European Commission Approves Daklinza (daclatasvir) for the Treatment of Genotype 1, 3 and 4 Chronic Hepatitis C Patients with HIV Coinfection, Advanced Cirrhosis and Post-liver Transplant Recurrence of HCV

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Updated label provides additional treatment options for multiple HCV patient populations, including difficult-to-treat patients with decompensated cirrhosis

HIV/HCV coinfected patients experience more rapid fibrosis progression than mono-infected HCV patients

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) announced today that the European Commission has approved Daklinza for the treatment of chronic hepatitis C (HCV) in three new patient populations. The expanded label allows for the use of Daklinza in combination with sofosbuvir (with or without ribavirin, depending on the indication and HCV genotype) in HCV patients with decompensated cirrhosis, HIV-1 (human immunodeficiency virus) coinfection, and post-liver transplant recurrence of HCV in all 28 Member States of the European Union.

“The European Commission’s approval of these new indications for Daklinza is an important step forward for a significant group of patients with chronic hepatitis C who are still in need of treatment options that can deliver high cure rates,” said Douglas Manion, M.D., head of Specialty Development, Bristol-Myers Squibb. “The complex clinical considerations for physicians treating HCV/HIV coinfected patients and patients with cirrhosis, decompensated cirrhosis or post-transplant recurrence of HCV reinforces the vast diversity of this disease, and we have worked hard to continue to identify and address those patients who require additional solutions for cure.”

Daklinza is contraindicated in combination with medicinal products that strongly induce CYP3A and P-glycoprotein transporter, as this may lead to lower exposure and loss of efficacy of Daklinza. Daklinza must not be administered as a monotherapy.

Daklinza is already approved by the European Commission for use in combination with other medicinal products across genotypes 1, 2, 3 and 4 for the treatment of chronic HCV infection in adults, and the Daklinza + sofosbuvir regimen is the only approved 12-week, all-oral treatment for genotype 3 HCV patients without cirrhosis. The new indications are based on data from the ALLY-1 clinical trial (in post-transplant patients and patients with advanced cirrhosis) and ALLY-2 clinical trial (in HIV-coinfected patients). The recommended treatment regimens and durations are as follows:

<table>
<thead>
<tr>
<th>Patient population*</th>
<th>Regimen and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV GT 1 or 4</strong></td>
<td></td>
</tr>
<tr>
<td>Patients without cirrhosis</td>
<td>Daklinza + sofosbuvir for 12 weeks</td>
</tr>
<tr>
<td>Patients with cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh Class (CP) A or B</td>
<td>Daklinza + sofosbuvir + ribavirin for 12 weeks</td>
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<tr>
<td></td>
<td>or Daklinza + sofosbuvir (without ribavirin) for 24 weeks</td>
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<tr>
<td>CP C</td>
<td></td>
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<tr>
<td>Patients without cirrhosis</td>
<td>Daklinza + sofosbuvir +/- ribavirin for 24 weeks</td>
</tr>
<tr>
<td><strong>HCV GT 3</strong></td>
<td></td>
</tr>
<tr>
<td>Patients without cirrhosis</td>
<td>Daklinza + sofosbuvir for 12 weeks</td>
</tr>
</tbody>
</table>
Recurrent HCV infection post-liver transplant (GT 1, 3 or 4)

<table>
<thead>
<tr>
<th>Patients with cirrhosis</th>
<th>Daklinza + sofosbuvir +/- ribavirin for 24 weeks (see section 5.1 of the Summary of Product Characteristics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without cirrhosis</td>
<td>Daklinza + sofosbuvir + ribavirin for 12 weeks</td>
</tr>
<tr>
<td>Patients with CP A or B cirrhosis</td>
<td>Daklinza + sofosbuvir + ribavirin for 12 weeks</td>
</tr>
<tr>
<td>GT 1 or 4</td>
<td>Daklinza + sofosbuvir +/- ribavirin for 24 weeks</td>
</tr>
<tr>
<td>GT 3</td>
<td>Daklinza + sofosbuvir +/- ribavirin for 24 weeks</td>
</tr>
<tr>
<td>Patients with CP C cirrhosis</td>
<td>Daklinza + sofosbuvir +/- ribavirin for 24 weeks</td>
</tr>
</tbody>
</table>

* Includes patients coinfected with human immunodeficiency virus (HIV). For dosing recommendations with HIV antiviral agents, refer to full Summary of Product Characteristics.

