The Pharmacist Activist

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Editorial

Express Scripts

Made the Wrong Formulary Decision that is a Disservice to its Customers

An estimated 3.2 million Americans have chronic hepatitis C virus (HCV) infection. Although many of these individuals are asymptomatic and unlikely to experience serious consequences, many others experience complications such as jaundice, cirrhosis of the liver, and, possibly, liver cancer, and a need for transplantation. Until 2011 the standard treatment of patients with chronic HCV infection was a regimen of peginterferon alfa (administered by injection) and ribavirin for a period of 48 weeks. However, most patients experienced adverse events with these medications and the success rate in achieving a cure (a sustained virologic response [SVR]) was less than 50%.

In 2011, boceprevir (Victrelis) and telaprevir (Incivek) were marketed as the first agents that inhibited an enzyme that is essential for the replication of HCV. Each of these agents was used with peginterferon alfa and ribavirin in regimens that provided significantly higher cure rates in a shorter period of treatment. However, many patients experienced adverse events and/or drug interactions, and the new agents had a short duration of action that necessitated administration several times a day.

In late 2013, simeprevir (Olysio) and sofosbuvir (Sovaldi) were marketed and had important advantages over their predecessors. The combination regimens in which they were included were more effective and could be used for shorter treatment periods, and simeprevir and sofosbuvir were well tolerated and could be administered once a day. Sofosbuvir was the first agent that permitted, for some patients, the use of combination regimens that did not include interferon. It was a "game-changer," and the benefits of the regimens that include it have been so impressive that the marketing of boceprevir and telaprevir is being discontinued.

The $1,000 tablet

Sofosbuvir (Sovaldi – Gilead Sciences) is administered once a day (as part of a combination regimen) and the duration of treatment for most patients is 12 weeks, requiring a total of 84 tablets. The cost in the United States for this number of tablets is $84,000. The cost of the drug has been a "lightning rod" in generating concerns and criticism, although there is universal agreement regarding the benefits of the drug and the increased hope for cures of HCV infection. Express Scripts, the largest pharmacy benefit manager (PBM) in the country, has voiced the strongest criticisms, as well as a determination to force a price war and/or other cost-reduction alternatives, as soon as

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options became available. In the meantime, Express Scripts, and many other PBMs and payers have established restrictions that limit and/or delay the initiation of treatment in certain patients with HCV infection.

Progress continues

In October 2014, Gilead Sciences received FDA approval for a combination formulation (Harvoni) containing sofosbuvir with the new drug ledipasvir. This became the first regimen for the treatment of patients with chronic HCV genotype 1 infection that does not require use with either interferon or ribavirin. The cure rate with the new two-drug combination administered as one tablet a day for 12 weeks is approximately 95%, and shorter treatment regimens (8 weeks) can be used in some patients. The cost of a 12-week (84 tablets) regimen is $94,500. Less than a month later, simeprevir and sofosbuvir were approved for use as the second combination regimen that did not include interferon or ribavirin. However, these two agents are marketed by different companies and the cost of this regimen is much higher.

In December, AbbVie received approval to market Viekira Pak, a regimen for the treatment of patients with chronic HCV infection that includes three new antiviral agents (ombitasvir, paritaprevir, and dasabuvir) with activity against HCV plus ritonavir to inhibit the metabolism and prolong the duration of action of paritaprevir. Ribavirin is added to this regimen for many patients. The cost of a 12-week course of treatment with this regimen (not including ribavirin) is $83,319.

The price war

Almost immediately following the approval of Viekira Pak, Express Scripts announced that it had obtained a significant discount from AbbVie and that Viekira Pak would have preferred status on its formulary for patients with HCV infection. Soon thereafter, CVS, the second largest PBM, announced that it would give preferred status on its formulary to Gilead's products Harvoni and Sovaldi. Other PBMs have subsequently announced their decisions, with most designating Harvoni as their preferred regimen and some enabling ready access to both regimens. Neither the PBMs nor the pharmaceutical companies have disclosed any information regarding the costs or other terms of their "deals," thereby further contributing to the reputation of manipulation and lack of credibility with respect to the prices of drugs. There is no transparency!

How do the regimens compare?

I have included my New Drug Reviews for both Harvoni and Viekira Pak in this issue of *The Pharmacist Activist*. Because Harvoni was approved first, I compared it with simeprevir and sofosbuvir that were available at that time. When Viekira Pak was subsequently approved, Harvoni was the most appropriate product to which to compare it. I gave Harvoni a New Drug Comparison Rating of 5, the highest rating that represents an important advance. I gave Viekira Pak a rating of 2, representing significant disadvantages.

