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Special Points of Interest:

- P&T Update-Formulary Addition/Deletion
- Policy and Procedures Update
- Sentinel Event Update: Single-Dose vs. Multi-Dose Vials
- Ebola: A Growing Healthcare Crisis
- Update in Diabetes Research: Amylin Production Associated with onset of Type-1 and Type-2 Diabetes in Mice
- New Cholesterol Guidelines
- Atrial Fibrillation (A Fib) Treatment
- The Role of an Ambulatory Care Pharmacist
- New Classification of Tramadol as a Controlled Substance
- New HIV Combination Therapy Approved by FDA

P&T Update

Formulary Addition/Deletion

1. IV Tranexamic Acid (Cyklokapron®) – The requesting physicians noted that tranexamic acid has been added to the formulary of other trauma centers nationwide, including the military. The use of Factor VII may also decrease with the availability of tranexamic acid. Formulary addition of IV tranexamic acid approved.
2. Dexmedetomidine (Precedex®) – 200 mcg/50mL premixed vials. Motion made to add dexmedetomidine 200mcg/50mL to the UH Formulary. Line extension of dexmedetomidine approved.
3. Argatroban 50mg/50mL pre-mixed vials – line extension. Motion made to add argatroban 50mg/50mL pre-mixed vials to the UH Formulary. Line extension of argatroban approved.
4. Dalteparin 5000 units/0.2mL injectable – formulary deletion. Motion made to delete dalteparin 5000 units/0.2mL injectable from the UH Formulary as recommended by the NPSG Safe Anticoagulant Use Committee. The medication has not been used in the past 36 months. Formulary deletion of dalteparin approved.
5. Daptacel® (DTaP; diphtheria, tetanus toxoid, acellular pertussis vaccine) – formulary deletion. The formulary alternative that is being used is Infanrix®. Motion was made to delete this product from the formulary. Formulary deletion approved.
6. Tripedia® (DTaP; diphtheria, tetanus toxoid, acellular pertussis vaccine) – formulary deletion. Tripedia® has been discontinued by the manufacturer. The formulary alternative is Infanrix®. Motion was made to delete Tripedia® from the formulary. Formulary deletion approved.

Policies & Procedures/Floor Stock Update

1. 707-500-107 STAT/NOW Medication Orders - revision. The STAT/NOW Medication Orders policy was revised to include a statement that providers will notify the unit whenever a STAT order is entered into Epic.
2. 707-600-128 Warming of IV/Irrigation Solutions/Contrast Media - revision. The Warming of IV/Irrigation Solutions/Contrast Media policy was revised with an updated UH warmer inventory.
3. 707-700-105/601-100-1209 Administration of IV Medications - revised. The Administration of Intravenous Medications policy was revised to address proper labeling of IV solutions, including plain IV fluids supplied by Central Supply/Materials Management and pre-mixed IV piggyback bags, once hung on the patient.
4. 707-500-122 Automatic Substitution Policy - revision. 0.9% NS Base for Neurosurgery ICU. Pharmaceutical division recommends allowing pharmacy to automatically substitute medications ordered for neurosurgery to 0.9% saline base when compatible and available.

(Continued on page 2)

Policies & Procedures/Floor Stock Update

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5. 707-600-117 Investigational Drug P&P - revision. Policy was presented to ensure drugs brought into clinics by subjects in clinical trials are kept in a locked space.
6. 707-700-108 Computerized Order Entry and Verification of Medication Orders - policy revision. The revisions include ordering and administering the first doses of all antibiotics orders as STAT doses (within 30-60min), allow pharmacists to adjust administration schedules upon verification to implement first-dose STAT for antibiotics unless the prescriber explicitly indicates that first dose of the antibiotic should not be STAT and given at the time scheduled by the prescriber.

