

APRIL 2015

FDA Approves First Biosimilar Product

The Food and Drug Administration (FDA) has approved the first biosimilar product in the United States. Filgrastim-sndz (Zarxio™; Sandoz) was approved as a biosimilar to filgrastim (Neupogen®; Amgen), which was originally approved by the FDA in 1991. Like Neupogen, Zarxio is indicated in patients with cancer receiving myelosuppressive chemotherapy, patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, patients with cancer undergoing bone marrow transplantation, patients undergoing autologous peripheral blood progenitor cell collection and therapy, and patients with severe chronic neutropenia. It is important to note that Zarxio has been approved as biosimilar to the reference product (Neupogen), not as interchangeable.

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of the Affordable Care Act (ACA) and signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product, called the “reference product.” A biosimilar product is approved based on evidence that it is “highly similar” to the reference product, demonstrating that it has no clinically meaningful differences in safety and effectiveness from the reference product. A biosimilar product has the same mechanism of action, route of administration, dosage forms and strengths as the reference product. Also, a biosimilar product is only approved for the same indications and conditions of use as the reference product. Under the BPCI Act, a biological product that has been approved as “interchangeable” is biosimilar to the reference product and may be substituted for the reference product by a pharmacist without the intervention of the prescriber; whereas a biosimilar product that is not interchangeable cannot be substituted without prescriber intervention. Interchangeability in the biosimilar space is not expected in the near future. Furthermore, state-level laws impact the decision to allow substitutions.

The FDA expects to approve more biosimilars in the future which could lead to wider treatment options for patients, greater competition in the marketplace, and ultimately to less expensive alternatives. The agency has established the Purple Book, which lists biological products, including any biosimilar and interchangeable biological products. In addition, the FDA plans to issue guidance on the naming of biosimilar products. Currently, “filgrastim-sndz” is a placeholder nonproprietary name for Zarxio. Launch of Zarxio is pending litigation with Amgen.

Updated Guidelines for ART in Pediatrics with HIV Infection

The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy (ART) and Medical Management of HIV-Infected Children released updated Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. These guidelines address the use of combination antiretroviral therapy (cART) for HIV-infected infants, children, and adolescents. The guidelines include updated recommendations for when to initiate therapy in antiretroviral (ARV)-naive HIV-infected children, including age-specific CD4 values. The revised guidelines now include stratification for the urgency for initiation of cART. Urgent initiation is recommended in all children younger than 12 months. It is also recommended in children ages 12 months and older with Centers for Disease Control and Prevention (CDC) Stage 3-defining opportunistic illnesses or Stage 3 CD4 counts,

Drug Information Highlights

- Merck is voluntarily discontinuing the distribution of the PegIntron® Redipen® (peginterferon alfa-2b) in the U.S. The current inventory of the product is expected to be exhausted around July 2015. Merck states this decision is not based on safety or efficacy, rather due to changes in HCV treatment practices and reduced demand for the product. Merck will continue to distribute PegIntron vials in the U.S.
- Postmarketing cases of symptomatic bradycardia, including one fatal cardiac arrest and cases requiring pacemaker insertion, have been reported in patients concurrently taking amiodarone with either ledipasvir/sofosbuvir (Harvoni™) or sofosbuvir (Sovaldi®) in combination with another direct-acting antivirals (DAA). Coadministration of amiodarone with either ledipasvir/sofosbuvir or sofosbuvir in combination with another DAA is not recommended.
- The FDA is cautioning that the benefit and safety of prescription testosterone products have not been established for the treatment of low testosterone levels due to aging. These products are approved only for men who have low testosterone levels caused by certain medical conditions. The labels of all prescription testosterone products will clarify the approved uses of these medications. The FDA is also requiring product labels to include a warning of a possible increased risk of heart attacks and strokes in patients taking testosterone.
- The FDA has warned that varenicline (Chantix®; Pfizer) can alter the way people react to alcohol. Patients may experience increased intoxicating effects of alcohol, which can be associated with aggressive behavior and/or amnesia. In addition, rare accounts of seizures have been reported in patients treated with varenicline, including individuals with no history of seizures or with a seizure disorder that had been well-controlled. The Warnings section of this smoking cessation drug label will also include data from a study that found no increased risk of neuropsychiatric side effects on mood, behavior, or thinking while taking the drug; however, there were limitations to the studies and not all possible neuropsychiatric side effects were examined.
- All multidose diabetic pen devices now require labeling stating “For single patient use only”

