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The Pharmacy Newsletter for Physicians

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Update: Oral Antidiabetic Agents in ICU

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Due to risk of hypoglycemia when nutritional intake is compromised, the Corporate Diabetes/Endocrine Subcommittee has revised Corporate Medication Manual Policy #1040.1 "Pharmacologic Management of Adult Diabetes Patients" to **prohibit the use of any oral hypoglycemic / anti-hyperglycemic agent in any of the Intensive Care Units (ICUs)**. Previously, CCU (6E) patients awaiting transfer to another floor could receive these agents if the appropriate laboratory and diet orders were ordered.

Formulary Deletion:

Hydroxyethyl Starch Solutions

Recent evidence comparing the colloidal Hydroxyethyl starch (HES) solutions (Hespan and Voluven) for fluid resuscitation with other fluids showed no added benefit and potential for significant harm in critically ill patients. In June 2013, the FDA issued a safety alert for all HES solutions, which included extensive restrictions and monitoring recommendations. Due to this newly recognized risk and availability of alternatives (i.e. crystalloids such as dextrose/sodium chloride and non-HES colloids such as albumin), HES solutions have been removed from the Beaumont Formulary.

FDA MedWatch Alerts

Acetaminophen and Severe Skin Reactions

The FDA has reviewed reports of acetaminophen-associated severe skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). Symptoms may include reddening of the skin, rash, blisters, and detachment of the upper skin surface. Although occurrence is low, because these skin reactions can be severe or fatal, the FDA is requiring prescription and OTC acetaminophen-containing products to include a warning of this risk. If a severe skin reaction is thought to be caused by acetaminophen, the drug should be stopped immediately and a health care professional notified.

PO Ketoconazole (Nizoral) & Hepatotoxicity

Due to risk of severe hepatotoxicity and adrenal insufficiency, the FDA is making the following recommendations for the oral antifungal, ketoconazole:

- Restrict use to endemic mycosis (e.g., blastomycosis, coccidiomycosis, histoplasmosis) when alternative antifungal agents are not effective or tolerated
- Do not use for treatment of fungal skin or nail infections
- Contraindicated in acute or chronic liver disease
- Monitor LFTs at baseline and weekly

Patients requiring ketoconazole treatment should be informed of the signs and symptoms of liver damage: appetite loss, pain or discomfort in the abdominal region or right upper quadrant, jaundice, and dark urine or lightening of stools. Topical formulations of ketoconazole (i.e. creams, shampoos, foams, and gels) have not been associated with liver damage and recommendations for topical use have not changed.

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Formulary Addition:

Apixaban (Eliquis)

By: Mona Ali, Pharm.D.

Apixaban is a factor Xa inhibitor (anticoagulant) approved on Formulary for reduction in the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Apixaban is an oral tablet and does not require anticoagulation monitoring. There is no reversal agent available, and due to lack of data in patients with severe renal impairment (CrCl < 25 ml/min), the American Heart Association and American Stroke Association recommend to avoid use in this patient population.

In clinical trials (ARISTOTLE), apixaban was found to be superior to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The primary safety outcome of major bleeding occurred less frequently in the apixaban group vs. warfarin. It is notable that the median age of patients in the ARISTOTLE trial was 70 years. Patients had a mean CHADS2 score of 2.1, ~35% of patients had a history of heart failure, and ~15% patients had moderate to severe renal dysfunction (CrCl 25-50 mL/min). Patients were excluded from the trial if they required treatment with both aspirin and a thienopyridine (i.e. clopidogrel), if they required aspirin alone in doses greater than 165 mg, or if they had a CrCl < 25 ml/min.

Dosing and administration is as follows:

- Usual dose: 5 mg PO q12 hrs
- Reduce dose to 2.5 mg PO q12 hours* in patients with at least two of the following:
  - Age ≥ 80 years
  - Weight ≤ 60 kg
  - Serum Creatinine ≥ 1.5 mg/dL
    OR
  - If concomitant strong dual ***inhibitors*** of CYP3A4 and P-gp (i.e. itra- /ketoconazole, ritonavir, clarithromycin)

* Automatic substitution was approved by Medication Management Committee for patients that meet criteria for reduced 2.5 mg dose.

It is important to avoid apixaban use in patients with the following:

- CrCl < 25 ml/min
- High bleeding risk (i.e. recent bleed or recently diagnosed NSAID-induced ulcers)
- Moderate or severe hepatic impairment (Child-Pugh B or C)
- Concomitant anticoagulants (i.e. heparin, warfarin, enoxaparin, argatroban) or thrombolytics
- Concomitant strong dual ***inhibitors*** of CYP3A4 & P-gp (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) in those who already require the lower dose of 2.5mg PO q12 hrs.
- Concomitant strong dual ***inducers*** of CYP3A4 & P-gp (i.e. rifampin, carbamazepine, phenytoin, St. John's Wort)
- Pregnant patients and nursing mothers
- Concomitant antiplatelet drugs (including aspirin and NSAIDs), selective serotonin re-uptake inhibitors (SSRIs), and serotonin–norepinephrine reuptake inhibitors (SNRIs) unless benefits outweigh the risk of increased risk of bleeding

Apixaban Patient Discharge Instructions in oneChart

"Apixaban discharge instructions" will be available under "*Anticoagulation Instructions"* within the After Visit Summary (AVS) in EPIC. As with warfarin, dabigatran and rivaroxaban, these include a reminder for the nurse or pharmacist to review education materials with the patient prior to discharge. The apixaban patient education handout is available on the Anticoagulation Resources website, and in the Forms Library (#8526). Also, refer to the same Anticoagulation Resources website to view the apixaban medication guideline for more clinically-relevant information.

Apixaban Patient Education: Refer to the checklist in the apixaban patient education handout and review the importance of compliance, taking the medication with food, monitoring for signs/symptoms of bleeding, and notifying the prescriber and asking a prescriber or pharmacist before taking any new medications.