

JANUARY 2015

Hot Topic: Hepatitis C Spotlight

The Food and Drug Administration (FDA) approved AbbVie's ombitasvir, paritaprevir, and ritonavir fixed-dose combination tablets co-packaged with dasabuvir tablets (Viekira Pak™), for the treatment of patients with chronic hepatitis C virus (HCV) genotype (GT) 1 infection, including patients with cirrhosis. This breakthrough therapy contains three direct-acting antivirals (DAAs): ombitasvir, a NS5A inhibitor; paritaprevir, a NS3/4A protease inhibitor; and dasabuvir, a non-nucleoside NS5B polymerase inhibitor. Each DAA has a distinct mechanism of action and resistance profile allowing for multiple steps in the HCV lifecycle to be targeted. Viekira Pak also contains ritonavir, a CYP3A inhibitor currently used in HIV treatment regimens, which increases blood levels of paritaprevir. Viekira Pak can be prescribed with or without ribavirin (RBV). Please consult the Viekira Pak package insert for warning and precautions for its use.

FDA approval of Viekira Pak for treatment of chronic HCV infection was supported by six pivotal phase 3 trials. For patients with GT1a and no cirrhosis a sustained virologic response (SVR) was reported in at least 96% of patients after 12 weeks of Viekira Pak + RBV therapy, regardless of prior treatment. For patients with GT1a and cirrhosis, a longer duration of 24 weeks with Viekira Pak + RBV was beneficial and demonstrated SVR of 95%. SVR of 100% was reported for patients with GT1b with or without cirrhosis after 12 weeks of therapy. The high cure rate of GT1b virus was seen in cirrhotic patients on RBV-containing therapy; and in non-cirrhotic patients regardless of RBV use. The most common adverse events reported with Viekira Pak were nausea, pruritus, and insomnia. Fatigue was also commonly reported when combined with RBV.

The approved dosage is two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal. The weight-based RBV dose is taken twice daily. Recommended regimens include:

- Genotype 1a without cirrhosis: Viekira Pak + RBV for 12 weeks
- Genotype 1a with cirrhosis: Viekira Pak + RBV for 24 weeks; 12 week duration may be considered for some patients based on prior treatment history
- Genotype 1b, without cirrhosis: Viekira Pak for 12 weeks
- Genotype 1b, with cirrhosis: Viekira Pak + RBV for 12 weeks

The recommended treatment in post liver transplant patients with GT1a or GT1b is Viekira Pak + RBV for 24 weeks. Interim results of an ongoing trial in this population show SVR of 97%. Also, interim results of a study in HCV/HIV-1 co-infected patients demonstrate SVR of 93.5% and 90.5%, with 12 and 24 weeks of Viekira Pak + RBV, respectively. Recommended treatment regimens are similar for co-infected and non-co-infected patients. Administration of HIV antiviral agents that contain ritonavir are not recommended during HCV treatment with Viekira Pak.

Viekira Pak is the fourth FDA approved DAA product used as part of an all-oral DAA regimen to treat chronic HCV GT1 infection. Other oral DAAs include ledipasvir/sofosbuvir (Harvoni®; Gilead), simeprevir (Olysio®; Janssen), and sofosbuvir (Sovaldi®; Gilead). Each all-oral DAA regimen is associated with SVR above 90% with 12 and 24 weeks of therapy; however a total of eight weeks may be considered for ledipasvir/sofosbuvir for certain non-cirrhotic patients. Baseline HCV polymorphism is not a concern with Viekira Pak use,

Drug Information Highlights

- In December 2014, the CDC reported that influenza A (H3N2) viruses have been reported most frequently during the current 2014-2015 influenza season. Historically, a predominance of H3N2 virus has been associated with higher rates of hospitalization and increased mortality, particularly among the elderly, very young children, and those with certain chronic illnesses, as compared to seasons when H1N1 viruses dominated. In addition, surveillance data has identified that 67.4% of the H3N2 viruses collected and analyzed between since October 1, 2014 differed antigenically, or drifted, from the H3N2 virus contained in the vaccine. Although, this may lead to decreased vaccine effectiveness, the vaccine may provide some protection against drifted viruses and may reduce the likelihood of hospitalization and death. The CDC stresses the importance of antiviral drugs such as oseltamivir (Tamiflu®; Genentech) and zanamivir (Relenza®; GlaxoSmithKline) when indicated as adjunct to vaccination for the treatment and prevention of influenza, as these agents have demonstrated benefit in reducing duration and severity of influenza infection. Individuals experiencing influenza-like symptoms who are at high risk for influenza complications should be promptly evaluated for the need for influenza antiviral treatment. The CDC maintains that all patients six months of age and older should be vaccinated against influenza.
- The FDA has issued a safety alert regarding the first confirmed case of death due to progressive multifocal leukoencephalopathy (PML) associated with dimethyl fumarate (Tecfidera®; Biogen), an oral agent used as first-line treatment of relapsing forms of multiple sclerosis (MS). PML, a rare and serious brain infection that can lead to severe disability or death, is caused by the John Cunningham (JC) virus, which is common and harmless in most individuals, but can lead to PML in those who are immunocompromised. PML occurred in a patient who had been taking dimethyl fumarate for over four years. The patient was not taking other drugs that affect the immune system or are thought to be associated with PML. The patient had experienced prolonged lymphopenia, a risk factor for PML. The patient died due to complications of pneumonia. Incidence of PML have been previously reported in patients

