U.S. FDA Approves Expanded Use of Bristol-Myers Squibb’s Daklinza (daclatasvir) for Additional Challenging-to-treat Patients with Genotype 1 or Genotype 3 Chronic Hepatitis C

Release Date:
Friday, February 5, 2016 12:47 pm EST

Terms:
#HepC #MEDIA Bristol-Myers daclatasvir Daklinza FDA Genotype hepatitis hepatitisC HepC liver

Dateline City:
PRINCETON, N.J.

Updated label provides new treatment option for patients with HIV-1 coinfection, advanced cirrhosis, and post-liver transplant HCV recurrence

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) announced today that Daklinza™ (daclatasvir, 60 mg), an NS5A replication complex inhibitor, has been approved by the U.S. Food and Drug Administration (FDA) in combination with sofosbuvir (with or without ribavirin) in genotypes 1 and 3. The expanded label includes data in three additional challenging-to-treat patient populations: chronic hepatitis C virus (HCV) patients with HIV-1 coinfection, advanced cirrhosis, or post-liver transplant recurrence of HCV. The Daklinza plus sofosbuvir regimen is already available for the treatment of chronic HCV genotype 3, and is currently the only 12-week, once-daily all-oral treatment option for these patients. Sustained virologic response (SVR) rates are reduced in genotype 3 patients with cirrhosis receiving Daklinza and sofosbuvir for 12 weeks without ribavirin. The recommended dosage of Daklinza is 60 mg in combination with sofosbuvir with or without (+/-) ribavirin for 12 weeks.

“The expanded indication for Daklinza offers an additional treatment option for multiple subsets of patients who have genotype 1 or 3 chronic HCV,” said Chris Boerner, Head of U.S. Commercial, Bristol-Myers Squibb. “HCV/HIV-coinfected patients and patients with advanced cirrhosis or post-transplant recurrence of HCV still pose a treatment challenge to physicians. As part of our commitment to the HCV community, we have sought to make new treatment options available for these and other targeted populations that have not yet been able to fully benefit from currently available next-generation medicines.”

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 co-administered with sofosbuvir and amiodarone. Please see full Important Safety Information below for more details.

The efficacy and safety of the Daklinza regimens were evaluated in the Phase 3 ALLY-1 and ALLY-2 clinical trials.

ALLY-2 (Daklinza + sofosbuvir)

The ALLY-2 trial enrolled 153 treatment-naïve (n=101) and treatment-experienced (n=52) HCV/HIV-coinfected patients treated with Daklinza plus sofosbuvir for 12 weeks. Sustained virologic response was the primary endpoint and was defined as HCV RNA below the LLOQ at post-treatment week 12 (SVR12) in genotype 1 treatment-naïve patients.

<table>
<thead>
<tr>
<th>SVR12 (Genotypes 1 and 3)</th>
<th>12-week treatment duration (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>97% (123/127)</td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>98% (103/105)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>91% (20/22)</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>100% (10/10)</td>
</tr>
</tbody>
</table>

In ALLY-2, SVR12 rates were high regardless of baseline subgroup, including Black/African-American (98%, n=50 in all genotypes studied), and high baseline viral load (≥6,000,000 IU/mL) (97%, n=62 in all genotypes studied). Rates of SVR12 were also similar among the concomitant HAART (highly active antiretroviral therapy) regimens used, which included protease inhibitors (97%, n=70 in all genotypes), non-nucleoside reverse transcriptase inhibitors (100%, n=40 in all genotypes), and integrase inhibitors (95%, n=39 in all genotypes).
Among the 153 patients in ALLY-2, 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% in ALLY-2 were fatigue (15%), nausea (9%), headache (8%) and diarrhea (7%).

“The high SVR rates achieved with the daclatasvir-based (Daklinza) regimen in HCV/HIV-coinfected patients are extremely encouraging for potentially helping to address a serious health concern for individuals with HIV,” said Kenneth Sherman, M.D., Ph.D., Gould Professor of Medicine and Director, Division of Digestive Diseases, University of Cincinnati College of Medicine. “Approximately a quarter of all HIV patients in the U.S. are coinfected with HCV, and have historically been particularly challenging to treat due to the complexities of the overlapping therapeutic regimens used to treat each infection. New options that allow for the treatment of HCV without altering HIV medicines are still a significant need for these patients.” The dose of Daklinza may need to be adjusted when used with some antiretroviral regimens.

ALLY-1 (Daklinza + sofosbuvir + ribavirin)

The ALLY-1 trial enrolled 113 patients with chronic HCV infection and Child-Pugh A, B, or C advanced cirrhosis (n=60) or HCV recurrence after liver transplant (n=53) treated with Daklinza plus sofosbuvir with ribavirin for 12 weeks. The primary endpoint was SVR12 in each treatment cohort.

