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# Drugs & Therapy

## B • U • L • L • E • T • I • N

## FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met September 17, 2013. 3 products were added in the *Formulary,* 3 drugs were designated nonformulary and not available, and 1 therapeutic interchange was approved. Criteria for use was evaluated for 1 agent with no recommended changes.

### ◆ ADDED

**Dolutegravir** (Tivicay®)

**Levomilnacipran** (Fetzima®)

**Levonorgestrel Intrauterine Device** (Mirena®)

### ◆ NON-FORMULARY AND NOT AVAILABLE

**Esomeprazole strontium** (Generic)§

*§Therapeutic Interchange*

**Ferric carboxymaltose injection** (Injectafer®)

**Norethindrone, estradiol, ferrous fumarate** (Lo Minastrin Fe®)*

**Patient may use their own*

### ◆ CRITERIA FOR USE CHANGES

**Activated Factor VII** (NovoSeven®) for use in Liver Transplant*

**No changes in the current criteria recommended*

**Dolutegravir** is an integrase inhibitor indicated for the treatment of HIV-1 infection in adults in combination with other antiretroviral agents. This agent should be considered for use in patients who are both treatment naïve or treatment-experienced. Dosing of this medication is 50 mg once or twice daily dependent upon the concomitant antiretroviral regimen.

Due to the complex nature of antiretroviral therapy, it was recommended that this agent be added in

*(continued on next page)*

DRUG POLICY

## Oral Contraceptive Use in the Inpatient Setting

The Affordable Care Act (ACA), a federal healthcare reform bill, was signed into law in 2010 with the majority of provisions taking effect in August 2011.[1] The ACA mandates the coverage of certain preventative services for women as recommended by the Institute of Medicine.[2-3] Included in this provision is contraception and as such, women are to receive any FDA approved contraceptive medication at zero percent cost-sharing.[2-4] This includes all available oral contraceptives as well as implantable devices and injections. If a generic product exists for a particular brand-name contraceptive, only the generic must be covered at no cost. This is applicable in the outpatient setting only, with hospital formularies able to dictate the products provided to inpatients.

Since January 2013, there have been six new contraceptive agents brought to market.[5] Each of these agents is very similar to other products available, however, they may have slightly different variations in hormone content and combinations. Iron addition to a product is another way to obtain FDA approval as a new agent. With insurance companies mandated to provide coverage for contraceptive agents, it stands to reason that development of these agents is likely to continue.

In February 2010, the Pharmacy and Therapeutics Committee voted to approve one oral contraceptive agent for use in the inpatient setting. Lo/Ovral® (norethindrone and ethinyl estradiol) or its generic equivalent is the only oral contraceptive agent available in the *Formulary*. Since the addition of this agent, all other contraceptive agents have been designated non-formulary and not available with patients able to take their own medications.

In September 2013, the Pharmacy and Therapeutics Committee approved a policy designating all newly approved oral contraceptives (with the exception of the current formulary agent) as non-formulary and not available. All new contraceptive agents will continue to be evaluated at the Formulary Subcommittee for informational purposes. Newly approved agents will automatically be designated non-formulary and not available with patients able to take their own medications. This policy also dictates that the P&T Committee will be notified of the non-formulary and not available status of the medication via submission of the Formulary Subcommittee minutes as well as through the Drugs and Therapy Bulletin.

Any requests for changes in the *Formulary* for contraceptive agents should follow standard procedure with formulary request and disclosure forms submitted to the Secretary of the Pharmacy and Therapeutics Committee.

*– Carrie Lagasse, PharmD, BCPS*

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### INSIDE THIS ISSUE

***Formulary update,*** *from page 1*

the *Formulary* barring any dissention from the Anti-Infective Subcommittee (AIS). The Anti-Infective Subcommittee voiced their agreement with this decision and the Committee approved the addition of this agent in the *Formulary*.

**Levomilnacipran** is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder. Levomilnacipran is the 1S-2R enantiomer of milnacipran [Savella®] which is approved for the treatment of fibromyalgia. Of note, levomilnacipran is not approved for the treatment of fibromyalgia nor has it been evaluated for this indication.

As there is no information on conversion of this agent to other SNRI agents, the Committee voted to add this medication in the *Formulary*. This product is expected to be commercially available sometime in Q4 2013.