Sentinel Event Update: Single-Dose vs. Multi-Dose Vials

This past June, The Joint Commission (TJC) released Sentinel Event Alert, Issue #52 "Preventing Infection from the Misuse of Vials". The improper use of single-dose vials (SDV), multi-dose vials (MDV), and injectable medical products has led to potential exposures to unsafe injections and at least 49 infectious outbreaks. According to the CDC, more than 150,000 patients required notification during this time frame to undergo subsequent blood borne pathogen testing. Resulting outcomes included death from preventable blood borne and bacterial infections, sometimes life-long treatment, and exacerbation of underlying health conditions. There can be tremendous financial costs associated with treating infected patients and containing an outbreak. Providers purposely or inadvertently causing harm may also face significant legal ramifications or disciplinary action. The alert was written to raise awareness of the issue, educate readers, and provide implementation strategies for risk reduction.

Significant contributing factors to infections as a result of the misuse of vials are the reuse of SDVs for multiple patients and a lack of adherence to safe infection control practices within health care organizations. Surveys have found healthcare professionals reported having used the same syringe to re-enter a vial multiple times, sometimes even for multiple patients, and saving SDVs for use on other patients. Harm resulting from SDVs is often underestimated due to the difficulty of tracing the misuse to infections and, typically, the adverse impact is not seen immediately. Moreover, adverse events related to unsafe injection and infection control practices are underreported, creating a challenge to measure the occurrence of true events. Often times, attempts to prevent waste may compromise infection control practices. Unfortunately, adverse outcomes in patients can negate these hypothetical savings or even increase costs to the healthcare facility.

Preventative action taken by staff to safely dispense and administer injections and medications can help accomplish TJC requirements as well as decrease waste and costs. Aseptic technique, hand-hygiene, one-time-use of syringes, and proper use of multi-dose vials can help with proper injection and infection control practices.

SDVs are preservative-free, whereas MDVs contain preservatives. SDVs should be punctured only once and then discarded. Use of MDVs should be dedicated to a single patient whenever possible. These vials must be dated appropriately and remain in the medication preparation room to be considered multi-patient or

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Sentinel Event Update: Single-Dose vs. Multi-Dose Vials

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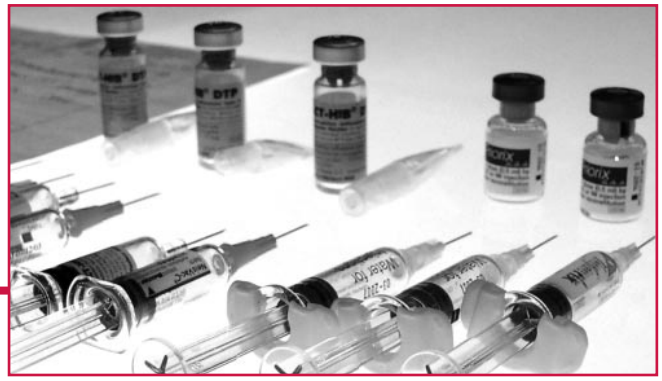

multi-use. Any area, including the bedside, where an invasive procedure is being performed turns into a procedure area. Once a multidose vial leaves the med room, it becomes a single-dose/single-use vial and must be discarded. Similar to SDVs, all syringes and needles must be discarded after one use. The expiration date for a MDV is 28 days from the date of opening or puncture regardless of manufacturer's expiration date on the vial. However, if the manufacturer's expiration date is earlier than the revised expiration date, the earlier date must be used.

It is always important to follow proper infection control practices during preparation and administration of injectable medications. An IV bag with mixed medication is considered a single-use, single-patient product. Spiked bags must be dated, timed, and the infusion must begin within one hour of spiking. Vials must be discarded appropriately immediately after use. Empty vials should be disposed of in the regular garbage. Used but not empty vials must be discarded in blue Stericycle containers.

University Hospital has already implemented various policies and procedures in light of TJC's requirements. The pharmacy department has begun to purchase more SDVs and smaller vial sizes. Instead of purchasing 20ml lidocaine vials, University Hospital has purchased more 10 mL vials. Similarly, succinylcholine has now been stocked as unit-dosed, 7mL syringes. Education for staff has been conducted regarding the One & Done Initiative, policies and procedures, and the importance of recognizing and reporting the misuse of vials to managers or to the Patient Safety Net (PSN). Posters have been placed throughout the hospital, as well. Findings will be reported to the Patient Safety Committee and P&T Committee.
Bottom line: When in doubt, throw it out!