SVR12 rates were comparable between genotype 3 (5/6 with Child-Pugh B or C cirrhosis and 10/11 post-liver transplant) and genotype 1 subjects with or without decompensated cirrhosis.

Among all patients in ALLY-1, there were no treatment-related SAEs. Of the 15 (13%) patients who discontinued study drug for adverse events, 13 (12%) patients discontinued ribavirin only and 2 (2%) patients discontinued all study drugs. The most common treatment-related AEs at a frequency of ≥5% in either cohort of ALLY-1 were headache (12%, 30%), anemia (20%, 19%), fatigue (15%, 17%), nausea (15%, 6%), rash (8%, 2%), diarrhea (3%, 6%), insomnia (3%, 6%), dizziness (0%, 6%), and somnolence (5%, 0%) in the advanced cirrhotic and post-transplant treatment groups, respectively.

The ALLY-1 and -2 trials demonstrated that Daklinza is able to be administered with the most commonly used medications for the treatment of HIV and post-transplant immunosuppression. Based on the drug-drug interaction profile, there is no need to change or adjust HAART regimens, including darunavir-ritonavir, atazanavir-ritonavir, lopinavir-ritonavir, efavirenz, raltegravir, dolutegravir, nevirapine and rifampin. The dose of Daklinza was adjusted for some HAART regimens. Daklinza is also compatible with many immunosuppressive regimens, with no treatment-limiting drug-drug interactions. The ALLY-1 trial studied most immunosuppressants: cyclosporine, tacrolimus, sirolimus, everolimus, corticosteroids, or mycophenolate mofetil.

“Post-liver transplant patients with HCV recurrence and patients with advanced cirrhosis can be difficult to manage because of the potential for drug-drug interactions associated with immunosuppressive treatments and the complex conditions of liver disease,” said Fred Poordad, M.D., ALLY-1 Lead Investigator and Clinical Professor of Medicine, Chief, Hepatology, University of Texas Health Science Center and VP, Academic and Clinical Affairs, Texas Liver Institute. “Transplant patients need to take a variety of immunosuppressive medications to prevent organ rejection, and treatment with Daklinza plus sofosbuvir and ribavirin allows patients to preserve their new liver by treating HCV before its progression to more severe disease, while still maintaining the critical regimens required to manage immunosuppression.”

Daklinza Regimens Dosing

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daklinza + sofosbuvir 12 weeks</td>
<td>Genotype 1 or Genotype 3 without cirrhosis</td>
</tr>
<tr>
<td>Daklinza + sofosbuvir + ribavirin 12 weeks</td>
<td>Genotype 1 with compensated cirrhosis (Child-Pugh A)</td>
</tr>
<tr>
<td>Daklinza + sofosbuvir</td>
<td>Genotype 3 with compensated cirrhosis (Child-Pugh A)</td>
</tr>
<tr>
<td>Daklinza + sofosbuvir + ribavirin</td>
<td>Genotype 1 or Genotype 3 with decompensated cirrhosis (Child-Pugh B and C)</td>
</tr>
<tr>
<td>Daklinza + sofosbuvir + ribavirin</td>
<td>Genotype 1 or Genotype 3 post-transplant</td>
</tr>
</tbody>
</table>

For genotype 1a patients with cirrhosis, prior to the initiation of treatment with Daklinza-based regimens, consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93.

About the ALLY-2 Clinical Trial

ALLY-2 was an open-label trial that included 153 patients (genotypes 1-4) with chronic HCV and HIV co-infection. Patients received Daklinza 60 mg (dose-adjusted for concomitant antiretroviral use) plus sofosbuvir 400 mg once daily for 12 weeks and were monitored for 24 weeks post-treatment.

The 153 patients had a median age of 53 years (range, 24-71); 88% of the patients were male; 63% were white, 33% were black, and 1% were Asian. Most patients (80%) had baseline HCV RNA levels greater than or equal to 800,000 IU/mL. Sixty-eight percent of patients had HCV genotype 1a, 15% had HCV genotype 1b, 8% had genotype 2, 7% had genotype 3, and...
WARNINGS AND PRECAUTIONS

CONTRAINDICATIONS

Chronic hepatitis

Daklinza™ (daclatasvir) is indicated for use with sofosbuvir, with or without ribavirin, for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1 or genotype 3 infection.

Limitations of Use:

- Sustained virologic response (SVR12) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving Daklinza in combination with sofosbuvir for 12 weeks.

CONTRAINDICATIONS

When used in combination with other agents, the contraindications applicable to those agents are applicable to the combination regimen; refer to the respective prescribing information.

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.
- 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.
- Bradycardia generally resolved after discontinuation of HCV treatment.

Risks Associated with Ribavirin Combination Treatment: If ribavirin is used as part of the regimen, the warnings and precautions for ribavirin, particularly the pregnancy avoidance warning, apply. See the ribavirin full prescribing information for complete information.