**Levonorgestrel Intrauterine Device** (L-IUD) was approved by the FDA in 2000 for intrauterine contraception. In 2009, an indication for treatment of heavy menstruation for women who choose intrauterine contraception was added to the product labeling. This was the first drug-device combination for intrauterine use with a documented lifespan of five years. L-IUD is one of the most effective forms of birth control with a reported efficacy rate of over 99%. This agent was requested for review from the Department of Obstetrics and Gynecology for use in patients where surgical sterilization is not optimal.

L-IUD is supplied in a box with one sterile intrauterine system consisting of a T-shaped polyethylene frame with a steroid reservoir containing 52 mg levonorgestrel packaged within a sterile inserter. L-IUD should be inserted by a trained healthcare provider.

L-IUD releases low doses of levonorgestrel into the uterine cavity after insertion with an initial release rate of approximately 20 mcg/day with this rate decreasing progressively to about half of that value after 5 years. It is thought that the pharmacological efficacy of L-IUD is predicated on local progestogenic effects on the uterine cavity where high concentrations of levonorgestrel lead to morphological changes in the uterine wall including stromal pseudodecidualization, glandular atrophy, leukocytic infiltration, and a decrease in both glandular and stromal proliferation.

Systemic absorption of levonorgestrel from L-IUD is extremely low with a stable serum concentration of 150-200 pg/mL occurring within the first few weeks following insertion. Levonorgestrel is not subject to first-pass hepatic metabolism. It is highly protein-bound to sex hormone-binding globulin (SHBG), albumin, and alpha1-glycoprotein. The elimination half-life of systemically absorbed levonorgestrel is 17-24 hours, and it undergoes hydroxylation that is catalyzed by hepatic cytochrome P450 isoenzymes, namely CYP3A4 followed by subsequent conjugation to sulfate and glucuronide salts. No entero-hepatic recycling occurs and excretion occurs in the urine (45%) and feces (32%).

L-IUD is an extremely effective form of contraception. Clinical trials leading to approval reported 12-month pregnancy rates were less than or equal to 0.2 per 100 women (0.2%) and the cumulative 5-year pregnancy rate was approximately 0.7 per 100 women (0.7%).

Adverse effects include: ectopic and/or intrauterine pregnancy, pelvic inflammatory disease, irregular bleeding, oligomenorrhea, amenorrhea, embedment that decreases the efficacy of the product, perforation of the urine wall or cervix that may occur during insertion, and partial or complete expulsion.

Literature analysis showed that it is both safe and effective to use this product immediately after childbirth with the only documented adverse effect being an increased risk of expulsion. The Committee recommended adding this product in the *Formulary* as a long-term contraceptive option in patients for which surgical sterilization is not optimal as well as in patients where risk for loss to follow-up is likely. The Committee recommended an evaluation of use be performed six months after the addition of L-IUD in the *Formulary*.

**Esomeprazole strontium** is a proton pump inhibitor indicated for the treatment of GERD, risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication, and pathological hypersecretory conditions. This agent is available in 24.64 mg esomeprazole strontium (equivalent to 20 mg esomeprazole) and 49.3 mg esomeprazole strontium (equivalent to 40 mg of esomeprazole). This agent is currently in litigation regarding patent infringement.

Currently, esomeprazole is designated Non-formulary and Not available with the following therapeutic interchange:

Esomeprazole 20 mg = Pantoprazole 40 mg (same interval)

Esomeprazole 40 mg = Pantoprazole 80 mg (same interval)

A therapeutic interchange for esomeprazole strontium was approved as follows:

Esomeprazole strontium 24.64 mg = Pantoprazole 40 mg (same interval)

Esomeprazole strontium 49.3 mg = Pantoprazole 80 mg (same interval)

**Ferric Carboxymaltose Injection** (Injectafer®) is an iron replacement product indicated for the treatment of iron-deficiency anemia in adult patients who are unable to tolerate oral iron or have had an unsatisfactory response to oral iron and in those patients who have non-dialysis dependent chronic kidney disease.

In January 2011, iron sucrose was designated the intravenous iron formulation of choice in the *Formulary*. Other formulations of intravenous iron, including sodium ferric gluconate and ferumoxytol were designated non-formulary and not available at that time. The P&T Committee voted to designate ferric carboxymaltose injection as non-formulary and not available in line with previous decisions on intravenous iron products.

