FDA Approves Gilead's Hep C Drug Harvoni (Ledipasvir/Sofosbuvir)

The first once-daily fixed-dose combination therapy to treat hep C has hit the scene, with neither interferon nor ribavirin in tow.

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The U.S. Food and Drug Administration (FDA) has approved Gilead Sciences' hotly anticipated new hepatitis C virus (HCV) therapy Harvoni (ledipasvir/sofosbuvir). Boasting high cure rates, this first-ever fixed-dose combination tablet is indicated for the treatment of people with genotype 1 of the virus, who make up 70 percent of the HCV-positive U.S. population.

Importantly, the therapy does not require interferon—thus freeing those undergoing treatment from that drug's onerous, flu-like side effects and the need for weekly injections. Nor must Harvoni be taken with ribavirin, which can cause anemia and other side effects. While interferon and ribavirin have long been mainstays in hep C treatment, advancements in treatment over the past year saw the need for them begin to dissipate. Harvoni solidifies that trend.

Harvoni is a daily pill that includes Gilead's NS5A inhibitor ledipasvir plus the company's nucleotide analog polymerase inhibitor sofosbuvir. The latter drug was approved in December 2013 under the brand name Sovaldi, which quickly became a blockbuster.

Recommended treatment lengths for Harvoni are either 8, 12 or 24 weeks, depending on an individual's previous experience with treatment, cirrhosis status and hep C viral load when embarking on treatment. Specifically, physicians may consider eight weeks—the shortest HCV treatment length to date—for those who do not have cirrhosis, who have not attempted a cure before (also known as "treatment naive") and who have a baseline viral load below 6 million. Twelve weeks is recommended for those who do not have cirrhosis, regardless of previous treatment experience, and for those who do have cirrhosis and who are treatment naive. Twenty-four weeks is recommended for treatment-experienced people with cirrhosis.

Respectively, zero percent, less than 1 percent and 1 percent of participants taking Harvoni for 8, 12 and 24 weeks in the Phase III clinical trials discontinued treatment because of adverse side effects. The most common side effects, occurring in at least 5 percent of participants, were fatigue, headache, nausea, diarrhea and insomnia.

Gilead has priced Harvoni at $94,500 for 12 weeks of treatment. This is up from $84,000 for 12

weeks of Sovaldi, but is in line with the combined price of Sovaldi, ribavirin and interferon. Gilead estimates that half of people with genotype 1 of hep C will require just eight weeks of treatment, which will reduce the cost of treatment to $63,000.

Unlike Sovaldi, Harvoni did not receive any indication for use among those coinfected with HIV, who make up an estimated quarter of HCV-positive Americans. A recent Phase II study of Harvoni among HIV/HCV coinfected participants yielded a 100 percent cure rate, so physicians may use those findings as a guide for off-label prescribing.

Harvoni enters the highly competitive hep C treatment field all but certain to become the new juggernaut. Thanks to pent-up demand for improved hep C treatment options, Gilead reaped $5.78 billion in Sovaldi sales in the first half of this year; by the end of the first quarter, it shattered the sales record for any new drug's first year on the market. According to data from CVS Health Sovaldi sales have dropped off precipitously in recent months, however, as clinicians and their patients awaited Harvoni's approval.

The FDA is also expected to rule by mid-December on AbbVie's so-called "3D" regimen, which has an uphill climb to compete against Harvoni because of a high pill burden, and because it will likely require ribavirin.

Harvoni represents a significant advancement over Sovaldi for a host of reasons, including the potential for eight weeks of treatment instead of 12 and the opportunity to jettison ribavirin. Also, while Sovaldi offered the chance for interferon-free treatment for some, others were still compelled to endure the injectable drug.

According to Zobair M Younossi MD, MPH, chairman of the Department of Medicine at Inova Fairfax Hospital, "There is also significant evidence that this regimen is associated with improvement of patient related outcomes such as fatigue, quality of life and work productivity during treatment and after achieving sustained viral eradication."

Harvoni led to 94 percent to 99 percent cure rates in the three Phase III studies that Gilead submitted to the FDA in its application for approval. (The studies were called ION-1, ION-2 and ION-3 and included nearly 2,000 people with genotype 1 of hep C.) This is compared with 82 to 90 percent cure rates in clinical trials of Sovaldi plus interferon and ribavirin.

On the other hand, combining Sovaldi with Janssen's oral nucleotide analog polymerase inhibitor Olysio (simeprevir) offers cure rates in the mid-90 percent range, results that are relatively comparable to Harvoni's. While the this regimen is not yet FDA approved—a decision is expected in the new year—the American Association for the Study of Liver Diseases has recommended 12 weeks of the two drugs plus ribavirin to treat those with genotype 1 of the virus. Physicians have been free to prescribe the combination off-label and have apparently done so relatively widely, and without including ribavirin, according to CVS Health.

But considering that a course of Olysio costs $66,360, the total cost for a cure with Olysio and Sovaldi tops $150,000. Eight- and 12-week courses of Harvoni offer a significant savings, though a

24-week course would increase the cost to $189,000.

Activists who have pilloried Sovaldi's exorbitant price tag continued their rhetorical assault against Gilead.

While praising Harvoni as "a remarkable breakthrough in hepatitis C treatment," Lynda Dee, co-chair of the Fair Pricing Coalition (FPC), a collection of HIV and viral hepatitis treatment activists, says that "unconscionable pricing sours our appreciation of these long-awaited agents, particularly now that we have examples that curative treatment is inaccessible to many because of out-of-control escalator drug pricing."

In a statement, Gilead defended its pricing, saying, "We believe the price of Harvoni reflects the value of the medicine. Unlike long-term or indefinite treatments for other chronic diseases, Harvoni offers a cure at a price that will significantly reduce hepatitis C treatment costs now and deliver significant health care savings to the health care system over the long-term."

FPC members point out that hep C drugs are priced in the same realm as treatments that are much more expensive to produce and which target rare diseases, while there are an estimated 3.5 million HCV cases in the United States. The activist group expects insurers to place Harvoni in "specialty tiers," leading to higher co-pays and other cost sharing for consumers, as is often the case with Sovaldi.

And then there is the thorny matter of public health coverage. FPC co-chair Murray Penner points out that many "resource-constrained programs, such as Medicaid, have only been covering [Sovaldi]-containing regimens for patients with advanced liver disease, despite the fact that people with early stages of disease can transmit the virus to others and may suffer health consequences of infection if left untreated.

"People living with hepatitis C are also being asked to undergo degrading and scientifically unsubstantiated evaluations before they qualify in order to prove that they are abstinent from drugs and alcohol and can be expected to complete treatment," Penner says.

To read the FDA press release, click here.

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