Hot Topic: AASLD/IDSA Releases Updated Guidelines for Treatment of Chronic Hepatitis C Infection

On August 11, 2014, the American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) released updated guidelines for the treatment of chronic hepatitis C virus (HCV) infection. The guidelines now include the new section “When and in Whom to Initiate HCV Therapy,” which provides guidance to identify patients with chronic HCV infection in immediate need of treatment and those who can safely wait for drugs in the pipeline to become available. Recognition is given to limitations of workforce and societal resources that may limit the treatment of all patients within a short timeframe. The treatment goal is the reduction in all-cause mortality and liver-related adverse health consequences, including end-stage liver disease and hepatocellular carcinoma, as achieved by sustained virologic response (SVR). When resource limitations exist, therapy initiation should be prioritized to allow treatment for those patients who will derive the most benefit or who will have the most impact on reducing further HCV transmission.

Antiviral therapy is recommended for patients with chronic HCV infection. Prioritization of treatment is recommended as follows:

- The highest priority for treatment due to highest risk of severe complications is given to the following:
  - Patients with advanced fibrosis (Metavir F3) or patients with compensated cirrhosis (Metavir F4) (Class I, Level A) since the risk of developing complications of liver disease, such as hepatic decompensation or hepatocellular carcinoma, is significant and could happen in a relatively short period of time.
  - Liver transplant recipients (Class I, Level B) in whom viral replication was ongoing at the time of transplantation, since allograft infection will occur. Within six months of transplantation histologic features of hepatitis occur in about 75 percent of patients. If left untreated, approximately 30 percent of patients will progress to cirrhosis by the fifth post-operative year. If SVR is achieved prior to transplantation, post-transplant recurrence of HCV infection can be prevented. Treatment of HCV infection post-transplantation also leads to significant improvement in patient and graft survival.
  - Patients with Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations, such as vasculitis (Class I, Level B).
  - Patients with proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis (Class Ia, Level B).

- High priority should be given to patients at high risk of liver-related complications and severe extrahepatic hepatitis C complications, including:
  - Patients with fibrosis (Metavir F2) (Class I, Level B).
  - Patients co-infected with HIV (Class I, Level B), as this contributes to more rapid HCV disease progression, which may be mitigated to some extent by HIV replication control and CD4+ cell count restoration.
  - Patients co-infected with hepatitis B virus (Class Ia, Level C), as this contributes to more rapid HCV disease progression, development of hepatocellular carcinoma.
  - Patients with other coexistent liver disease, such as nonalcoholic steatohepatitis (NASH) (Class Ia, Level C), as this contributes to more rapid HCV disease progression.

Drug Information Highlights

- Vertex Pharmaceuticals announced on August 11, 2014, their plans to discontinue the United States (U.S.) sale and distribution of telaprevir (Incivek®), the HCV NS3/4A protease inhibitor for the treatment of genotype 1 chronic HCV infection in adults with compensated liver disease, used in combination with injectable peginterferon alfa and oral ribavirin. Market withdrawal is to occur by October 16, 2014. This decision was based on the decreasing demand for the drug and availability of alternative therapies. New patients should not be started on telaprevir; however, current therapy with telaprevir should be completed.

- The National Institute for Health and Care Excellence (NICE) has developed preliminary recommendations for use of sofosbuvir (Sovaldi®) for the treatment of HCV infection in England’s National Health Service (NHS). Further review by the Appraisal Committee will take place on September 10, 2014, after which final guidelines will be released. Preliminary recommendations for sofosbuvir in combination with peginterferon and ribavirin are for adults with chronic HCV infection with genotype 1, genotype 3 with cirrhosis, and those without cirrhosis who have had prior HCV treatment. Triple therapy is not recommended for genotypes 4, 5, and 6. Sofosbuvir, in combination with ribavirin alone, is not recommended for genotype 1, 4, 5, or 6. Dual therapy is an option for genotype 2 if the patient is treatment naïve and intolerant to or ineligible for interferon, or has had treatment, regardless of interferon eligibility. Dual therapy is an option for genotype 3 chronic HCV only in adults with cirrhosis.

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

- Sept. 7: Zerenex™; oral ferric citrate; iron-based phosphate binder; hyperphosphatemia; Keryx.
- Sept. 11: Contrave®; oral naltrexone/bupropion; weight loss; Orexigen/Takeda.
- Sept. 15: rectal budesonide foam; distal ulcerative colitis; Salix.
- Sept. 16: Movantik™; once daily oral naloxegol oxalate; opioid-induced constipation; AZ/Nektar.
- Sept. 18: Xtandi®; oral enzalutamide; expanded indication: metastatic castration-resistant prostate cancer in patients who have not received chemotherapy; Astellas.
- Sept. 27: Nepa; oral fixed-dose netupitant/ palonosetron; chemotherapy induced nausea and vomiting; Helsinn/Eisai.

Contact

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Prior to therapy, the degree of liver fibrosis should be assessed using noninvasive testing or liver biopsy; liver biopsy is the diagnostic standard.