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unlike simeprevir combined with peginterferon alfa and RBV in patients with HCV GT1a.

Guidance for hepatitis C therapy continues to evolve as new antiviral agents become available. In December, 2014 the AASLD American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) revised sections of their Treatment of HCV Infection guidelines, The Initial, Retreatment, Monitoring, and Unique Populations (HIV/HCV Coinfection, Cirrhosis, Post-Liver Transplantation, and Renal Impairment) based on newly available therapies and data. In addition, the California Technology Assessment Forum (CTAF) Panel, an independent committee of medical experts, released a draft report examining the comparative clinical effectiveness and financial impact of the new all-oral direct-acting HCV antiviral regimens developed by Gilead, AbbVie, and Bristol-Myers Squibb. Although, the CTAF final report has not been released, a draft report has been posted for public comment.

Health and Human Service Guidelines for HIV/Hepatitis C Co-Infection

The Department of Health and Human Services (HHS) has updated their Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. This update includes a revised HIV/HCV Co-infection section, with an emphasis on guidance for concomitant use of HCV and antiretroviral therapy (ART) and potential drug interactions. All HIV-infected patients should be screened for HCV infection on an annual basis if at high risk or whenever HCV infection is suspected. Recommendations for initial ART are the same for patients with or without HCV co-infection. Careful consideration should be taken for potential drug-drug interactions and overlapping toxicities with concurrent use of ART and HCV agents. ART should be initiated for most patients with HIV and HCV regardless of CD4 cell count; although in ART-naïve patients with CD4 > 500 cells/mm³, ART may be deferred until HCV treatment is completed. For patients with CD4 < 200 cells/mm³, ART should be started promptly and HCV therapy may be delayed until the patient is stable on ART. ART may slow the progression of liver disease, a benefit that outweighs the concern of drug-induced hepatic injury. However, patients taking older ART agents are at greater risk of hepatotoxicity and may require dosage adjustments, particularly if cirrhosis is present. HHS advises that drug-drug interactions between the newer direct-acting HCV antivirals, simeprevir (Olysio), sofosbuvir (Sovaldi), and ledipasvir/sofosbuvir (Harvoni), and certain ART agents can occur. The newest HCV antiviral ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak), was not available at the time these guidelines were released. Viekira Pak is associated with drug interactions with ART agents. Ritonavir-containing HIV antivirals are not recommended during Viekira Pak therapy. HHS refers clinicians to www.hcvguidelines.org for guidance on diagnosis and treatment of HCV infection.

Center for Disease Control and Prevention Guidance on HIV Prevention

The Centers for Disease Control and Prevention (CDC) released new guidelines for HIV Prevention with Adults and Adolescents with HIV in the U.S as an update to their 2003 Recommendations for Incorporating HIV Prevention into the Medical Care of Persons Living with HIV guidelines. The new guidelines focus on prevention of new HIV infections, increase proportion of persons with HIV who are aware of their infection, prevention of HIV-related illness and death, and reduction of HIV-related health disparities. Highlights include creation of a multidisciplinary partnership between the patient and clinical and nonclinical professionals, prompt linkage of newly diagnosed persons to HIV medical care and support of long-term retention in care and ART adherence, support of safer sexual and drug-abuse behaviors, screening of sexually transmitted diseases in persons with HIV, provision of contraceptive services and reproductive health counseling to HIV+ women and men who are of reproductive age, and increasing awareness of preexposure prophylaxis (PrEP) or nonoccupational postexposure prophylaxis (nPEP).