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both of which classify the illness as acquired immunodeficiency syndrome (AIDS). The updated guidelines add a number of agents to the list of treatment options for initial cART for treatment-naïve children:

- Integrase strand transfer inhibitor (ISTI)-based regimens in combination with two nucleoside analogue reverse transcriptase inhibitors (NRTIs)
- Raltegravir in children ages 2 years and older
- Dolutegravir in children ages 12 years and older
- Ritonavir-boosted atazanavir as an alternative protease inhibitor in children ages 3 months through 5 years
- Zidovudine plus lamivudine or emtricitabine is now an alternative combination for adolescents older than 13 years

The updated guidelines include a new section on the use of cART in neonates to address specific concerns in this patient population, including dosing and safety of individual ARV drugs in term and pre-term infants. Throughout the guidelines, drug information specific to the pediatric population has been updated when relevant.

CTAF Final Report for Combination Hepatitis C Virus Therapy

The California Technology Assessment Forum (CTAF) reviews evidence reports and provides a public venue to discuss the evidence on the effectiveness and value of health care services. CTAF attempts to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care. On December 18, 2014, CTAF held a public meeting to discuss the comparative clinical effectiveness and value of new interferon-free combinations of direct-acting antiviral (DAA) drugs for the treatment of chronic hepatitis C virus (HCV) genotype 1. The review included four all-oral, DAA combination therapies: simeprevir (Olysio®) + sofosbuvir (Sovaldi), ledipasvir/sofosbuvir (Harvoni), daclatasvir (investigational) + sofosbuvir, and paritaprevir/ritonavir/ombitasvir + dasabuvir (Viekira Pak™) with ribavirin, as well as three single-DAA regimens: simeprevir + pegylated interferon-alfa + ribavirin, sofosbuvir + ribavirin, and sofosbuvir + pegylated interferon-alfa + ribavirin. After a complete evaluation of the available clinical data, the panel concluded that there was sufficient evidence to demonstrate that multiple-DAA therapy is clinically superior to single-DAA therapy or pegylated interferon-alfa + ribavirin alone but that there was insufficient evidence to distinguish clinical effectiveness between the multiple-DAA regimens.

In addition, data from the Institute for Clinical and Economic Review (ICER) cost-effectiveness analysis of ledipasvir/sofosbuvir regimens was reviewed. All panel members voted that ledipasvir/sofosbuvir represents either a reasonable or high care value. However, given concerns of the potential budget impact, ten of 12 panelists voted that ledipasvir/sofosbuvir therapy represents an overall low value to the health care system. The roundtable participants discussed the benefits and potential health impact of HCV treatment given the simplified dosing regimens and greater safety of new agents. It was noted that due to both the high costs and the need to identify and treat those most in need of care, it may be required to prioritize treatment for patients with more advanced liver disease and those at high risk of infecting others.