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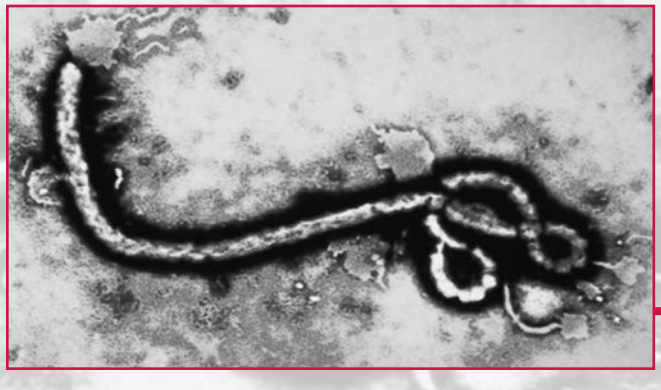
Ebola: A Growing Healthcare Crisis

Ebola has been making headlines daily. A plague that is exponentially growing, has a high mortality, and causes gruesome bleeding seems like the plot of some cheap Hollywood survival-horror flick. But Ebola is real, it is a growing worldwide crisis, and is something healthcare is going to have to tackle before it gets out of control.

We have heard the media reports, but the nature of journalism means us practitioners only hear what can be conveyed in lay terms. What is the science behind Ebola? Ebola is a negative-sense (3' to 5') RNA-



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Ebola: A Growing Healthcare Crisis

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enveloped virus. It is not a retrovirus like human immunodeficiency virus (HIV), meaning Ebola is not chronic and active immunity is granted to any survivors.

The virus is transmitted through bodily fluids and once infected, the incubation period can be up to three weeks. The virus enters the body infecting dendritic cells, preventing its expression on their surface and stopping the formation of antibodies. It also inhibits interferon- a protein that normally fights viral infections. The white blood cells do not activate as they normally would due lack of stimulation. Instead, the body fights the disease by using macrophages to engulf the viruses, triggering inflammatory and coagulation pathways. These reactions damage endothelial cells and produce the stereotypical hemorrhagic symptoms seen with the Ebola virus disease. The pro-inflammatory response is especially pronounced in the liver, where the virus kills vital cells that produce key plasma proteins, and the adrenal glands, where the steroids that regulate blood pressure are produced. This combination of damaged blood vessels, inflammation, and destruction of key vascular regulatory cells triggered by the sepsis results in hypotension, shock, MODS (multiple organ dysfunction syndrome), and ultimately death.[1]

Treatment for Ebola, beyond supportive care, is being rapidly developed. The treatment that has been making the most headlines, ZMapp®, is a triple-antibody combination against three proteins that compose Ebola. Its use in humans has been limited. Two American doctors received the antibodies and recovered, making headlines however, a Spanish missionary died despite treatment. But with supplies of ZMapp® diminishing and efficacy in question, ZMapp® may just be a dead-end. Another parenteral treatment that has recently made news is an anti-Ebola siRNA enclosed in a liposomal shell called TKM-Ebola.[2] This treatment is currently untested in infected patients, but shows promise in primate models. Alternative treatments with pre-existing medications have been proposed. Statins, ACE Inhibitors, and Angiotensin Receptor Blockers have been shown to dampen immune reaction to sepsis, allowing the body to mount an immune response at a steadier pace and not to overwhelm the uninfected cells.[3] The anti-estrogens, clomiphene and toremifene, were shown to possibly inhibit viral entry into uninfected host cells by an unknown, likely off-target, mechanism.[4] Time will tell which treatments prove most effective in fighting this new epidemic.

