These genetic polymorphisms are responsible for alterations in proteins and enzymes which are responsible for the metabolism of the drug. Advancements in technology have allowed an individual’s genome to be analyzed, this information can then be used to determine whether or not a patient is a candidate for a particular drug. Methods to determine genomic makeup are becoming more cost effective and will be used to usher in a new era of personalized medicine.

CYP2D6 is a notable enzyme that has been extensively studied. A common drug affected by an alteration in this enzyme is codeine. Codeine must be metabolized to morphine by CYP2D6 in order for patient to have any analgesic effect. Patients with a specific polymorphism can be classified as a poor metabolizer; this means that the patient would be unable to convert codeine to its active metabolite morphine, therefore having no therapeutic effect.

With the advancement of technology and a better understanding of genetic makeup, prescribers will be able to better predict which patients will receive maximal benefits from the drug while diminishing potential risks.

References:

Contributed by:
Mark Santos, Pharm D Candidate, Class of 2019
Fairleigh Dickinson University
Ivabradine’s Addition to the Formulary with Specific Considerations

With its recent FDA approval in April 2015, ivabradine is a new drug in the changing landscape for heart failure (HF) treatment in many hospitals. Its FDA-approved indication for reducing the risk of hospitalization in patients with worsening heart failure is unique due to its novel mechanism-of-action. Ivabradine is a selective inhibitor of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels found within the sinoatrial node of cardiac tissue. By inhibiting HCN channels, ivabradine disrupts ion transport, resulting in a prolonging of diastolic depolarization, ultimately leading to a reduction in heart rate without a drop in blood pressure. While ivabradine may be indicated for heart failure patients, current guidelines limit its use to special populations who meet current qualifications. In order to receive ivabradine, heart failure patients must have symptomatic chronic heart failure with a left-ventricular ejection fraction ≤ 35%, who also have a resting heart rate ≥ 70 bpm and are either on a maximally tolerated dose of a beta-blocker or have a contraindication to beta-blockers. Patients must also be in normal sinus rhythm. The current recommendation is to first achieve maximum tolerated doses of an ACE inhibitor, beta-blocker, and an aldosterone antagonist. Side-effects of the medication including the development of arrhythmias and changes in vision due to the induction of phosphenes.

In a recent study analyzing the number of HF patients needed-to-treat to prevent recurrent hospitalizations, it was concluded that ivabradine resulted in a lower number needed-to-treat compared to the effect on the time for first hospitalization vs placebo. Another recent study evaluated the use of ivabradine in patients who had stable coronary artery disease without clinical heart failure and found ivabradine to be ineffective in improving outcomes for these patients. However, these two clinical trials provide little insight to the eagerness and/or reservation clinicians have when prescribing this medication. Therefore, use of the drug should be limited to those who have stable, but symptomatic chronic HF, normal sinus rhythm, LVEF ≤ 35%, resting heart rate ≥ 70 bpm, and those either on maximally tolerated beta-blocker dose or not on beta-blockers due to a contraindication.

References:
1. Drugs for chronic heart failure. Med Lett Drugs Ther 2015;57:9

Contributed by:
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Sacubitril/Valsartan (Entresto®): The Novel Blockbuster Medication

Sacubitril/Valsartan is an oral fixed-dose combination of the neprilysin inhibitor (sacubitril) and the angiotensin receptor blocker (ARB) (valsartan), indicated to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure with reduced ejection fraction (HFrEF). Sacubitril is the first neprilysin inhibitor to become available in the US and was approved by the FDA in 2015.

Sacubitril/Valsartan belongs to a new class of medications called Angiotensin-receptor neprilysin inhibitor (ARNI).

Mechanism of Action
The combination of sacubitril plus valsartan inhibits neprilysin (neutral endopeptidase) via LBQ657, the active metabolite of the pro-drug sacubitril, and blocks the angiotensin II type-1 (AT1) receptor via valsartan.

Dosage and Administration
Sacubitril/valsartan is available in 3 oral tablets:
- 50 mg (sacubitril 24 mg/valsartan 26 mg)
- 100 mg (sacubitril 49 mg/valsartan 51 mg)
- 200 mg (sacubitril 97 mg/valsartan 103 mg)

The recommended initial dosing is 100 mg twice daily (BID) and dose adjusted as tolerated after 2-4 weeks, to target a maintenance dose of 200 mg BID.

