China FDA Approves Country’s First All-Oral Regimen for Chronic Hepatitis C, Daklinza® (daclatasvir) in Combination with Sunvepra® (asunaprevir)

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Daklinza and Sunvepra combination approved for genotype 1b, the most common chronic hepatitis C (HCV) genotype in China; combination has a 91-99% cure rate

Daklinza also approved in China for use in combination with other agents, including sofosbuvir, for HCV genotypes 1-6

PRINCETON, N.J. -- (BUSINESS WIRE) -- Bristol-Myers Squibb Company (NYSE:BMY) announced today that the China Food and Drug Administration (CFDA) has approved a direct-acting antiviral regimen comprised of Daklinza® (daclatasvir) and Sunvepra® (asunaprevir), for the treatment of treatment-naive or -experienced patients, with or without compensated cirrhosis, infected with genotype 1b chronic hepatitis C virus (HCV). This is China’s first all-oral, interferon- and ribavirin-free HCV treatment regimen. In addition, Daklinza has been approved in China for combination use with other agents, including sofosbuvir, for adult patients with HCV genotypes 1-6 infection. This is the only all-oral pan-genotypic regimen recommended by China’s HCV Prevention and Treatment Guideline. Daklinza must not be administered as monotherapy. Sofosbuvir is under review by the CFDA, and is not currently licensed in China.

In more than 60 countries, Daklinza is approved as part of a regimen with either Sunvepra or sofosbuvir. In China, Daklinza-based regimens provide a shorter treatment duration (12 or 24 weeks) compared to 48 weeks of treatment with previously approved regimens. The Daklinza and Sunvepra regimen is already approved by regulatory authorities in multiple countries across the Asia Pacific, Latin America, and Eastern Europe regions. Sunvepra is not approved in the United States.

“The burden of HCV in China is extremely high, and now for the first time, we have an all-oral treatment option in the combination of Daklinza and Sunvepra, which is a significant step forward for patients and doctors alike,” said Hui Zhuang, a professor at the Beijing University Medical School and a member of the Chinese Academy of Engineering. “This new option helps to address many of the unmet needs for our HCV genotype 1b patients, and is also included in the latest edition of China’s HCV Prevention and Treatment Guideline.”

The approval is based primarily upon results of the first completed Phase 3 036 trial of the Daklinza and Sunvepra regimen for HCV among Chinese patients, which was published in the November 2016 issue of the Journal of Gastroenterology and Hepatology. In the trial, 91% (145/159) of genotype 1b patients who had been previously interferon-ineligible or interferon-intolerant achieved sustained virologic response (“SVR”, or cure) at post-treatment week 24. The cure rate was higher, at 99%, in patients without baseline NS5A resistance-associated variants (RAVs; L31M or Y93H; n=137/139).

As detailed in the published Phase 3 trial, one death (0.6%), five on-treatment serious adverse events (3%), and three grade 4 laboratory abnormalities (2%) occurred on-treatment; none were considered related to study drugs. Two patients (1%) discontinued due to adverse events (AEs). The most common grade 1-4 on-treatment AEs (>5% of patients) were platelet count decrease (14, 9%), upper respiratory tract infection (13, 8%), ALT increase (a diagnostic indication of liver disease or damage) (11, 7%), neutrophil count decrease (11, 7%), monocyte (large white blood cell) count decrease (10, 6%), white blood cell count decrease (10, 6%), thrombocytopenia (decrease in the number of platelets in the blood) (10, 6%), and pruritus (itchiness) (9, 6%); most were mild or moderate in intensity. Treatment was generally well-tolerated regardless of cirrhosis status.

“We are proud to build on our legacy, infrastructure and experience in treating viral hepatitis throughout Asia by bringing Daklinza-based regimens to patients in China,” said Murdo Gordon, executive vice president and chief commercial officer, Bristol-Myers Squibb. “Beginning with our efforts to treat chronic hepatitis B, Bristol-Myers Squibb has been committed to combating viral hepatitis in China for over a decade.”

HCV represents a significant public health burden in China and is now the fourth most commonly reported infectious disease countrywide, with an estimated 10 million people currently living with the disease. Until now, standard of care in China has been interferon- and ribavirin-containing regimens which have left some patient groups with unmet needs. The cure rate for
interferon- and ribavirin- containing regimens varies in a number of recent Chinese studies. In CCgenos, a real-world observation study, the cure rate for interferon- and ribavirin- containing regimens among GT-1b naive patients is 62.4%.

Karl Lintel, MD, President of Bristol-Myers Squibb (China) Investment Co. Ltd and the Sino-American Shanghai Squibb Pharmaceutical Co., commented, “Today’s approval of Daklinza and Sunvepra is great news for patients in China, as we continue the global fight against chronic hepatitis C. This milestone is testament to our ongoing collaboration with multiple stakeholders, and aligning with government policies to provide continuing support to HCV patients at the community level.”