Both regimens are highly effective (i.e., cure rates of 90+%) and, for practical purposes in the absence of direct comparisons, can be considered equally effective. However, with respect to patient safety and convenience of administration, the comparisons clearly favor Harvoni. Many of the patients treated with Viekira Pak should also receive ribavirin that is associated with additional risks and precautions. Hepatic laboratory testing is recommended with the use of Viekira Pak, and the regimen's components interact with numerous other medications. Treatment with the Viekira Pak regimen is more complex (i.e., more products, more doses), and the effectiveness of treatment regimens shorter than 12 weeks has not been demonstrated, whereas treatment with Harvoni for 8 weeks is effective in some patients.

Express Scripts made the wrong decision

Express Scripts has a valid concern regarding the cost of the medications for HCV infection. However, it appears that it has permitted its obsession about cost to preclude an objective evaluation of what is best for its customers. By designating Viekira Pak as having preferred formulary status, it severely restricts access to Harvoni that would be a better choice for many of its customers. Even if "medical exceptions" permit access to Harvoni, the process for being approved for such status is often long and frustrating. Express Scripts made the wrong decision!

Express Scripts has held its own customers hostage by preventing ready access to the best treatment, and has done them a great disservice. Its customers should challenge this decision! Express Scripts wants to be viewed as a leader for initiating the price war. However, leadership must be characterized by sound judgment and decisions, and not by a self-serving agenda.

Daniel A. Hussar

New Drug Review

Ledipasvir/sofosbuvir
(Harvoni – Gilead Sciences)

Antiviral Agent

New Drug Comparison Rating (NDCR) = 5
(important advance)
in a scale of 1 to 5 with 5 being the highest rating

Indication:
Treatment of chronic hepatitis C virus (HCV) genotype 1 infection in adults.

Comparable drugs:
Simeprevir (Olysio), sofosbuvir (Sovaldi), ribavirin.

Advantages:
- Is the first regimen for chronic HCV genotype 1 infection that does not require administration with interferon or ribavirin;
- Is the first combination formulation approved for the treatment of chronic HCV genotype 1 infection;
- Used in shorter treatment regimens (8 weeks) in some patients (treatment-naïve and without cirrhosis).

Disadvantages:
- Labeled indication is more limited (compared with sofosbuvir and ribavirin that have indications that include use in combination regimens for the treatment of HCV genotype 2, 3, and 4 infections, and patients with HCV infection and hepatocellular carcinoma and those with HCV/HIV-1 co-infection).

Most important risks/adverse events:
Concurrent use with other products containing sofosbuvir is not recommended; concurrent use with simeprevir may increase concentrations of both simeprevir and ledipasvir, and concurrent use is not recommended; both ledipasvir and sofosbuvir are substrates of P-glycoprotein (P-gp) and concentrations and action may be reduced by a P-gp inducer (e.g., rifampin, St. John's wort; concurrent use is not recommended); concentration and action of ledipasvir may be reduced by drugs that increase gastric pH (should be administered 4 hours apart from an antacid; should be administered simultaneously with or 12 hours apart from an H2-receptor antagonist in a dosage that does not exceed a dose comparable to famotidine 40 mg twice daily; can be administered under fasted conditions simultaneously with a proton pump inhibitor in a dosage that does not exceed a dose comparable to omeprazole 20 mg); may increase the action of digoxin, rosuvastatin, and tenofovir (coadministration with rosuvastatin is not recommended).

Most common adverse events (incidence with a 12-week course of treatment):
Headache (14%), fatigue (13%), nausea (7%).

Usual dosage:
One tablet (90 mg ledipasvir/400 mg sofosbuvir) once a day with or without food, for 12 weeks in treatment-naïve patients with or without cirrhosis and in treatment-experienced patients without cirrhosis, and for 24 weeks in treatment-experienced patients with cirrhosis; treatment for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

Products:
Film-coated tablets – 90 mg ledipasvir and 400 mg sofosbuvir.

Comments:
The marketing of sofosbuvir, a nucleotide analog inhibitor of HCV NS5B polymerase, and simeprevir, an inhibitor of HCV NS3/4A protease, in late 2013 represented important progress in the treatment of chronic HCV infection. However, although sofosbuvir was effective in some patients in combination antiviral regimens that did not include interferon, the recommended combination regimens containing sofosbuvir or simeprevir also included ribavirin and, in most patients, interferon. Ledipasvir is an inhibitor of the HCV NS5A protein that is required for viral replication. It is not available as a single agent but is supplied with sofosbuvir in a combination formulation that represents the first regimen for chronic HCV genotype 1 infection that does not require administration with either interferon or ribavirin. This combination formulation provides the advantage of convenience of a highly-effective oral regimen that involves the administration of only one tablet once a day.

