NICE Recommends Daklinza (daclatasvir) for Treatment of Certain Patients with Chronic Hepatitis C Genotypes 1, 3 and 4

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PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb (NYSE:BMY) today announced that the National Institute for Health and Care Excellence (NICE) has recommended Daklinza (daclatasvir) in England and Wales for the treatment of adult patients with chronic hepatitis C virus (HCV) infection. Specifically, NICE recommended Daklinza, an oral, once-daily medication used in combination with other agents, to treat certain patients with HCV genotypes 1, 3 and 4. Approximately 214,000 people in the UK are thought to have chronic HCV, and roughly 100,000 of those patients are estimated to have genotype 3, a difficult-to-treat and often aggressive form of chronic HCV.

"It is a challenge to treat patients with hepatitis C virus infection, including the significant number of patients with genotype 3, whose condition tends to progress rapidly," said Anna Maria Geretti, Professor of Virology and Infectious Diseases, University of Liverpool. "In the past there have been limited treatment options available and therefore this decision is an important milestone. Daclatasvir in combination with other agents represents a much needed oral treatment regimen that has been shown to cure the infection in the majority of patients, and we have already seen positive results in the real-life setting in patients with advanced disease."

HCV genotype 3 is associated with accelerated progression of fibrosis compared to other genotypes, which can make treatment time critical. Recent research has also shown that the risk of cirrhosis for patients infected with HCV genotype 3 is 31% greater than for those with HCV genotype 1.

"The burden of genotype 3 hepatitis C in the United Kingdom is one of the highest anywhere in Europe," said Douglas Manion, M.D., head of Specialty Development, Bristol-Myers Squibb. "England has now joined Italy, France, The Netherlands, Sweden, Belgium, Switzerland, Denmark, Scotland and Ireland in recognizing the value of Daklinza for the treatment of genotype 3 HCV, and we are excited to make it available to help address what is still a significant unmet need among the UK HCV population."

In the EU, Daklinza is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults. In genotype 3 HCV, Daklinza is currently approved in combination with sofosbuvir for 12 weeks in patients without cirrhosis and for 24 weeks in patients with cirrhosis with the optional use of ribavirin based on clinical assessment of the patient. Until recently, treatment options for genotype 3 patients in England were limited, and included interferon. Daklinza plus sofosbuvir, with or without ribavirin, is currently one of only two all-oral treatment regimens recommended by the European Association for the Study of the Liver's (EASL) treatment guidelines for patients with HCV genotype 3.

About the NICE guidance

Following a submission by Bristol-Myers Squibb, NICE has issued final guidance on the use of Daklinza, in combination with other medicinal products, for use within NHS England as an option for the treatment of chronic HCV infection in adults. NICE has recommended its use as specified in the following table.

<table>
<thead>
<tr>
<th>HCV genotype, liver disease stage</th>
<th>Treatment</th>
<th>Duration (weeks)</th>
<th>Recommendation according to treatment history</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daclatasvir + sofosbuvir</td>
<td>12</td>
<td>Untreated: Recommended only if the person has significant fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treated: Recommended only if the person has significant fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interferon-ineligible or intolerant: Recommended only if the person has significant fibrosis</td>
</tr>
<tr>
<td>1 without cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 without cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Severe or Fulminant Hepatitis C</th>
<th>Daclatasvir + sofosbuvir (with or without ribavirin)</th>
<th>24</th>
<th>Not recommended</th>
<th>Not recommended</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 without cirrhosis</td>
<td>Daclatasvir + sofosbuvir</td>
<td>12</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>3, with compensated cirrhosis</td>
<td>Daclatasvir + sofosbuvir + ribavirin</td>
<td>24</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Recommended if the person has significant fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>Daclatasvir + peginterferon alfa + ribavirin</td>
<td>24</td>
<td>Recommended only if the person has significant fibrosis or compensated cirrhosis</td>
<td>Recommended only if the person has significant fibrosis or compensated cirrhosis</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Significant fibrosis is defined as METAVIR fibrosis stages F3 and F4. Treated – the person's hepatitis C has not adequately responded to interferon-based treatment.

For further information on the guidance, please visit: [https://www.nice.org.uk/](https://www.nice.org.uk/).

**About the Bristol-Myers Squibb HCV portfolio**

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, an NS5A complex inhibitor which continues to be investigated in multiple treatment regimens and in patients with high disease burden, such as pre- and post-transplant patients and HIV/HCV coinfected patients, as part of the ongoing 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 in more than 50 countries, including the United States, several countries across Europe, and in numerous other countries in North, 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 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. 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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