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Update in Diabetes Research: Amylin Production Associated with onset of Type-1 and Type-2 Diabetes in Mice

Amylin is a hormone that is released along with insulin from pancreatic β-cells after meals. Amylin prevents the liver from breaking down glycogen to produce glucose, slows the rate at which food is released from the stomach to the small intestine, and increases satiety[1]. Amylin-deficiency is present in both type-1 and type-2 diabetes and it is caused by the loss of β-cells. Previous studies have shown that amylin oligomerize, form amyloid fibers, and lead to the destruction of pancreatic β-cells[2,3]. Amyloid fibers cover much of the pancreas of patients with type-2 diabetes and are thought to be responsible for the disease's progression[3]. The study, "The Pathogenic Mechanism of Diabetes Varies with the Degree of Expression and Oligomerization of Human Amylin in the Pancreatic Islet β cells," published in August 20, 2014 in the *FASEB Journal*, is the first to show that amylin oligomerization (and not necessarily mature amyloid fibers) is associated with the onset and progression of type-1 and type-2 diabetes. Spontaneous diabetes developed in mice that overexpressed amylin but did not have mature amyloid fibers in the pancreas[2].

Transgenic mice having multiple genes for human amylin had elevated fasting blood glucose levels and impaired glucose tolerance at prediabetic and early-stage diabetes when compared to nontransgenic mice. Homozygous mice developed diabetes earlier than hemizygous mice. The more amylin is expressed and produced, the earlier diabetes onset. Amylin levels in the blood and pancreas were high in the pre- and early-stage diabetes, but gradually decreased as more amylin aggregated and more islet cells underwent apoptosis.

Oligomerization increased as insulin and human amylin levels in the pancreas increased. Oligomerization was abundant in the prediabetic stage in mice having the most genes for human amylin. B-cell death by apoptosis occurred the most during the prediabetic stage in homozygous mice because of the high levels of amylin and amylin oligomers. In hemizygous mice, amylin aggregated slowly and the most oligomerization and B-cell death was seen during mid- and late-stage diabetes.

The results of this study suggest that new drugs that prevent amylin oligomers from forming or target the amylin clumps could be developed. Currently, there is a drug that mimics amylin. Pramlintide (Symlin®), a stable synthetic analog of amylin, is taken with insulin to control glucose levels after meals[1]. Unlike human amylin, it has good solubility and does not aggregate[4]. The same antibody used to stain and detect the amylin oligomers also protects the cells from the amylin clumps' cytotoxic effects[5]. A drug that binds specifically to the amylin oligomers or blocks the pathogenic mechanism could prevent further loss of pancreatic β-cells.

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New Cholesterol Guidelines

The new cholesterol guidelines focus on prevention measures through four critical focus areas: cholesterol, lifestyle, obesity, and risk assessment. In this new prevention strategy, a greater focus has been placed on drugs that lower cholesterol to prevent heart disease and stroke. These drugs, known as statins, have recently gained greater focus by the healthcare industry. Originally, when the American Heart Association and American College of Cardiology suggested the revised criteria that healthcare providers should follow, a massive increase in statin prescriptions was projected by many reports. However, experts state that statins are alternative methods for prevention in addition to lifestyle changes[1].

Dr. Donald Lloyd Jones, M.D., an American Heart Association volunteer states, "Physicians now have to shift their thinking away from only looking at cholesterol levels. A patient's overall risk is really the playing field on which people need to understand whether they need statin medication."[2] For instance, a physician can utilize other assessing factors in determining risk such as a patient's age, gender, race, blood pressure, and family history[3].

According to the revised guidelines, statin therapy is recommended for the following groups: patients without cardiovascular disease who are 40 to 75 years old and have a 7.5 percent or higher risk for having a heart attack or stroke within 10 years; patients with a history of a cardiovascular event; patients 21 of age and older who have a very high level of LDL (190 mg/dL or higher); and patients with Type-1 or Type-2 diabetes who are 40 to 75 years old. Nonetheless, therapy is not restricted to just the listed groups. Ultimately, prescribing statins should be deciding based on the physician's judgment after thorough risk assessment[4].