There is a recommended 36-hour washout period when switching from an angiotensin-converting enzyme inhibitor (ACE-I) due to increased risk of angioedema. Patients previously taking a low dose ACE-I or an Angiotensin II receptor blocker (ARB), and patients not currently taking an ACEI/ARB should be initiated at a lower dose of 50 mg BID.

PARADIGM-HF Trial
Approval of Entresto was based on a double-blind trial (PARADIGM-HF) where 8442 patients with class II-IV heart failure and a reduced ejection fraction of 40% or less that were randomized to Entresto 200 mg (sacubitril 97 mg/valsartan 103 mg) twice daily or an ACE inhibitor enalapril (Vasotec) 10 mg twice daily, in addition to recommended therapy. The study was stopped early after 27 months of follow-up because a pre-specified interim analysis showed lower cardiovascular mortality in patients randomized to sacubitril/valsartan. Results also showed a relative risk reduction (RRR) of 16% (17.0% vs. 19.8%) for all-cause-mortality with sacubitril/valsartan versus enalapril.

Adverse Events
Side-effect profile for sacubitril/valsartan in the trial was very similar to that of enalapril. The most common adverse reactions (incidence =5%) with sacubitril plus valsartan included hypotension, hyperkalemia, cough, dizziness, and renal failure. Overall, 10.7% of patients who received sacubitril/valsartan in the PARADIGM-HF trial discontinued treatment because of an adverse event versus 12.2% of patients who received enalapril.

Guidelines Update
The 2016 ACC/AHA/HFSA updated guidelines recommend using an ACE inhibitor, ARB, or ARNI in combination with background therapy, including beta-blockers and aldosterone antagonists, to reduce morbidity and mortality. For patients with chronic symptomatic class II or III HF with reduced ejection fraction who tolerate an ACE inhibitor or ARB, the guidelines recommend replacing the existing ACE inhibitor or ARB with an ARNI to reduce morbidity and mortality.

References:

Contributed by:
Beshoy Saad
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Assimilating Biosimilars

Biological products are medications that are created from various natural sources such as from microorganisms or animals. Most biological products are more complex in structure and have larger molecules or mixtures of molecules than conventional drugs (also called small molecule drugs).

They are made to prevent or treat medical maladies. A biosimilar is a form of biological products that is highly analogous to another FDA approved reference product. Biosimilars and their reference products are not clinically divergent from each other through which they have no differences in safety and efficacy. However some differences do exist due to the biosimilar being made from a natural source as opposed to its reference product. Furthermore, biosimilars are not bioequivalent with their reference product such as how a generic drug is to its brand name drug. Therefore there is no expectation for a biosimilar to yield an identical clinical result like its reference product within a patient. A biosimilar can only be FDA approved if it shares the same mechanism of action, administration route, dosage form, and strength with the reference product.

Despite patient benefits of affordability and accessibility, there exists concern with healthcare providers regarding the safety in prescribing newly developed biosimilars. According to the Director of medical affairs for Sciformix Corporation, Suhasini Sharma, any discernable difference between a biosimilar and its reference product can only be detected through continuously intense scrutiny of the collection and assessment of post-marketing data. Another solution to alleviating prescriber worry is by studying European safety and efficacy data on biosimilars. For instance, the biosimilar for infliximab has had a presence in European markets for over a year, while it was approved in the US in April 2016. Once prescribers become comfortable writing for biosimilars, an avenue of cost-effective and alternative treatment to patients will be greatly enhanced.

References:

Contributed by: Jazzmine Paz, PharmD Candidate 2019, Fairleigh Dickinson University School of Pharmacy and Health Sciences
Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory autoimmune disease that causes pain and disfigurement in joints. It is well-established that cytokines are the driving force of inflammation in RA. Cytokines are small protein messengers that effect intercellular communication. They bind to cell receptors and start a downstream cascade of events that ultimately coordinate a cellular response. Cytokines promote autoimmunity, maintain chronic inflammation, and drive the destruction of joint tissue. Some classes of cytokine receptors are themselves kinases, while other classes rely on intracellular kinases, like janus kinases, to mediate the downstream effects.