Harvoni for Hepatitis C in HCV/HIV Co-infected patients

Ledipasvir/sofosbuvir (Harvoni; Gilead) is a fixed-dose combination of an HCV NS5A inhibitor and an HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of adults with chronic HCV genotype 1 infection. The ION-4 study demonstrated high HCV cure rates with ledipasvir/sofosbuvir treatment in the most difficult-to-treat patients, including individuals with cirrhosis, those who failed previous HCV treatment, and those co-infected with HIV. This 12-week, phase 3, open-label study evaluated safety and efficacy of ledipasvir/sofosbuvir in 335 patients with chronic HCV genotypes 1 or 4 and HIV co-infection. Subgroups included patients with genotypes 1a (75%), 1b (23%), or 4 (2%); HCV treatment-naïve (45%) or treatment-experienced (55%). In addition, 20% of patients had compensated cirrhosis. Overall, sustained virologic response 12 weeks post treatment (SVR12) was achieved in 96% of participants. SVR rate did not differ significantly based on prior HCV treatment, presence of cirrhosis, or HIV ART regimen. Ledipasvir/sofosbuvir is currently only indicated for use in adults with HCV genotype 1.

to be affixed to the pen device and pen carton, and included in the prescribing information and patient Medication Guide. The FDA is requiring the additional labeling in an effort to reduce the spread of serious infections, such as HIV and hepatitis, through sharing of pen devices intended for single patient use only.

- Asenapine (Saphris®; Forest) has received an additional indication as monotherapy for the acute treatment of mania or mixed episodes associated with bipolar I disorder in patients 10 to 17 years of age. Asenapine is already indicated for schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder in adults as monotherapy or adjunctive therapy. A 2.5 mg sublingual (SL) tablet for use in pediatric patients will be available in addition to the currently available 5 mg and 10 mg SL tablets.
- An oral granule formulation of ivacaftor (Kalydeco®; Vertex) has been approved with an expanded indication to treat cystic fibrosis (CF) in patients 2 years and older who have a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H mutation in the CF transmembrane conductance regulator gene. Ivacaftor was previously approved only for patients 6 years and older with these gene mutations and available as a 150 mg tablet. The new oral granule formulation is available in 50 mg and 75 mg packets that can be mixed in liquids and soft food for pediatric patients who are unable to swallow a tablet.

Pipeline News: Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- **April 30, 2015:** Breo® Ellipta™; fluticasone furoate/vilanterol; inhaled corticosteroid and long-acting beta-2 agonist; asthma; GlaxoSmithKline/Theravance.
- **April 30, 2015:** Tuzistra™ XR; CCP-01; oral cough and cold preparation; Tris/Vernalis.
- **2nd Quarter 2015:** cariprazine, oral dopamine receptor partial agonist; manic/mixed treatment of bipolar disorder, schizophrenia; Gedeon Richter USA/Actavis.
- **2nd Quarter 2015:** MuDelta; eluxadolone; oral Mu and Delta opioid receptor agonist; diarrhea predominant irritable bowel syndrome (IBS-D); Actavis.
- **May 27, 2015:** Xifaxan®; rifaximin; oral antibacterial; IBS-D; Salix.



Perspectives on Reasons for Psychiatric Medication Non-Adherence

The World Health Organization has reported the ratio of medication adherence of approximately 50% in individuals with chronic diseases. Medication adherence is particularly important in patients with a psychiatric illness, and non-adherence can be linked to hospitalization in 20% to 25% of cases. To evaluate factors resulting in medication nonadherence within six months prior to admission, 203 members suffering from various psychiatric diagnoses, including schizophrenia/schizoaffective disorder, bipolar disorder, depression, and other psychiatric diagnoses, were asked to fill out a standardized form upon discharge from hospital psychiatry service. Items documented were attendance to follow-up appointments within six months before admission; and reasons of medication nonadherence (not willing to use medication, not accepting the disease, being disturbed by side effects, feeling well, not knowing how long the medication would be taken, being unaware that the medication should be taken regularly, and other reasons) were examined. Those who self-reported not taking any medicine for at least one week during the six-month term before the study were regarded as medication nonadherent.