Additionally, with the revision of these guidelines, for patients currently taking statins, there is no longer a target LDL (low-density lipoprotein) cholesterol required[5]. Instead, a patient's risk level is the primary focus with the intensity of the statin treatment. Another change is statins alone can provide the same therapeutic outcome without additional cholesterol-lowering medications. Therefore, doctors are advised not to prescribe additional cholesterol-lowering medications with the statins[6].

Through these revised cholesterol guidelines, it is evident that a greater emphasis is being placed on prevention measures such as healthy living. As stated, though statins have proved to be effective in reducing risk of cardiovascular disease, primary prevention strategies reduce the chances of resorting to statin therapy.

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Atrial Fibrillation (A Fib) Treatment

Atrial Fibrillation (A Fib), a type of irregular heartbeat, is a condition that affects millions of Americans. Anticoagulant therapy is required in these patients to prevent a blood clot from forming, which can otherwise cause a myocardial infarction (MI) or an ischemic stroke in the brain.[1] The mainstay of therapy in treating patients with A Fib has been warfarin (Coumadin©) because it was the only oral anticoagulant therapy available. While warfarin has been used for many years, patients taking this medication face several complications. Warfarin requires frequent blood testing to monitor the therapeutic efficacy of the drug, and patients receiving warfarin have certain dietary restrictions.[2] In recent years, several other oral anticoagulants have been approved by the FDA. These new drugs are more convenient for patients because they do not require blood testing and do not have any dietary restrictions.

One of the newer oral anticoagulants is dabigatran (Pradaxa®). Dabigatran acts as an anticoagulant by inhibiting thrombin, a protein that leads to blood clot formation.[3] Dabigatran was approved by the FDA in 2010 and within three years, approximately 6.2 million prescriptions for dabigatran had been written.[3] Using data from 2010 to 2012, the FDA performed a cohort study, examining approximately 134,000 Medicare patients to compare warfarin and dabigatran.[4] In new users of these drugs, dabigatran was found to have a lower risk of ischemic stroke, bleeding in the brain, and death.[4] Dabigatran showed no advantage over warfarin in preventing an MI.[4] However, it was discovered that dabigatran was associated with an increased risk of gastrointestinal bleeding compared to warfarin.[4] Gastrointestinal bleeding is a serious problem because it can lead to life-threatening bacterial infections or bleeding because there is not a reversal agent available. Furthermore, these patients are taking a drug which inhibits blood clotting, worsening the severity of the bleed.

The risks and benefits of each must be taken into account when comparing the two drugs. Warfarin is cheaper and more information is available on its use, but it requires frequent monitoring and dietary restrictions. Dabigatran is more convenient for the patient and has a lower rate of stroke, but it is significantly more expensive than warfarin and there is not a reversal agent. The new oral anticoagulants that have come out in the past decade may be the main treatment course for patients with A Fib, but additional studies must be done in order to discover any other potentially dangerous side effects.

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The Role of an Ambulatory Care Pharmacist

An ambulatory care facility provides various outpatient medical services including diagnosis, observation, treatment, and rehabilitation. Physician offices, dialysis facilities, cancer centers, imaging centers, urgent care centers, ambulatory surgical centers, endoscopy clinics, public health clinics, and other outpatient clinics are all considered ambulatory care settings.

The Board of Pharmacy Specialties (BPS) defines Ambulatory Care Pharmacy Practice as the provision of integrated, accessible health care services by pharmacists who are accountable for addressing medication needs, developing sustained partnerships with patients, and practicing in the context of family and community[2]. This is accomplished by pharmacists through direct patient care and medication management for ambulatory care patients. Ambulatory care pharmacists foster long-term relationships, coordinate care, advocate for their patients, promote health and wellness, triage and refer, and educate their patients on self-management.