FDAs Releases Final Rule on Pregnancy and Lactation Labeling

The FDA published a final rule requiring labeling changes for prescription drugs and biological agents regarding their use during pregnancy and lactation. The FDA states that the current letter categories, A, B, C, D and X, can be misinterpreted as a grading system which can lead to an over-simplified view of the product risks. The new labeling will include three subsections: Pregnancy, Lactation, and Females and Males of Reproductive Potential. The Pregnancy and Lactation subsections will be further divided with subheadings of Risk Summary, Clinical Considerations, and Data. The new subsections will provide detailed explanations of the potential risks and benefits for the mother, fetus, and breastfeeding child to aid in prescribing and counseling decisions. The new format will be required for all newly approved drug and biological applications as of June 30, 2015, and will be phased in for existing products. Draft guidance is available by the FDA to help industry meet the terms of the new labeling requirement.

while on oral fingolimod (Gilenya®; Novartis) or intravenously administered natalizumab (Tysabri®; Biogen).

- Aripiprazole (Abilify®; Otsuka) oral formulations carry a new indication for the treatment of Tourette's Disorder in patients aged six to 18 years of age. The recommended dosage range for Tourette's Disorder is 5-20 mg/day. Oral formulations are also indicated for use in the management of schizophrenia, with bipolar I, Autistic Disorder, and Major Depressive Disorder.
- Beclomethasone dipropionate (Qnasl®; Teva) is now indicated for the treatment of the nasal symptoms associated with seasonal and perennial allergic rhinitis in patients four years of age and older. This agent was previously also approved for patients 12 years and older. In conjunction with the new age indication, a 40 mcg nasal spray has also received FDA approval.

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

- Jan 9: Rytary™; carbidopa/levodopa; Parkinson's disease; Impax.
- Jan 24: Triferic™; Ferric pyrophosphate; Anemia in end stage renal disease; Rockwell
- 1st Quarter 2015: Cosentyx™; secukinumab; psoriatic arthritis; Novartis
- 1st Quarter 2015: Empagliflozin/linagliptin; Type 2 diabetes; Boehringer Ingelheim/Eli Lilly.



Antidepressants and Cognitive Decline in Older Adults with a History of Major Depression

Older patients with Major Depressive Disorder (MDD) often present with cognitive impairment to a greater extent than patients of similar age and education without a history of MDD. Evidence suggests that MDD may contribute to cognitive impairment and may be a risk factor for development of dementia. A study performed at the University of Pittsburgh examined MDD as a possible modifiable risk factor for dementia and studied the relationship between antidepressant use and cognitive performance. The study followed 185 older adults with a history of MDD for one to 10 years (mean 4.8 years). Subjects were assessed yearly for depression, neuropsychological status, medical burden, and medication exposure. Subjects were scored in five areas (delayed memory, attention/processing speed, executive function, verbal ability, and visuospatial ability) with age and education corrected scores. Use of anticholinergic medications was associated with a decline in delayed memory and use of sedative/hypnotic agents resulted in a reduction in visual spatial ability; both results are predictable based on the pharmacology of the medication classes. Use of selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs) were not associated with cognitive decline trends and trends suggested that they may even improve higher executive functioning. Limitations of the study include lack of lifetime depression treatment data and lack of drug administration in a controlled manner. The investigators plan to evaluate data from the long-term PROSPECT study to determine if intensive depression treatment delays, mitigates, or prevents cognitive decline in older adults with a history of MDD.

The Relationship between Syncope, Depression and Antidepressant Use in the Elderly

Syncope is defined as a sudden loss of consciousness associated with the inability to maintain postural tone followed by spontaneous recovery. This medical condition increases with advanced age and results in subsequent hospital admissions and increased morbidity and mortality. To determine the relationship between syncope advanced age, depression, and potential risks of different antidepressants, 7,933 participants age 50 years or older received an in-home assessment by trained social interviewers. During the assessments a computer assisted personal interview tool recorded information from participants about their lifetime and twelve month history of syncopal events, medication utilization, medical history, personal well-being, and general demographics. Initially it was determined that both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) resulted in statistically significant increased in syncopal events, but after controlling for demographic cofounders only TCAs resulted in an increased risk. Other key findings include: older adults (over 75 years) had a higher rate of syncope versus younger adults (50-64 years), patients suffering from depression have higher rates of self-reported syncope, and patients with moderate to severe depression have a higher risk of multiple syncope episodes.

The outcome of this study identified a clear association between depression and syncope. Clinicians should be aware of the risks and understand depression is a potentially modifiable condition in older patients who present with syncope. Careful consideration should be given for various treatment options, risks and benefits of each option, and past treatment response to determine the best treatment option for individual patients.

Benzodiazepine Use and Risk of Alzheimer's disease

Benzodiazepines are widely used to treat agitation, anxiety and insomnia, all of which may also be early signs of Alzheimer's disease in the elderly population. One study sought to examine the total exposure to benzodiazepines and the risk of developing Alzheimer's disease in patients over 66 years of age. The researchers used a case control study design using the large national Quebec health insurance program database, which covers 90% of the elderly population, to access prescription information. They assessed benzodiazepine treatment that was started greater than five years before the diagnosis of Alzheimer's disease and then matched a control group for age and gender.