This retrospective analysis revealed 104 (51.2%) of the patients took their medicines regularly during the six months before admission, while 99 (48.8%) patients experienced medication nonadherence. Medication nonadherence was significantly higher in the bipolar disorder group when compared to other diagnostic groups. Not willing to use medication, not accepting the disease, and disturbed by side effects were the leading causes of nonadherence in those with bipolar disorder. It was observed that lack of insight was the major factor in those having bipolar disorder and schizophrenia/schizoaffective disorder. Factors such as age, gender, marital status, level of education, smoking, living with others, and place of residence had no significant effect on medication nonadherence; while irregular follow-up attendance and diagnosis had a significant impact on medication nonadherence. The results obtained in this study and in previous studies documented in the literature suggest that medication adherence and attendance to follow-up appointments contribute to patient–physician relations and improved health outcomes.

Translocator Protein Density and Major Depression

A link between individuals suffering from major depressive episodes (MDE) and brain inflammation was reported in a recent study published in the Journal of the American Medical Association Psychiatry. Previous studies have attempted to identify markers of inflammation in the periphery, but this study demonstrated evidence of neuroinflammation during an acute episode of depression.

This case-control study, conducted over a 45-month period, evaluated positron emission tomography (PET) scans on 20 participants with a MDE secondary to major depressive disorder (MDD) in comparison to results from 20 age-matched healthy control participants. The PET scans, which utilized new generation radiotracers, help to quantify the extent to which expression of the translocator protein (TSPO) is increased in active inflammation. Study participants, ranging in age from 18 to 72 years, were considered to be in good health and were all nonsmokers. Patients with MDE were administered the 17-question Hamilton Depression Rating Scale (HDRS) at the time of enrollment and on the day the PET scan was performed. To be enrolled in the study, a minimum HDRS score of 17 was required and participants needed to be medication-free for a minimum of six weeks before the PET scan. Results demonstrated a significant elevation of TSPO in participants with depression, indicating brain inflammation. The highest TSPO levels were found among patients with the most severe depression.

The results of this study have important implications for identifying the complete pathology of a MDE and potential corresponding pharmacological treatments. Further research is needed in populations with varying degrees of severity of a MDE. The importance of discovering new treatment targets is ever increasing as a significant majority of individuals treated with an antidepressant do not respond to currently available medications.

Benzodiazepine Use and Risk of Alzheimer's disease

Serious mental illness puts patients at high risk for increased morbidity and mortality due to obesity-related conditions. The STRIDE weight loss and lifestyle intervention study was a randomized, controlled trial published in the American Journal of Psychiatry that evaluated the impact of lifestyle modification programs aimed at reduced weight and cardiometabolic risks in individuals with serious mental illnesses. The study enrolled 200 participants at least 18 years of age, who had been taking antipsychotic medications for at least 30 days and had a baseline body mass index (BMI) of 27 or greater.

During the initial six months, the intervention group attended weekly two-hour group meetings, which included 20 minutes of physical activity. Participants kept daily records of their meals, calories, exercise, and sleep. Participants were encouraged to self-monitor, create personalized plans, reduce portion size, increase physical activity and consumption of fruits and vegetables, manage high risk eating situations, and address effects of mental health on their change efforts. During the six month maintenance phase, monthly group sessions focused on maintaining weight loss. Group sessions were supplemented with monthly individual phone calls with the group leaders.