Product, Zohydro™ ER by Zogenix, which currently has Schedule II status.

Under federal law (whichever is more stringent), as long as the refill is dispensed prior to April 8, 2015. No change will be made for the hydrocodone-only product, Zohydro™ ER by Zogenix, which currently has Schedule II status.

Hydrocodone combination products (HCP) from Schedule III to Schedule II, which will take effect on October 6, 2014. The DEA cites that hydrocodone has a high potential for abuse, and adding nonnarcotic substances, like acetaminophen, do not lessen its abuse potential. Any prescription for a HCP was issued before October 6, 2014, and which was authorized to be refilled by the prescriber, may be refilled in accordance with state or federal law (whichever is more stringent), as long as the refill is dispensed prior to April 8, 2015. No change will be made for the hydrocodone-only product, Zohydro™ ER by Zogenix, which currently has Schedule II status.

Finally, a reason not to treat is limited life expectancy in HCV infected patients when treatment would not improve symptoms or prognosis. Prior to therapy, the degree of liver fibrosis should be assessed using noninvasive testing or liver biopsy; liver biopsy is the diagnostic standard. When antiviral therapy is deferred for a patient, ongoing assessment is recommended.

Hydrocodone Combination Products Designated as Schedule II Controlled Substances

On August 22, 2014, the U.S. Drug Enforcement Agency (DEA) published the final rule in the Federal Register changing hydrocodone combination products (HCP) from Schedule III to Schedule II, which will take effect on October 6, 2014. The DEA cites that hydrocodone has a high potential for abuse, and adding nonnarcotic substances, like acetaminophen, do not lessen its abuse potential. Any prescription for a HCP that was issued before October 6, 2014, and which was authorized to be refilled by the prescriber, may be refilled in accordance with state or federal law (whichever is more stringent), as long as the refill is dispensed prior to April 8, 2015. No change will be made for the hydrocodone-only product, Zohydro™ ER by Zogenix, which currently has Schedule II status.

CDC Releases 2014-2015 Influenza Season Recommendations

The Center for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) released 2014-2015 recommendations for the prevention and control of seasonal influenza. The 2014-2015 season influenza vaccine contains the same virus strains as those in the 2013-2014 vaccine. Routine annual vaccination is appropriate for those six months of age or older, unless contraindicated. Previously unvaccinated children, aged six months to eight years should receive two doses of the 2014-2015 vaccine. Only one dose is required for children who received at least one dose of the 2013-2014 vaccine or who received a total of at least two doses of seasonal influenza vaccine since July 1, 2010. Live attenuated influenza vaccine (LAIV) is recommended for those ages two to eight years. If LAIV is not immediately available, then inactivated influenza vaccine (IIV) can be used.