The effectiveness of ledipasvir/sofosbuvir was demonstrated in three studies involving more than 1,500 patients, with a primary endpoint of a sustained virologic response (SVR; virus no longer detected in the blood at least 12 weeks after finishing treatment). Participants were treated with ledipasvir/sofosbuvir with or without ribavirin. In treatment-naïve patients, 94% of those who received the new combination for 8 weeks and 96% of those who received it for 12 weeks achieved a SVR. In treatment-experienced patients with and without cirrhosis, 94% of those treated for 12 weeks and 99% of those treated for 24 weeks achieved a SVR.

Daniel A. Hussar

New Drug Review

Ombitasvir, paritaprevir, ritonavir, dasabuvir sodium monohydrate (Viekira Pak – AbbVie)

Antiviral Agents

New Drug Comparison Rating (NDCR) = 2
(significant disadvantages)
in a scale of 1 to 5 with 5 being the highest rating

Indication:
With or without ribavirin for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

Comparable drugs:
Ledipasvir/sofosbuvir (Harvoni).

Advantages:
- Labeled indication includes patients with HCV/HIV-1 co-infection, and liver transplant recipients with normal hepatic function and mild fibrosis.

Disadvantages:
- Ribavirin is included in the treatment regimen for most patients, necessitating additional precautions
- Effectiveness of treatment regimens shorter than 12 weeks has not been demonstrated (whereas treatment with ledipasvir/sofosbuvir for 8 weeks is effective in some patients)
- Is not recommended for use in patients with decompensated liver disease
- Interacts with numerous other medications
- Hepatic laboratory testing should be performed during at least the first 4 weeks of treatment
- Treatment regimen is more complex (e.g., more doses, additional doses if ribavirin is included in regimen).

Most important risks/adverse events:
Contraindicated in patients with severe hepatic impairment and is not recommended in patients with moderate hepatic impairment; increased risk of ALT elevations (risk is greater in women using ethinyl estradiol-containing medications [e.g., combination oral contraceptives; should be discontinued and alternative methods of contraception used]; hepatic laboratory testing should be performed at least during the first 4 weeks of treatment); contraindicated in patients with known hypersensitivity to ritonavir; concurrent use with drugs that are highly dependent on CYP3A for clearance (e.g., triazolam, oral midazolam, simvastatin), strong inducers of CYP3A (e.g., carbamazepine, rifampin, St. John's wort) and CYP2C8, and strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated; concurrent use with alfuzosin, ergot derivatives, ethinyl estradiol, pimozide, and efavirenz is also contraindicated; interactions occur with numerous other medications and concurrent use must be closely monitored.

Most common adverse events (incidence in regimens without ribavirin):
Nausea (8%), pruritus (7%), insomnia (5%).

Usual dosage:
Two tablets containing ombitasvir, paritaprevir, and ritonavir once daily in the morning with a meal; one tablet containing dasabuvir twice a day in the morning and evening with a meal; regimen should be administered for 12 weeks in patients with genotype 1b, without cirrhosis; regimen should also include ribavirin and be administered for 12 weeks in patients with genotype 1a, without cirrhosis, and patients with genotype 1b, with cirrhosis, and for 24 weeks in patients with genotype 1a, with cirrhosis.

Products:
Film-coated tablets – ombitasvir – 12.5 mg; paritaprevir – 75 mg; ritonavir – 50 mg.
Film-coated tablets – dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir.

Comments:
Ombitasvir, paritaprevir, and dasabuvir are three new antiviral agents that act to inhibit replication of hepatitis C virus. Ombitasvir acts as a HCV NS5A inhibitor, paritaprevir as a HCV NS3/4A protease inhibitor, and dasabuvir as a HCV non-nucleoside NS5B palm polymerase inhibitor. Ritonavir is not active against HCV but is a CYP3A inhibitor that inhibits the CYP3A mediated metabolism of paritaprevir.

The effectiveness of the regimen (Viekira Pak) was evaluated in 6 studies that included more than 2,300 patients with chronic HCV infection with and without cirrhosis. In the different studies, patients were randomly assigned to receive Viekira Pak or placebo, Viekira Pak with or without ribavirin, or Viekira Pak with ribavirin for 12 or 24 weeks. The primary endpoint of the studies was a sustained virologic response (SVR; virus no longer detected in the blood at least 12 weeks after finishing treatment). An SVR was achieved by 91% to 100% of the participants who received Viekira Pak at the recommended dosage.

Daniel A. Hussar