There are four important principles that comprise the practice of ambulatory care pharmacy. The first is comprehensive medication management within integrated health systems, community pharmacies, and clinical practices. Second is the increasing need of qualified and board-certified clinical pharmacists. The third is a growing emphasis on specialty and subspecialty training across ambulatory care practice settings. The last principle comprising the practice is the improvement in health care outcomes for patients in ambulatory care settings. Overall, this pharmaceutical care framework demonstrates the commitment and accountability of pharmacists in optimizing health outcomes[3].

In 2012, eighty-three ambulatory care pharmacists responded to a survey from American Pharmacists Association (APhA) where several different job factors were ranked based on their applicability to ambulatory care pharmacy. Results showed the following as the most prevalent critical job factors: unique practice environment, interaction with patients, applying medical knowledge, continuity of relationships, collaboration with other professionals, helping people, and multiple task handling.

Ambulatory care pharmacists have the opportunity to promote safe medication use and enhance medication therapy for patients with a variety of health conditions such as diabetes, asthma, cardiovascular disease, and renal disease. When ambulatory care pharmacists are directly involved in patient care, physician time is saved, care is more affordable and accessible, and preferential clinical outcomes are achieved. By advancing and promoting ambulatory care practice in the hospital and community setting, pharmacists can help improve patient care, patient health, pharmacoeconomic outcomes, and help advocate the entire profession.

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New Classification of Tramadol as a Controlled Substance

On July 2, 2014, the Drug Enforcement Administration (DEA) published in the Federal Register its final ruling on the classification of tramadol (ULTRAM®) as a schedule IV substance. It was effective August 18, 2014.[1] The procedure for enacting this ruling commenced in 2005 when petitions to enlist tramadol as a controlled substance were received by the DEA. In response the DEA investigated necessary information according to Title 21 United States Code Section 811 (21 U.S.C. 811(b)) and presented its research to Health and Human Services (HHS), which responded with the approving evaluation "Basis for the Recommendation to Schedule Tramadol in Schedule IV of the Controlled Substances Act". The DEA in November 2013 then released a notice of proposed rulemaking: "Schedules of Controlled Substances: Placement of Tramadol Into Schedule IV", which finalized the decision.[2]

The criteria by which the DEA and HHS have researched and approved this motion are dictated by 21 U.S.C. 811(b). These included tramadol's potential for abuse, prevalence of diversion and abuse, similarity of mechanism of action to other controlled substances, and risk to public health. Consequently, most of the eight criteria of 21 U.S.C. 811(b) suggested prominent evidence supporting tramadol's control. Its classification specifically as a schedule IV was then determined by the DEA's Deputy Administrator based on comparisons to already scheduled drugs, namely propoxyphene, a narcotic schedule IV drug.[2]

Tramadol is a centrally-acting, synthetic opioid analgesic that has seen widespread inpatient and outpatient usage since its initial marketing in 1995.[1,3] Supporters of its new classification called tramadol a "loophole drug" because its non-controlled status downplayed its abusability and diversion despite being the only opioid drug on the market.[1] Its potency and convenience should not be underestimated. Tramadol is as effective as schedule II drugs morphine or meperidine for mild to moderate pain. It possesses a primary O-demethylated metabolite that is 2-4 times as potent as the parent drug. However, tramadol has been shown to cause less respiratory depression than morphine in equianalgesic uses and possesses reasonably mild common side effects.[4]

Opponents of the ruling claimed that tramadol's classification would impede pain medication access to the elderly and discourage prescribers due to fear of criminal action. The DEA affirmed that as with other schedule IV drugs, the procedure of dispensing controlled substances is irrelevant to whether they should be controlled, and legal access to tramadol is not hindered by its scheduling. Likewise, prescribers in normal professional operation without clear violation of the Controlled Substance Act (CSA) should not fear any criminal action. The DEA reminds that prescriptions for schedule IV drugs are allowed to be transferred between pharmacies, called-in by telephone, and refilled up to five times in a six month period.[1]

Related industry and dispensaries must update to comply with tramadol's new scheduling. Any place and person possessing the drug is subject to the regulations imposed by the CSA and DEA, which cover the drug in its entirety from manufacturer to patient. Therefore, from July 2 to August 18, a 45-day period has been given to make accommodation.[5]