Ninety-one percent of participants completed the initial six months and 85% completed the full 12 months of the study. The intervention group lost 4.4 kg more weight at six months and 2.6 kg more at 12 months than the control group. Intervention participants were more likely to achieve at least a 5% weight loss from baseline (40% versus 17%) and were more than twice as likely to have normal fasting blood glucose levels at twelve months. Changes in systolic and diastolic blood pressures in either group were not clinically significant. A direct correlation was found between the number of food and/or sleep logs kept plus meeting attendance and weight loss. The rate of hospitalization for medical reasons was significantly lower for the intervention group (6.7% versus 18%; $p=0.01$). There was no difference in the rate of hospitalization due to psychiatric reasons.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
avibactam/ceftazidime	Avycaz™	Avibactam/ceftazidime (Avycaz), a combination product containing a previously approved cephalosporin and a new beta-lactamase inhibitor, was FDA approved for the treatment of the following infections in adults caused by designated susceptible microorganisms: complicated intra-abdominal infections (cIAI) in combination with metronidazole and complicated urinary tract infections (cUTI), including pyelonephritis. It should be reserved for patients who have limited or no other treatment options. The product is available in single-use vials containing 2 grams of ceftazidime and 0.5 grams of avibactam (2.5 grams total). Patients with normal renal function are dosed 2.5 grams every eight hours, intravenously (IV) over two hours. Recommended treatment durations are five to 14 days for cIAI and seven to 14 days for cUTI including pyelonephritis.	Cerexa	FDA NDA approval 2/25/2015
insulin glargine recombinant	Toujeo®	Insulin glargine 300 U/mL (Toujeo), a long-acting human insulin analog, is indicated to improve glycemic control in adults with diabetes mellitus. It is not recommended for the treatment of diabetic ketoacidosis and is contraindicated during hypoglycemic episodes. Insulin glargine 300 U/mL is administered subcutaneously (SC) once daily, at the same time each day. It is available in a 1.5 mL disposable Solostar® prefilled pen. The dose will vary depending on patients' type of diabetes, blood glucose monitoring results, and glycemic control goals. Insulin glargine 100 U/mL (Lantus®) continues to be available for SC once daily dosing in vials and Solostar pens.	Sanofi	FDA NDA approval 2/25/2015
levetiracetam extended-release	Elepsia™ XR	The FDA has approved levetiracetam extended-release (ER) tablets (Elepsia XR) for adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older with epilepsy. Elepsia XR will be available as 1,000 mg and 1,500 mg tablets. Treatment should be initiated with a dose of 1,000 mg once daily and can be increased in increments of 1,000 mg every two weeks, not to exceed a maximum daily dose of 3,000 mg. UCB Pharma's Keppra XR® (levetiracetam ER) is approved as 500 mg and 750 mg tablets for the same indication and dosing regimen as Elepsia XR.	Sun Pharma	FDA NDA approval 3/02/2015
isavuconazonium sulfate	Cresemba®	Isavuconazonium sulfate (Cresemba), an azole antifungal, has received approval for the treatment of invasive aspergillosis and invasive mucormycosis in adults. It is available as 186 mg oral capsules or for injection in 372 mg single-dose vials. Following six loading doses (372 mg every eight hours via oral or IV administration), isavuconazonium 372 mg should be administered once daily (oral or IV) starting 12 to 24 hours after the last loading dose. Coadministration with strong CYP3A4 inhibitors and inducers is contraindicated. Serious hepatic reactions have been reported.	Astellas	FDA NDA approval 3/06/2015
dinutuximab	Unituxin™	The FDA has approved the first therapy, dinutuximab (Unituxin), in combination with granulocyte-macrophage colony-stimulating factor, interleukin-2, and 13-cis-retinoic acid, for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy. Dinutuximab is a GD2-binding monoclonal antibody that was granted priority review and orphan product designation. It is available as 17.5 mg/5 mL in single-use vials and is dosed 17.5 mg/m ² /day IV over 10 to 20 hours for four consecutive days for up to five cycles. Dinutuximab carries boxed warnings for life-threatening infusion reactions and painful neuropathy requiring IV opioid use before, during, and for two hours after the infusion.	United Therapeutics	FDA BLA priority approval 3/10/2015
cholic acid	Cholbam®	Cholic acid (Cholbam) is the first drug to be FDA approved for the treatment of rare bile acid synthesis disorders; indicated in patients as young as three weeks old for the treatment of bile acid synthesis disorders that are due to single enzyme defects (SEDs) and for adjunctive treatment of peroxisomal disorders (PDs), including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption. Safety and efficacy of cholic acid on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs have not been established. Cholbam will be available as 50 mg and 250 mg capsules. The recommended dosage is 10 to 15 mg/kg once or twice daily. Warnings include exacerbation of liver impairment.	Asklepiion	FDA NDA Priority approval 3/17/2015

References

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