Recent FDA Approvals

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>empagliflozin</td>
<td>Jardiance®</td>
<td>The FDA has approved empagliflozin (Jardiance), an oral sodium glucose co-transporter 2 (SGLT2) inhibitor, as an adjunct to diet and exercise to improve glycemic control for adults with type 2 diabetes mellitus. The recommended starting dose is 10 mg daily, taken in the morning. Empagliflozin is available as 10 mg and 25 mg tablets.</td>
<td>Boehringer Ingelheim</td>
<td>FDA NDA approval 08/01/2014</td>
</tr>
<tr>
<td>oritavancin</td>
<td>Orbactiv™</td>
<td>Oritavancin (Orbactiv), a lipoglycoprotein antibacterial agent, was approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) due to specified gram positive bacteria, including methicillin-resistant <em>staphylococcus aureus</em> (MRSA). Oritavancin is given as a single 1,200 mg dose, administered via intravenous infusion over three hours. It is available as a single-use vial containing 400 mg of powder for reconstitution. Oritavancin joins dalbavancin (Dalvance™) and tedizolid (Sivextro™) as the third new antibiotic approved for the treatment of ABSSSI this year.</td>
<td>Medicines Company</td>
<td>FDA NDA approval 08/06/2014</td>
</tr>
<tr>
<td>canagliflozin/metformin</td>
<td>Invokamet™</td>
<td>The FDA has approved canagliflozin/metformin (Invokamet), a SGLT2 inhibitor and metformin combination product, as an adjunct to diet and exercise to improve glycemic control for adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing either metformin or canagliflozin or for patients who are already being treated with both individual components. Invokamet is administered twice daily. Starting doses should be individualized based on the patient’s current regimen; however, the maximum daily dose should not exceed 2,000 mg of metformin or 300 mg of canagliflozin. Invokamet is available as 50 mg/500 mg, 50 mg/1,000 mg, 150 mg/500 mg, and 150 mg/1,000 mg tablets.</td>
<td>Janssen</td>
<td>FDA NDA approval 08/08/2014</td>
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<tr>
<td>suvorexant</td>
<td>Belsomra®</td>
<td>Suvorexant (Belsomra), the first orexin receptor antagonist, was approved for the treatment of insomnia. It is a Schedule IV controlled substance. The recommended starting dose is 10 mg taken within 30 minutes of bedtime with at least seven hours of sleep time remaining. Suvorexant should not be taken more than once per night. The dose may be increased to a maximum of 20 mg once per night. Suvorexant will be available as 5 mg, 10 mg, 15 mg, and 20 mg tablets.</td>
<td>Merck Sharp and Dohme</td>
<td>FDA NDA approval 08/13/2014</td>
</tr>
<tr>
<td>peginterferon beta-1a</td>
<td>Plegridy™</td>
<td>Peginterferon beta-1a (Plegridy) has been approved for the treatment of patients with relapsing forms of multiple sclerosis. The recommended dose is 125 mcg subcutaneously every 14 days; however, the dose should be started at 63 mcg on day 1, 94 mcg on day 15, and 125 mcg on day 29. It will be available as 125 mcg/0.5 mL prefilled pens and prefilled syringes. A starter pack will also be available containing two single-dose prefilled pens or syringes; dose 1 provides 63 mcg, and dose 2 provides 94 mcg.</td>
<td>Biogen</td>
<td>FDA BLA approval 08/15/2014</td>
</tr>
<tr>
<td>apixiban</td>
<td>Eliquis®</td>
<td>The FDA has expanded the indication of apixiban (Eliquis) to include the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as to reduce the risk of recurrent DVT or PE after initial treatment. Apixaban was already approved for DVT prophylaxis following knee or hip replacement surgery, and to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.</td>
<td>Bristol Myers Squibb</td>
<td>FDA sNDA approval 08/19/2014</td>
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<tr>
<td>eliglustat</td>
<td>Cerdelga™</td>
<td>Eliglustat (Cerdelga), a glucosylceramide synthase inhibitor, was approved for the long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs). Eliglustat may not be effective in CYP2D6 ultra-rapid metabolizers since adequate concentrations may not be achieved. It is the first oral enzyme replacement therapy for patients with Gaucher disease. The recommended starting dose is 84 mg twice daily for CYP2D6 EMs or IMs, and 84 mg once enzy me replacement therapy for patients with Gaucher disease. The recommended starting dose is 84 mg twice daily for CYP2D6 EMs or IMs, and 84 mg once every other day for CYP2D6 PMs. It is available as an 84 mg capsule.</td>
<td>Genzyme</td>
<td>FDA NDA approval 08/15/2014</td>
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<tr>
<td>fluticasone furoate</td>
<td>Arnuity™ Elipta®</td>
<td>The inhaled corticosteroid, fluticasone furoate (Arnuity Ellipta) was FDA approved for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. It is not indicated for the relief of acute bronchospasms. The recommended dosage is one inhalation daily of 100 mcg or 200 mcg powder for inhalation.</td>
<td>GlaxoSmithKline</td>
<td>FDA NDA approval 08/20/2014</td>
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<tr>
<td>abacavir/ dolutegravir/ lamivudine</td>
<td>Triumeq®</td>
<td>The FDA approved the fixed-dose combination agent, Triumeq, for the treatment of HIV-1 infection. Triumeq contains the integrase strand transfer inhibitor (INSTI), dolutegravir, and two nucleoside reverse transcriptase inhibitors (NRTIs), abacavir and lamivudine. Boxed warnings include the risk of hypersensitivity reactions, lactic acidosis, severe hepatomegaly, and exacerbations of hepatitis B. Triumeq is dosed once daily. Oral tablets contain abacavir 600 mg, dolutegravir 50 mg, and lamivudine 300 mg.</td>
<td>Viiv</td>
<td>FDA NDA approval 08/22/2014</td>
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<tr>
<td>diclofenac</td>
<td>Zovorex™</td>
<td>The nonsteroidal anti-inflammatory drug (NSAID), diclofenac (Zovorex), has an expanded indication for the management of osteoarthritis (OA) pain. The recommended dosage for OA is 35 mg taken three times daily. Zovorex is already FDA-approved for the treatment of mild to moderate acute pain. It is available as 18 mg and 35 mg submicronized capsules. Zovorex is not interchangeable with other formulations of oral diclofenac.</td>
<td>Iroko</td>
<td>FDA sNDA approval 08/22/2014</td>
</tr>
<tr>
<td>eltrombopag</td>
<td>Promacta®</td>
<td>Eltrombopag (Promacta), a thrombopoietin receptor agonist, has gained approval for the treatment of patients with severe aplastic anemia after an insufficient response to immunosuppressive therapy. The recommended starting dose for this indication is 50 mg once daily. Reduced doses are required with hepatic impairment or East Asian ancestry. Eltrombopag is also indicated for the treatment of chronic immune thrombocytopenia (ITP) or chronic hepatitis C. It is available as 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg oral tablets.</td>
<td>GlaxoSmithKline</td>
<td>FDA sNDA approval 08/22/2014</td>
</tr>
</tbody>
</table>

### References
- aasld.org
- cdc.gov
- medscape.com
- dea.gov
- pubmed.gov