Bristol-Myers Squibb is committed to working with stakeholders to seek timely reimbursement for Daklinza and Sunvepra at the national and provincial levels, to ensure patients have access to these important products.

About the 036 Clinical Trial

In the multi-center Asian study, interferon-ineligible and -intolerant patients with genotype 1b infection received Daklinza 60 mg tablets once-daily plus Sunvepra 100 mg soft capsules twice-daily for 24 weeks. Of the 159 patients enrolled, 127 were from mainland China. The primary endpoint was SVR at post-treatment Week 12 (SVR12). In the overall study population, the SVR24 was 91% (145/159) and was similarly high in cirrhotic patients (47/52, 90%). SVR24 rates were higher (137/139 [99%]) in patients without baseline NS5A RAVs (L31M or Y93H), and lower in patients with baseline NS5A RAVs (8/19 [42%]).

Prevalence of baseline NS5A RAVs was 12% (19/159) overall, and 8% in mainland China patients (10/127). HCV NS5A RAVs exist naturally (albeit in lower prevalence vs wild type) and can emerge after virologic response failure. Screening for the presence of specific NS5A mutations can help physicians determine the most suitable patients for treatment by identifying those most likely to achieve cure with an NS5A-containing regimen.

Data from other studies conducted outside of China investigating Daklinza in combination with sofosbuvir were also considered as part of the approval.

About the 114 Clinical Trial

In a multi-center study, treatment-naive patients with genotype 1b infection received Daklinza 60 mg tablets once-daily plus Sunvepra 100 mg soft capsule twice-daily for 24 weeks. Of the total 206 patients, 161 were from mainland China. Patients were randomized 3:1 into two treatment arms: an immediate Daklinza and Sunvepra treatment group (n=155) or a placebo-deferred Daklinza and Sunvepra treatment group (n=52). The primary endpoint was SVR at post-treatment Week 12 (SVR12) in the immediate treatment arm, for comparison with the historical SVR rate achieved with pegIFN/RBV (70%).

The SVR12 rate was 92% in treatment-naive patients with HCV genotype 1b infection in the immediate treatment arm. Baseline NS5A-L31 or Y93H polymorphisms were present in 11% (17/154) of these patients. The SVR12 rate was 96% (132/137) in patients without these baseline polymorphisms; 89% (17/19) with cirrhosis, 97% (115/118) without cirrhosis.

Discontinuations due to AEs were infrequent (1%). The most common AEs (any grade, ≥5%) in the overall population were ALT increase, upper respiratory tract infection, hypertension, AST elevation, INR elevation, blood bilirubin elevation, and fatigue.

Bristol-Myers Squibb’s Leadership in Viral Hepatitis

Bristol-Myers Squibb’s heritage in virology in China began with Baraclude®, a market-leading oral treatment for patients suffering with chronic hepatitis B virus (CHBV). Baraclude is indicated in China for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum alanine aminotransferase (ALT) or histologically active disease. Since its approval in China in 2005, Bristol-Myers Squibb has worked to not only provide access to Baraclude, but also to coordinate with government, local hospitals and physicians, and NGOs to raise the standard of care and improve the quality of life and survival of patients with HBV. In China, more than 1 million patients have been treated with Baraclude, and Asia has accounted for more than two-thirds of all Baraclude prescriptions.

Since 2002, the Bristol-Myers Squibb Foundation also has been leading efforts at the community level in Asia in HBV and HCV awareness, destigmatization, prevention, and care through the Delivering Hope program. The multi-pronged program includes a variety of disease education and vaccination efforts, including prevention of the most common means of transmission, from mother to child. It also includes capacity building, and training in partnership with local NGOs, governments and healthcare workers. In China alone, more than 8 million people at high risk of hepatitis infection across 28 provinces have benefitted from these programs over the past decade. The Foundation has committed more than $9.6 million (U.S.) in grants to a diverse group of organizations for programs targeting specific populations.

About Daclatasvir

Daclatasvir, marketed as Daklinza, is a NS5A replication complex inhibitor which targets the NS5A protein by directly disrupting its normal function. The NS5A protein plays essential roles in the HCV viral life cycle, including viral RNA replication and virion (viral particle) assembly. Daklinza is approved by the U.S. Food and Drug Administration (FDA) for use with sofosbuvir, with or without ribavirin, for the treatment of patients with HCV genotype 1 or genotype 3 infection. Sustained virologic response (SVR12) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving Daklinza in combination with sofosbuvir for 12 weeks. Daklinza is approved by the European Medicines Agency (EMA) for patients with HCV genotypes 1, 3, or 4.

