FDA Approves Daklinza (daclatasvir) for the Treatment of Patients with Chronic Hepatitis C Genotype 3

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Daklinza in combination with sofosbuvir is the first 12-week, all-oral therapy that offers SVR12 for the vast majority of genotype 3 patients

Hepatitis C genotype 3 is one of the most difficult-to-treat genotypes

Announcement marks the first approval of Daklinza in the United States

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) announced today that Daklinza™ (daclatasvir), an NS5A replication complex inhibitor, has been approved by the U.S. Food and Drug Administration (FDA). This approval marks the first time patients with chronic hepatitis C virus (HCV) genotype 3 have a 12-week, once-daily, all-oral treatment option. Daklinza is indicated for use with sofosbuvir for the treatment of patients with chronic HCV genotype 3 infection. Sustained virologic response (SVR) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving this regimen. The recommended dosage of Daklinza is 60 mg in combination with sofosbuvir for 12 weeks.

"The U.S. approval of Daklinza means that chronic HCV genotype 3 patients may now complete treatment in just 12 weeks with an all-oral, once-daily regimen," said Chris Boerner, Head of U.S. Commercial, Bristol-Myers Squibb. "We believe this Daklinza-based regimen may be a solution to improving the standard of care for these patients. This approval is the result of many years of partnership with the HCV community to address the complexities of genotype 3, and an important achievement in our ongoing Daklinza development program, which focuses on patients that are most challenging to treat."

The pivotal Phase III open-label ALLY-3 clinical trial enrolled 152 patients with chronic HCV genotype 3 infection and compensated liver disease (101 treatment-naïve patients and 51 treatment-experienced patients). The co-primary endpoints were sustained virologic response rates 12 weeks after completing therapy (SVR12) in each treatment group. The full study design is outlined below. In the trial the Daklinza plus sofosbuvir regimen demonstrated SVR12 in 90% of treatment-naïve and 86% of treatment-experienced chronic HCV genotype 3 patients. SVR12 rates were higher (96%) in genotype 3 patients without cirrhosis, regardless of treatment history. In the more difficult-to-treat patients with cirrhosis, SVR12 rates were reduced (63%). These SVR12 rates were achieved with 12 weeks of therapy without the use of ribavirin.

Daklinza is contraindicated in combination with drugs that strongly induce CYP3A and, thus, may lead to lower exposure and loss of efficacy of Daklinza. Daklinza also may be associated with the risk of adverse reactions or loss of virologic response due to drug interactions. In addition, there is a risk of serious symptomatic bradycardia when coadministered with sofosbuvir and amiodarone. Please see full Important Safety Information below for more details.

In the pivotal Phase III trial, there were no treatment-related serious adverse events (SAEs) and no discontinuations due to adverse events (AEs). The most common treatment-related AEs at a frequency of ≥5% were headache (14%), fatigue (14%), nausea (8%) and diarrhea (5%).

"The treatment landscape for HCV has radically evolved in recent years, and while we have achieved impressive SVR12 rates in genotype 1, genotype 3 still represents a clinical challenge," said David R. Nelson, M.D., Professor of Medicine, Molecular Genetics and Microbiology Director, UF Clinical and Translational Science Institute, and Assistant Vice President of Research for the University of Florida. "Not only are genotype 3 patients more complicated to manage, but the aggressive nature of their disease means there is a greater urgency to treat them. Daklinza in combination with sofosbuvir gives healthcare providers a new option to achieve a high overall SVR12 rate in this difficult-to-treat patient population."

Daklinza is an inhibitor of NS5A with dual modes of anti-viral activity that inhibits both RNA replication and virion assembly. In in vitro studies, Daklinza has shown anti-viral activity across genotypes 1-6, with EC50 values from picomolar (pM) to low nanomolar (nM) against wild type replicons.

Daklinza will be available and begin shipping within a week.

About the ALLY-3 Clinical Trial

The efficacy and safety of Daklinza in combination with sofosbuvir were evaluated in the Phase III ALLY-3 clinical trial. ALLY-3...
was an open-label trial that included 152 patients with chronic HCV genotype 3 infection and compensated liver disease who were treatment-naïve (n=101) or treatment-experienced (n=51). Patients received Daklinza 60 mg plus sofosbuvir 400 mg once daily for 12 weeks and were monitored for 24 weeks post treatment. The co-primary endpoints were defined as HCV RNA below the lower limit of quantification (LLOQ) at post-treatment week 12 (SVR12) in each treatment group. Most treatment-experienced patients had failed prior treatment with peginterferon/ribavirin, but seven patients had been treated previously with a sofosbuvir regimen and two patients with a regimen containing an investigational cyclophilin inhibitor. Previous exposure to NS5A inhibitors was prohibited. The 152 treated patients in ALLY-3 had a median age of 55 years (range, 24-73); 59% of the patients were male; 90% were white, 5% were Asian, and 4% were black. Most patients (76%) had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 21% of the patients had compensated cirrhosis, and 40% had the IL28B rs12979860 CC genotype.