About the ALLY-1 Clinical Trial

ALLY-1 was an open-label trial that included 113 patients (genotypes 1-4, 6) with chronic HCV infection and Child-Pugh A, B, or C cirrhosis or HCV recurrence after liver transplant. Patients received Daklinza 60 mg plus sofosbuvir 400 mg once daily with ribavirin for 12 weeks and were monitored for 24 weeks post-treatment. The recommended initial dose of ribavirin was 600 mg or less daily with food and could be adjusted up to 1000 mg per day if tolerated.

The 113 treated patients in ALLY-1 had a median age of 59 years (range, 19-82); 67% of the patients were male; 96% were white, 4% were black, and 1% were Asian. Most patients (59%) were treatment-experienced, and most (71%) had baseline HCV RNA levels greater than or equal to 800,000 IU/mL. Fifty-eight percent of patients had HCV genotype 1a, 19% had HCV genotype 1b, 4% had genotype 2, 15% had genotype 3, 4% had genotype 4, and 1% had genotype 6. Daklinza is indicated in genotype 1 and genotype 3 only. Among the 60 patients in the cirrhosis cohort, 20% were Child-Pugh class A, 53% were Child-Pugh class B, 27% were Child-Pugh class C, and 35% had a Baseline Model for End-Stage Liver Disease (MELD) score of 15 or greater. Most (55%) of the 53 patients in the post-transplant cohort had F3 or F4 fibrosis (based on FibroSURE® results).

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 is focused on helping to eradicate hepatitis C around the world, with a primary emphasis on difficult-to-treat patients, including those millions in countries where population-based HCV solutions remain a high unmet need.

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 hepatitis C. Since then, daclatasvir-based regimens have been approved in more than 50 countries across Europe, Central and South America, the Middle East and the Asia-Pacific region.

Indication and Important Safety Information - Daklinza™ (daclatasvir)

INDICATIONS

Daklinza™ (daclatasvir) is indicated for use with sofosbuvir, with or without ribavirin, for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1 or genotype 3 infection.

1. Sustained virologic response (SVR12) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving Daklinza in combination with sofosbuvir for 12 weeks.

2. When used in combination with other agents, the contraindications applicable to those agents are applicable to the combination regimen; refer to the respective prescribing information.

3. 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).

4. 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.
ADVERSE REACTIONS

- In clinical trials (Ally 2, 3) with the Daklinza and sofosbuvir regimen, the most common adverse reactions (≥5%) were, respectively: headache (8%, 14%), fatigue (15%, 14%), nausea (9%, 8%), diarrhea (7%, 5%).

- In clinical trials (Ally 1) with Daklinza, in combination with sofosbuvir and ribavirin, the most common adverse reactions (≥5%) were, in the cirrhosis cohort and the post-liver transplantation cohort, respectively: headache (12%, 30%), anemia (20%, 19%), fatigue (15%, 17%), nausea (15%, 6%), rash (8%, 2%), diarrhea (3%, 6%), insomnia (3%, 6%), dizziness (0, 6%), somnolence (5%, 0).

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 Sections 4, 7, and 12.3 of the Daklinza Full Prescribing Information for additional established and other potentially significant drug interactions and related dose modification recommendations. Refer to the prescribing information for other agents in the regimen for drug interaction information.

DAKLINZA IN PREGNANCY:

- No adequate human data are available to determine whether or not DAKLINZA poses a risk to pregnancy outcomes. Animal studies of Daklinza at exposure above the recommended human dose have shown maternal and embryofetal toxicity.

- If Daklinza and sofosbuvir are administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to the ribavirin prescribing information.

NURSING MOTHERS:

- It is not known whether DAKLINZA is present in human milk, affects human milk production, or has effects on the breastfed infant. Daklinza was present in the milk of lactating rats. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for DAKLINZA and any potential adverse effects on the breastfed child from DAKLINZA or from the underlying condition.

- When Daklinza is administered with ribavirin, the nursing mothers’ information for ribavirin also applies to this combination regimen. Refer to the nursing mothers’ information in the ribavirin prescribing information.

Please click here for the Daklinza full prescribing information.

* Genotypes 1-6 were eligible to enroll in ALLY-2 and ALLY-1.

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 or follow us on Twitter at 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. 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

Contact:

Bristol-Myers Squibb
Media:
Robert Perry, 407-492-4616
rob.perry@bms.com
or
Shelly Mittendorf, 609-897-2055
shelly.mittendorf@bms.com
or
Ticker Slug:
Ticker: BMY
Exchange: NYSE
@bmsnews
#MEDIA Bristol-Myers Squibb receives expanded FDA approval to treat additional GT1 or GT3 chronic #HepC patients