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with Daklinza. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate management for HBV infection as clinically indicated. Please see full
ADVERSE REACTIONS

WARNINGS AND PRECAUTIONS

CONTRAINDICATIONS

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with Daklinza. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate management for HBV infection as clinically indicated.

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 Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV (additional information): HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation may be increased in these patients.
- 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 5.3 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.

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%), and 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.

**Lactation**

- 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 see Full Prescribing Information, including Boxed WARNING here.

**U.S. Indication and Important Safety Information - Baraclude® (Entecavir):**

**Indication**

Baraclude (entecavir) is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults and pediatric patients 2 years of age or older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

The following points should be considered when initiating therapy with Baraclude:

- In adult patients, this indication is based on clinical trial data in nucleoside-inhibitor treatment-naïve and lamivudine-resistant subjects with HBeAg-positive and HBeAg-negative HBV infection and compensated liver disease and a more limited number of subjects with decompensated liver disease.

- In pediatric patients 2 years of age and older, this indication is based on clinical trial data in nucleoside-inhibitor-treatment-naïve and in a limited number of lamivudine-experienced subjects with HBeAg-positive chronic HBV infection and compensated liver disease.

**Important Safety Information**

**Warnings: Severe Acute Exacerbations of Hepatitis B, Patients Co-infected with HIV and HBV, and Lactic Acidosis and Hepatomegaly**

- Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

- Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if Baraclude is used to treat chronic HIV infection in patients with HIV infection that is not being treated. Therapy with Baraclude is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART).

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, alone or in combination with antiretrovirals.

**Warnings and Precautions**

- Before initiating Baraclude therapy, HIV antibody testing should be offered to all patients. Baraclude has not been studied as a treatment for HIV infection and is not recommended for this use.
Lactic acidosis with BARACLUDE use has been reported, often in association with hepatic decompensation, other serious medical conditions, or drug exposures. Patients with decompensated liver disease may be at higher risk for lactic acidosis. BARACLUDE should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

**Adverse Reactions**

- In clinical trials in patients with compensated liver disease, the most common (≥3%) adverse reactions of any severity with at least a possible relation to study drug for BARACLUDE-treated subjects were headache, fatigue, dizziness, and nausea. In these trials, the most common adverse reactions of moderate to severe intensity (grades 2-4) were diarrhea, dyspepsia, nausea, vomiting, fatigue, headache, dizziness, somnolence, and insomnia.

- In the decompensated liver disease trial, the most common adverse reactions of any severity among patients treated with BARACLUDE, regardless of causality, included: peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%). In this trial, 18% (18/102) of BARACLUDE patients and 20% (18/89) of adefovir patients died during the first 48 weeks of therapy. The majority of those deaths were due to liver related causes.

**Drug Interactions**

- BARACLUDE (entecavir) is primarily eliminated by the kidneys; therefore coadministration of BARACLUDE with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. Patients should be monitored closely when receiving BARACLUDE with other renally-eliminated drugs.

**Pregnancy and Nursing Mothers**

- There are no adequate and well-controlled studies of BARACLUDE in pregnant women. BARACLUDE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- There are no studies on the effect of BARACLUDE on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.

- It is not known whether BARACLUDE is excreted into human milk; however, many drugs are excreted into breast milk. Due to the potential for serious adverse reactions in nursing infants from BARACLUDE, risks and benefits should be considered when deciding whether to discontinue breast-feeding or discontinue BARACLUDE in nursing women.

**Pediatric Use**

- The adverse reactions observed in pediatric patients who received treatment with BARACLUDE were consistent with those observed in clinical trials of BARACLUDE in adults. Adverse drug reactions reported in greater than 1% of pediatric patients included abdominal pain, rash events, poor palatability (“product taste abnormal”), nausea, diarrhea, and vomiting.

- Due to limited data, in lamivudine-experienced pediatric patients, Baraclude should be used only if the potential benefit justifies the potential risk to the child. Consideration should be given to the impact of BARACLUDE on future treatment options.

**Renal Impairment**

- Dosage adjustment of BARACLUDE is recommended for patients with a creatinine clearance <50 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis. There is insufficient data to recommend specific dosage adjustments of BARACLUDE in pediatric patients with renal impairment, however dosage adjustments similar to those for adults should be considered.

**Liver Transplant Recipients**

Renal function must be carefully monitored both before and during treatment with BARACLUDE in a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus.

**Duration of Therapy**

- The optimal duration of treatment with BARACLUDE for patients with chronic HBV infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

**Additional Information**

BARACLUDE is not a cure for HBV. Patients should be advised that treatment with BARACLUDE has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.

**Please click here for the BARACLUDE full prescribing information, including Boxed WARNINGS.**

**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 about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

**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, 2016, 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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#BMY receives China FDA approval for #HCV regimen