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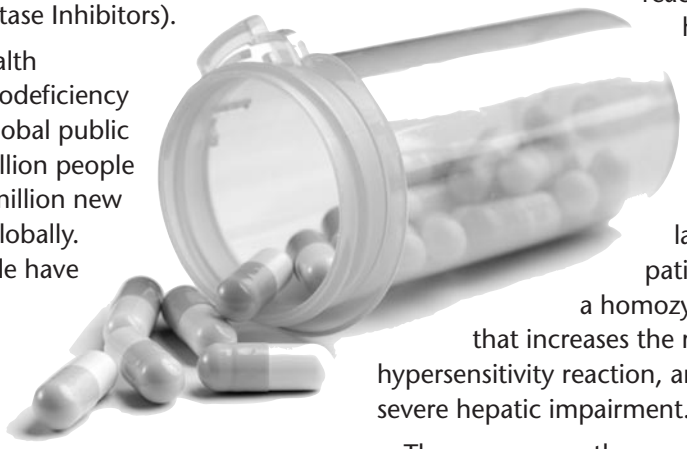
New HIV Combination Therapy Approved by FDA

The US Food and Drug Administration has approved Triumeq®, a new combination pill for the treatment of HIV in adults 18 years and older. Viiv Healthcare announced on August 22nd, 2014 that their new once daily fixed-dose pill will provide triple antiviral drug therapy consisting of dolutegravir 50mg (Integrase Inhibitor), abacavir 600mg and lamivudine 300mg (Nucleoside Reverse Transcriptase Inhibitors).



According to the World Health Organization, Human Immunodeficiency Virus (HIV) remains a major global public health issue with about 35 million people living with the virus and 2.1 million new infected individuals in 2013 globally. Additionally, 1.5 million people have died of HIV-related causes in 2013. It is estimated that 1.1 million Americans are living with HIV, whilst only 33% are taking the medications they need.

In August 2013, dolutegravir (Tivicay®) was approved for use in conjunction with other HIV medications. It works by blocking integrase, which prevents HIV replication in the body and reduces the amount of the virus found in the blood. Triumeq® is the first dolutegravir-based combination therapy and is the only single-tablet regimen that does not include tenofovir, a drug shown to increase the risk of kidney and bone toxicity in the aging HIV population. The other two drugs included in Triumeq® work by blocking reverse transcriptase, an enzyme necessary for replication of the virus into host DNA. In order to make new RNA copies, RNA must be converted into cDNA and then integrated into a host chromosome. Blockage of these two enzymes reduces viral replication and also prevents further infection of cells.

One clinical trial carried out by Viiv included a 96 week phase 3 trial that compared outcomes with treatment-naïve adults taking Triumeq® and those taking the most commonly prescribed single-pill regimen, Atripla® (efavirenz/emtricitabine/tenofovir). Results showed that 80% of patients taking the Triumeq® regimen achieved virological suppression of the virus (HIV-1 RNA <50 copies/mL), compared to 72% of individuals on Atripla®. In addition, there was a higher rate of discontinuation of Atripla® due to patient adverse reactions when compared to Triumeq®. The most common side effects seen in patients on Triumeq® include insomnia, headache, and fatigue. Black Box Warnings for Triumeq® include risk of hypersensitivity reactions, lactic acidosis, severe hepatomegaly, and exacerbations of Hepatitis B. Contraindications include patients who have had previous hypersensitivity to abacavir, lamivudine, or dolutegravir, patients who have a presence of a homozygous HLA-B*5701 allele as that increases the risk of abacavir-induced hypersensitivity reaction, and patients with moderate or severe hepatic impairment.

There are currently no reports on how the price of Triumeq® will compare to current therapies available, but some suggest that if Viiv Healthcare prices Triumeq® according to the generic status of abacavir and lamivudine it should be less expensive than other single-tablet regimens currently prescribed.

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