**Norethindrone acetate**, **ethinyl estradiol** and **ferrous fumarate** (Lo Minastrin FE®) is a chewable oral contraceptive tablet approved for the prevention of pregnancy in women. Each packet contains 24 tablets containing 1 mg norethindrone acetate and 10 mcg ethinyl estradiol, 2 tablets containing 10 mcg ethinyl estradiol, and 2 tablets containing 75 mg ferrous fumarate.

Currently, norgestrel and ethinyl estradiol (Lo/Ovral®) is the only available oral contraceptive in the *Formulary*. As with all other oral contraceptives, the P&T Committee voted to approve designation of this agent as non-formulary and not available with patients able to take their own medication.

**Activated Factor VII** (NovoSeven®) is a hemostatic agent approved for the prevention of bleeding during surgery in patients with hemophilia who have antibodies to factor VIII or factor IX. It was initially approved by the U.S. Food and Drug Administration (FDA) in 1999. This medication has been used off-label when conventional therapies have failed to stop bleeding. The Department of Transplant Surgery, has requested to use this medication off-label for the prevention of bleeding in orthotopic liver transplantation (OLT). The requested dose is 45 mcg/kg prior

*(continued on next page)*

***Formulary update,*** *from page 2*

to surgery with up to one repeated dose for a maximum total dose of 90 mcg/kg. The requested therapy is for patients with an international normalized ratio (INR) greater than 3.0 preoperatively. Also, rFVIIa would not be given to a patient that has a body temperature less than 35 degrees Celsius or a platelet count of less than 100,000 cells per $mm^3$.

NovoSeven® (rFVIIa) is currently listed in the *Formulary* for its FDA-labeled indications in addition to several off-label uses. It can be used during cardiothoracic (CT) surgery for refractory bleeding when the risk of continued bleeding outweighs the risk of thrombosis. Also, it can be used post-operatively in cardiothoracic surgery patients for refractory bleeding in the ICU defined as greater than 3 mL/kg/hr output from a chest tube. Any use outside of the OR or ICU is limited to hemophilia, anticoagulant overdose, or Hematology approval. The dose of rFVIIa for off-label uses in the *Formulary* is limited to an initial 45 mcg/kg, which can be repeated within 24 hours.

OLT is the main treatment for chronic or acute liver disease not responding to medical treatment. One of the most important complications of this surgery, corresponding to an increase in morbidity and mortality, is perioperative bleeding. Excessive blood loss can also increase the requirements for blood product transfusions. Blood products are expensive but rFVIIa is costly as well. rFVIIa is similar to endogenous factor VII and works by initiating the extrinsic coagulation cascade and forming a local hemostatic plug to prevent or stop bleeding.

The Agency for Healthcare Research and Quality (AHRQ) published an executive summary of off-label rFVIIa use in 2010. These guidelines consisted of a systematic review of rFVIIa vs. usual care. Overall, this review determined that the trials evaluated provided a low strength of evidence with fair applicability. The review found that there was no benefit from rFVIIa in comparison to usual care in regards to direct and indirect outcomes. The main outcomes explored were mortality, thromboembolisms, mean red blood cell transfusions, Operating Room (OR) time, and Intensive Care Unit (ICU) length of stay (LOS).

The P&T voted to not allow use of rFVIIa in the liver transplant population. The available literature shows no benefit from rFVIIa in comparison to usual care in regards to direct and indirect clinical outcomes.

**NEWS**

# Resistant to Change: Antimicrobial Resistance in 2013

In September 2013, the Centers for Disease Control (CDC) published a report entitled "Antimicrobial Resistance Threats in the Unites States, 2013." This 114 page document provides a snapshot of consequences of antimicrobial resistance today. It is estimated that two million patients develop an antimicrobial-resistant infection each year with a minimum of 23,000 individuals dying as a result.[1] Dr. Steven Solomon, the director of the CDC's office of antimicrobial resistance, noted that the report underestimates the numbers by design as the "researchers were instructed to be conservative and to base their calculations only on deaths that were a direct result of drug-resistant bacterial infection."[2] As clinicians, we are tasked with identifying areas of impact for the reduction of indiscriminate antimicrobial consumption.