ALLY-2 Study Design

In the ALLY-2 Phase 3 open-label clinical trial, 153 patients with chronic HCV coinfection with HIV (101 treatment-naïve patients and 52 treatment-experienced patients) received Daklinza 60 mg plus sofosbuvir 400 mg once daily for 12 weeks, and 50 treatment-naïve patients received Daklinza 60 mg plus sofosbuvir 400 mg once daily for 8 weeks. Patients with genotypes 1-6 were eligible to enroll, including those with compensated cirrhosis (Child-Pugh A), and the dose of Daklinza was adjusted for concomitant antiretroviral use. 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. The 153 patients who received 12 weeks of treatment had a median age of 53 years (range, 24-71); 63% of the patients were white and 33% were black. Sixty-eight percent of patients had HCV genotype 1a, 15% had HCV genotype 1b, 8% had genotype 2, 7% had genotype 3, and 2% had genotype 4. Sixteen percent of all patients had compensated cirrhosis.

In the 12-week arms, the Daklinza plus sofosbuvir regimen demonstrated overall SVR12 in 97% of patients, including 100% in genotype 3. SVR12 rates were greater than 94% across all combination antiretroviral therapy (cART) regimens, including boosted-protease inhibitor-, NNRTI-, and integrase inhibitor-based therapies.

In the trial, there were no treatment-related serious adverse events (SAEs) and no discontinuations due to adverse events (AEs). The most common treatment-related AEs (≥10%) were fatigue (17%), nausea (13%), and headache (11%).

ALLY-1 Study Design

In the ALLY-1 Phase 3 open-label clinical trial, 113 patients with chronic HCV and Child-Pugh A, B or C cirrhosis (n=60) or HCV recurrence after liver transplantation (n=53) received Daklinza 60 mg plus sofosbuvir 400 mg once daily with ribavirin (600 mg starting dose) for 12 weeks. Patients with genotypes 1-6 were eligible to enroll. 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. Among the 53 post-liver transplant patients: the median age was 59; 96% were white, 2% were black, and 2% were defined as other; and, 58% of patients had HCV genotype 1a, 19% had genotype 1b, 21% had genotype 3, and 2% had genotype 6. Among the 60 cirrhotic patients: the median age was 56; 95% were white and 5% were black; 20% were Child-Pugh class A, 53% were Child-Pugh class B, and 27% were Child-Pugh class C; and, 57% of patients had HCV genotype 1a, 18% had genotype 1b, 8% had genotype 2, 10% had genotype 3, and 7% had genotype 4. In the same cohort, median baseline Model for End-Stage Liver Disease (MELD) score was 13. Most (55%) of the 53 patients in the post-transplant cohort had F3 or F4 fibrosis (based on FibroSURE® results). The trial permitted a wide variety of immunosuppressants in the post-transplant cohort, including cyclosporine, tacrolimus, sirolimus, everolimus, corticosteroids, or mycophenolate mofetil.

In the trial, 94% of post-liver-transplant patients and 83% of patients in the cirrhosis cohort achieved SVR12, including 92-94% of patients with Child-Pugh A or B. In the cirrhosis cohort, 4 subjects with hepatocellular carcinoma underwent liver transplantation after 1 to 71 days of treatment; 3 of the 4 subjects received 12 weeks of post-liver transplant treatment extension and 1 subject, treated for 23 days before transplantation, did not receive treatment extension. All 4 subjects achieved SVR12.

In the trial, there were no treatment-related SAEs, and 16 patients discontinued study drugs due to AEs; 14 discontinued ribavirin only, and 2 discontinued the entire regimen. The most common treatment-related AEs (≥10%) in either cohort of ALLY-1 were headache (15%, 36%), fatigue (18%, 28%), anemia (20%, 19%), diarrhea (8%, 19%), nausea (17%, 6%) and arthralgia (2%, 13%) in the advanced cirrhotic and post-transplant treatment groups, respectively. The updated Summary of Product Characteristics will be available at [www.ema.europa.eu](http://www.ema.europa.eu).

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.

U.S. Indication and Important Safety Information (ISI) - Daklinza™ (daclatasvir)

The following ISI is based on information from U.S. Prescribing Information for Daklinza. Please consult the full Prescribing Information for all labeled safety information.
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 pharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit [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. 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.
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Ticker Slug:
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Exchange: NYSE