About Hepatitis C Genotype 3

Genotype 3 is estimated to affect 12 percent of chronic HCV patients in the U.S. and is the second most common hepatitis C genotype globally after genotype 1. Hepatitis C genotype 3 is considered one of the most difficult-to-treat genotypes.

About Bristol-Myers Squibb’s Patient Support Connect Program

Bristol-Myers Squibb is committed to helping patients through treatment with Daklinza. For patient support and financial assistance, patients and physicians may call (844) 44-CONNECT (844-442-6663). This number offers one-stop access to a range of support services for patients and healthcare professionals alike, including benefits investigation by care counselors, comprehensive coverage research and emergency shipment for access-related issues.

About Bristol-Myers Squibb in HCV

Bristol-Myers Squibb’s research efforts are focused on advancing compounds to deliver the most value to HCV patients with high unmet needs. At the core of our portfolio is daclatasvir, a NS5A complex inhibitor which continues to be investigated in multiple treatment regimens and in patients with co-morbidities. In addition to being approved in combination with sofosbuvir for patients with genotype 3, daclatasvir is being investigated in other high unmet need patients, such as pre- and post-transplant patients and HIV/HCV coinfected patients, as part of the ongoing Phase III ALLY Program.

In July 2014, Japan became the first country in the world to approve the use of a daclatasvir-based regimen for the treatment of chronic HCV. Since then, daclatasvir-based regimens have been approved across Europe, as well as numerous other countries in Central and South America, the Middle East and the Asia-Pacific region.

Indication and Important Safety Information - Daklinza™ (daclatasvir)

INDICATION

Daklinza™ (daclatasvir) is indicated for use with sofosbuvir for the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection.

Limitations of Use:

- Sustained virologic response (SVR) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving Daklinza in combination with sofosbuvir for 12 weeks.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- **Drugs Contraindicated with Daklinza:** strong inducers of CYP3A that may lead to loss of efficacy of Daklinza include, but are not limited to:
  - Phenytoin, carbamazepine, rifampin, St. John’s wort (Hypericum perforatum).

WARNINGS and PRECAUTIONS

-- Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions: Coadministration of Daklinza and other drugs may result in known or potentially significant drug interactions. Interactions may include the loss of therapeutic effect of Daklinza and possible development of resistance, dosage adjustments for other agents or Daklinza, possible clinically significant adverse events from greater exposure for the other agents or Daklinza.

- **Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone:** Post-marketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with another direct-acting antiviral, including Daklinza. A fatal cardiac arrest was reported with ledipasvir/sofosbuvir.
  - Coadministration of amiodarone with Daklinza in combination with sofosbuvir is not recommended. For patients taking amiodarone who have no alternative treatment options, patients should undergo cardiac monitoring, as outlined in Section 5.2 of the prescribing information.
  - Bradycardia generally resolved after discontinuation of HCV treatment.
  - Patients also taking beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone.

Adverse Reactions

- The most common adverse reactions were (≥ 5%): headache (14%), fatigue (14%), nausea (8%), and diarrhea (5%).
Drug Interactions

- **CYP3A**: Daklinza is a substrate. Moderate or strong inducers may decrease plasma levels and effect of Daklinza. Strong inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, ritonavir) may increase plasma levels of Daklinza.

- **P-gp, OATP 1B1 and 1B3, and BCRP**: Daklinza is an inhibitor, and may increase exposure to substrates, potentially increasing or prolonging their adverse effect.

See Section 7 of the Full Prescribing Information for additional established and other potentially significant drug interactions and related dose modification recommendations.

- **Daklinza in Pregnancy**: No data with Daklinza in pregnant women are available to inform a drug-associated risk. Animal studies of Daklinza at exposure above the recommended human dose have shown maternal and embryofetal toxicity. Consider the benefits and risks of Daklinza when prescribing Daklinza to a pregnant woman.

- **Nursing Mothers**: Daklinza was excreted into the milk of lactating rats; it is not known if Daklinza is excreted into human milk. Consider the benefits and risks to the mother and infant when breastfeeding.

Please click here for the Daklinza full prescribing information

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit [http://www.bms.com](http://www.bms.com) or follow us on Twitter at [http://twitter.com/bmsnews](http://twitter.com/bmsnews).

**Bristol-Myers Squibb Forward Looking Statement**

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that Daklinza will become a commercially successful product. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2014 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

**Language:**

English

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