In 2007, the Infectious Diseases Society of America (IDSA) published guidelines in association with the Society for Healthcare Epidemiology of America (SHEA) to outline antimicrobial stewardship practices.[3] At the time of publication, the impact of the guidelines was bolstered by decreasing antimicrobial development and emergence of multi-drug resistant organisms (MDRO). In fact, between 1983 and 1987, there were 16 new drug entities approved for use for infectious diseases, compared to only 7 agents from 1998 to 2002. This number was even further reduced between 2003 and 2007 with only 5 new agents approved.[4] As noted in the CDC 2013 report, throughout these same time periods we have seen increased reports of MDRO including carbapenemase-producing Enterobacteriaciae, vancomycin-resistant Enterococcus, as well as an increasing emergence of *Clostridium difficile*.[1] A need for greater optimization of antimicrobial therapy is evident, although sometimes inconsistently practiced at the bedside.

Imagine a patient in the emergency department (ED) complaining of chest pain is diagnosed with an acute myocardial infarction. Most institutions would give the patient a ß-blocker. Whether the physician chooses to initiate carvedilol, metoprolol, or another agent, it does not affect the next patient, or a patient 5 years from now, who comes in with a similar diagnosis. Now imagine that same patient in the ED with a diagnosis of community acquired pneumonia (CAP) caused by *Streptococcus pneumoniae*. The patient is treated with piperacillin/tazobactam. Will piperacillin/tazobactam cover the isolated pathogen? Absolutely. Is it the most appropriate agent for this patient? Probably not. Will it affect the next patient, or a patient 5 years down the road if the ED always treats CAP with piperacillin/tazobactam? Probably. For these reasons, the practice of infectious diseases is not simply about right and wrong. It is a matter of what is best for this patient as well as patients who will be treated in your facility in the future.

As a referral center, UF Health – Shands Hospital is at risk of both antimicrobial resistance generated here as well resistance acquired in the surrounding communities. We have very little control over the prescribing habits of a small, community hospital 200 miles away, yet our patient population is directly impacted by those practices. Targeted efforts have been developed in an attempt to combat the resistance that occurs in our facility as well as in our neighbor's backyards.

In 2004, UF Health – Shands Hospital instituted an antimicrobial stewardship team. This effort was at the forefront of practice at the time, 4 years prior to the publication of the IDSA/SHEA Guidelines. Today, this team works with pharmacy, the ID consult service, Infection Prevention and Control, and the Department of Microbiology to identify areas of antimicrobial optimization in our patients. Additionally, members of the Anti-Infective Subcommittee of the Pharmacy and Therapeutics Committee work to provide rational use criteria for broad-spectrum antimicrobials at our institution. Through these efforts, we have seen a decrease in certain gram negative susceptibilities, an overall stabilization of the antibiogram, as well as decreases in antibiotic consumption. The mainstay of these advances is a reduction in continued use of broad-spectrum empiric therapy.

Transition from broad-spectrum, empiric therapy to pathogen-directed therapy (once identified) is crucial to the reduction of antimicrobial resistance.

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***Antimicrobial Resistance,*** *from page 3*

Currently, polymerase chain reaction (PCR) testing and mass spectrometry are being utilized to decrease the time to identification of certain pathogens. Data has indicated that use of these technologies can lessen this time by an average of 2-3 days.[5-7] This reduction allows for decreased exposure to broad-spectrum antimicrobial agents.

PCR technology is currently being piloted at UF Health – Shands Hospital for select patients with positive blood cultures where *Staphylococcus sp.* or *Candida sp.* are isolated. For example, the absence of the mecA gene identified in a blood culture growing gram positive cocci in clusters would indicate oxacillin-susceptibility and allow for vancomycin de-escalation days earlier than waiting for the final read on the blood culture. Identification of this gene would potentially be available 6-12 hours after the positive culture is identified as compared to our current practice of 36-60 hours. As this is only a pilot project, clinicians should continue to screen culture results until they are finalized. Increased utilization of technologies such as these will allow for a timely transition to appropriate antimicrobial therapy and thereby a reduction of antimicrobial resistance potential.

With recent unit closures secondary to infectious causes, i.e. *Acinetobacter baumanii*, as well as continued identification of *C. difficile*, it is imperative that we continue to take action to reduce the risk of resistance-development in our patients at UF Health – Shands Hospital. Working cohesively to ensure that the right patients are being treated with the right antimicrobial agents for the right duration of therapy is paramount to our success.

*– Carrie Lagasse, PharmD, BCPS*

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