The janus kinase (JAK) family is a sub-class of kinases that has demonstrated strong links to the progression of RA. The JAK family consists of four non-receptor tyrosine kinases: JAK1, JAK2, JAK3, and TYK2. The JAK pathway starts when a cytokine binds to a transmembrane cytokine receptor. Binding of the ligand induces the receptor to dimerize with a cytokine receptor nearby. This dimerization activates the JAKs bound to the intracellular domain of the receptors. The activated JAKs then phosphorylate tyrosine residues on each of the receptors. This is followed by the recruitment of another type of protein called STAT (signal transducers and activators of transcription). The JAKs then perform a second phosphorylation, this time on the STATs. The phosphorylated STATs then detach from the receptor and dimerize. The dimerized form of the STATs is able to move through the cytoplasm and enter the cell nucleus, modifying gene transcription.

The gene transcription activated by the JAK-STAT pathway gives rise to more proinflammatory cytokines, fueling the destructive action of RA.

Elucidation of the JAK-STAT pathway during the last decade has encouraged researchers to target this pathway in the treatment of RA. In 2012, the FDA approved tofacitinib, an oral JAK inhibitor. It is a small molecular weight (312.4 Da), non-biologic that works at the intracellular level. Tofacitinib is a reversible, competitive inhibitor of the ATP binding site in the catalytic cleft of the kinase domain of JAK. In this manner, it inhibits phosphorylation and activation of JAK, shutting down the JAK-STAT pathway.

In the phase 3 clinical trial called ORAL Solo, tofacitinib demonstrated statistical significance in terms of change in baseline ACR20, ACR70, HAQ-DI, DAS28-4 (ESR) compared to placebo. In the ORAL Start study comparing tofacitinib to methotrexate, tofacitinib demonstrated significantly lower changes in mTSS score compared to methotrexate. The TEAEs collected from the study suggest that tofacitinib and methotrexate have similar adverse effects. The main adverse effects produced by tofacitinib throughout the various clinical trials include significant neutropenia (3.0% vs. <1.0% in placebo), serious infections, increased LDL, headache, diarrhea, and increased serum creatinine. Although the data collected on tofacitinib in clinical trials suggest its safety and efficacy, this information is limited by potential sponsorship bias arising from the fact that the drug’s manufacturer, Pfizer, funded the studies. Deeper analysis must be done before considering formulary addition.

References:

Contributed by:
Megan Huang, Pharm.D Candidate 2019, St. John’s University
Welcome to Three New Pharmacists

Matthew Wolfe, Pharm. D.

Dr. Matthew Wolfe earned his Doctor of Pharmacy degree from Temple University School of Pharmacy in Philadelphia in 2016. During his time in pharmacy school, he held a pharmacy internship at the Hospital of the University of Pennsylvania, which cemented his ambition to provide pharmacological care to hospital inpatients. Dr. Wolfe earned a Bachelor of Arts degree in History from the University of Michigan in Ann Arbor before deciding to pursue a career in pharmacy. He is originally from the Boston area and is a loyal New England Patriots and Michigan Wolverines fan, but has close family and friends in the New York metropolitan area.

Brian Mulroy, Pharm. D.

Dr. Brian Mulroy received his Doctor of Pharmacy degree from the Ernest Mario School of Pharmacy of Rutgers University in New Brunswick, in 2016. He used his time during his clinical rotations to explore a variety of careers within pharmacy, including community and hospital pharmacy, medical information, and rehabilitation medicine. He has worked at an independent community pharmacy for nine years during high school and college, before being hired by University Hospital. Brian is excited to join the UH team and to expand his knowledge in the field of pharmacy to provide better patient care. In his free time, Brian enjoys playing guitar, running, and watching baseball, hockey, and football.

Quoc D Vo, Pharm.D.

Dr. Vo graduated from Nesbitt School of Pharmacy, Wilkes University in 2015. He is currently working fulltime in retail pharmacy and joining University Hospital as a per-diem pharmacist. He enjoys traveling, exploring and being outdoors.