The results demonstrated that individuals who had taken a benzodiazepine for three months or less had similar risk of developing Alzheimer's disease as those who had never taken a medication from this class. However, an association was found when a benzodiazepine was taken for longer than three months, and those taking a long-acting benzodiazepine were at a greater risk compared to those taking a short-acting agent.

The study showed an association between higher cumulative benzodiazepine doses and a higher risk for developing Alzheimer's disease, but this study does not prove a causal relationship and further research is needed to determine if benzodiazepine use may be a factor in causing dementia or an indication that the disease might already be developing. It is important to keep in mind that benzodiazepines were designed and studied for short-term use and it is necessary to evaluate the risks and benefits for individual patients.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
blinatumomab	Blincyto™	The FDA approved blinatumomab, a CD19-directed CD3 T-cell engager, to treat patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL), an uncommon form of acute lymphoblastic leukemia. One cycle of treatment consists of four weeks of continuous intravenous infusion, followed by a two week treatment-free period. A treatment course consists of up to two cycles of induction followed by three additional cycles for consolidation treatment. For the first cycle, the dose is 9 mcg/day for days 1–7 and 28 mcg/day for days 8–28. For all remaining cycles, the dose is 28 mcg/day for days 1–28. Hospitalization is recommended for the first nine days of the first cycle and the first two days of the second cycle.	Amgen	FDA BLA approval 12/3/2014
ruxolitinib	Jakafi®	Ruxolitinib (Jakafi), an oral kinase inhibitor, is now indicated for the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea. The recommended starting dose of ruxolitinib for the treatment of polycythemia vera is 10 mg twice daily, with dose titrations recommended for safety and efficacy. Ruxolitinib is also indicated for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. Ruxolitinib is available as 5 mg, 10 mg, 15 mg, 20 mg and 25 mg tablets.	Incyte	FDA sNDA approval 12/4/2014
denosumab	Xgeva®	The FDA approved a new indication for denosumab (Xgeva), a RANK ligand inhibitor, for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. The dosage for this indication is 120 mg subcutaneously (SC) every four weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy. Denosumab is also indicated for the treatment of giant cell tumor of the bone and for prevention of skeletal related events in patients with bone metastases from solid tumors.	Amgen	FDA sBLA approval 12/5/2014
finafloxacin	Xtoro™	The FDA approved finafloxacin otic suspension (Xtoro), a quinolone antimicrobial, for the treatment of acute otitis externa (AOE) caused by susceptible strains of <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i> . Four drops should be instilled in the affected ear(s) twice daily for seven days. In patients requiring an otowick, the initial dose can be doubled to eight	Alcon	FDA NDA approval 12/17/2014
olaparib	Lynparza™	The FDA approved olaparib (Lynparza), a oral poly (ADP-ribose) polymerase (PARP) inhibitor, as monotherapy in patients with BCRA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The recommended dose is 400 mg twice daily with treatment continued until disease progression or unacceptable toxicity. Olaparib will be available as 50 mg oral capsules.	AstraZeneca	FDA NDA approval 12/19/2014
liraglutide	Saxenda®	Liraglutide (Saxenda), a GLP-1 receptor agonist, was FDA approved for chronic weight management along with a reduced-calorie diet and physical activity, in adults with a body mass index (BMI) ≥ 30 kg/m ² or a BMI < 27 kg/m ² and a least one weight-related condition such as hypertension, type 2 diabetes, or hyperlipidemia. Saxenda contains the same active ingredient as Victoza®, used to treat type 2 diabetes. The liraglutide dose for weight-loss is 3 mg SC daily, as compared to 1.2 mg or 1.8 mg for diabetes. Saxenda should not be used with other GLP-1 agonists, including Victoza. Precautions for use are similar to Victoza.	Novo Nordisk	FDA NDA approval 12/23/2014
memantine/ donepezil	Namzaric™	The FDA approved the fixed-dose combination of memantine extended-release (ER), a NMDA receptor antagonist, and donepezil, an acetylcholinesterase inhibitor, (Namzaric) for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on memantine and donepezil. The recommended dosage is one capsule daily. Namzaric will be available in two strengths, 28 mg/10 mg (memantine ER/donepezil) and 14 mg/10mg for patients with severe renal impairment. Launch is expected in second quarter 2015.	Actavis/ Adamas	FDA NDA approval 12/23/2014

References

<https://www.magellanmedicaid.com/news/clinicalalerts.asp>
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