Real-World Study Shows ZEPATIER® (Elbasvir and Grazoprevir) Resulted in High Rates of Sustained Virologic Response in Patients with Chronic Hepatitis C Infection Who Have Chronic Kidney Disease

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Observational Analysis Evaluated Patients in U.S. Veterans Affairs System

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside of the United States and Canada, today announced the presentation of findings from a retrospective database analysis of patients with chronic hepatitis C virus (HCV) genotype (GT) 1 or 4 infection who have chronic kidney disease (CKD) and were treated with ZEPATIER® (elbasvir and grazoprevir) in the U.S. Department of Veterans Affairs (VA) healthcare system. Among patients who completed therapy, the analysis showed 95.6 percent (714/747) of patients with severe CKD (stages 4-5, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²) and 97.1 percent (758/781) of patients with moderate CKD (stage 3, defined as eGFR 30-59 mL/min/1.73 m²) achieved sustained virologic response (SVR), defined as HCV RNA below the limit of quantification at least 10-12 weeks after the end of treatment. For patients with missing HCV RNA data after at least 10-12 weeks after treatment completion, analyses were conducted on a post-hoc basis using the last HCV RNA data available after week 4 after therapy completion. The response rates in the real-world setting of the VA further supplement findings from controlled clinical studies of ZEPATIER. These findings will be presented today at The Liver Meeting® 2017 taking place in Washington, D.C.

In the United States, ZEPATIER is indicated for the treatment of chronic HCV GT1 or GT4 infection in adults. ZEPATIER is indicated for use with ribavirin (RBV) in certain patient populations. The U.S. Prescribing Information for ZEPATIER includes a Boxed Warning about the risk of hepatitis B virus (HBV) reactivation in patients co-infected with HCV and HBV. In controlled clinical studies of ZEPATIER, SVR was the primary endpoint defined as HCV RNA less than lower limit of quantification at 12 weeks after the cessation of treatment (SVR12).

“These results demonstrate that U.S. veterans with chronic hepatitis C infection can achieve virologic cure in a real-world setting despite having co-morbid chronic kidney disease,” said Jennifer Kramer, investigator, Center for Innovations in Quality, Effectiveness and Safety at the Michael E. DeBakey VA Medical Center, Houston, Texas, and assistant professor of medicine, department of medicine, Baylor College of Medicine. “There is an ongoing need for an increased focus on screening and treating veterans and others who are disproportionately impacted by this disease.”

The retrospective observational analysis included 5,845 patients with chronic HCV infection who received ZEPATIER (elbasvir and grazoprevir) between February 1 and December 31, 2016. Patients were identified from the VA Corporate Data Warehouse, a national repository of VA electronic medical records. Presence of chronic kidney disease was measured via eGFR, per the National Kidney Foundation’s Modification of Diet in Renal Disease equation. Of 4,693 patients evaluated in the per-protocol population, 16.6 percent (781/4693) had CKD stages 4 or 5. Please see additional information below about the design, methodology and limitations of this observational analysis.

“Researching the needs of veterans is part of our collective responsibility to those who have served our country,” said Susan Shiff, senior vice president, Center for Observational and Real-World Evidence, Merck. “The robust nature of VA medical data enables us to study the effectiveness of ZEPATIER for the treatment of chronic hepatitis C infection in people with kidney disease and other comorbid conditions in that real-world setting.”

Adverse event data were not collected as part of this real-world data analysis.

Most patients with chronic kidney disease in the analysis were male (96.9%, 1481/1528); African American (67.5%, 1031/1528) and either had GT1a infection (52.2%, 798/1528) or GT1b infection (42.1%, 644/1528). The mean age for patients in the study with chronic kidney disease was 64.9 years. Comorbid conditions as defined by ICD-9/10 codes in the VA database included depression (58.5%, 894/1528), diabetes (69.2%, 1057/1528), compensated cirrhosis (18.6%, 284/1528), and HIV (5.0%, 76/1528). In the study, 19.9 percent of patients (304/1528) were coded as having decompensated cirrhosis;
ZEPATIER® is not for use in patients with moderate or severe hepatic impairment (Child Pugh B or C). See Selected Safety Information below for more information.

**Study Methodology**

The database included patients ages 18 and older with chronic HCV infection who initiated treatment with ZEPATIER between February 1, 2016, and December 31, 2016, and had at least one inpatient or outpatient visit within a year prior to treatment (n=5846). The study excluded patients without ≥2 eGFR values at least 90 days apart or on-treatment HCV RNA data, patients who did not receive 12-16 weeks of treatment with ZEPATIER and patients who received RBV >1 month after initiating treatment (n=1152).

SVR was defined in the protocol for these analyses as HCV RNA below the limit of quantification at least 10-12 weeks after the end of treatment. For patients with missing HCV RNA data at week 10-12 after treatment completion, analyses were conducted on a post-hoc basis using HCV RNA data captured starting from week 4 after therapy completion. SVR data at least 12 weeks after completion of therapy was available for 81.9% of the analysis population.

**About Real-World Data Analyses and Associated Limitations**

Real-world studies analyze data generated outside of randomized clinical trials, such as through analyses of electronic medical records or claims databases, to provide insight into how medicines perform or are used from a clinical and economic viewpoint in real-world clinical settings. Information from real-world analyses alone does not provide sufficient evidence to validate efficacy or safety of a therapeutic regimen and does not provide a substitute for evidence obtained from randomized controlled clinical trials.

This study is subject to certain limitations. The VA population may not be generalizable to the entire U.S. population, due in part to the potential for a differing demographic make-up and/or risk factors. Bias may exist as diagnoses and co-morbidities were identified through ICD-9/10 codes. Treatment completion was identified through prescription records which may not reflect adherence. Database analyses are also prone to errors in coding and missing data, including unavailable SVR data. Additionally, some laboratory data including data on the presence of baseline NS5A resistance associated substitutions was not available at the time of this analysis.

**About the VA Corporate Data Warehouse (CDW)**

The Department of Veterans Affairs Veterans Healthcare Administration (VHA) is supported by one of the largest integrated healthcare information systems in the United States. The VHA’s Corporate Data Warehouse (CDW) was developed in 2006 to accommodate the massive amounts of data being generated from more than 20 years of use and to streamline the process of knowledge discovery to application.

**About ZEPATIER® (elbasvir and grazoprevir) 50mg/100mg Tablets**

ZEPATIER is a fixed-dose combination product containing elbasvir, a HCV NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor. In the United States, ZEPATIER is indicated for the treatment of chronic HCV GT1 or 4 infection in adults. ZEPATIER is indicated for use with ribavirin (RBV) in certain patient populations. The efficacy of ZEPATIER has not been established in patients who have previously failed treatment with other regimens that included an NS5A inhibitor.

**Selected Safety Information about ZEPATIER**

The US Prescribing Information for ZEPATIER contains a Boxed Warning about the risk of hepatitis B virus (HBV) reactivation in patients coinfected with HCV and HBV. Healthcare professionals should test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating treatment with ZEPATIER. 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. Healthcare professionals should monitor HCV/HBV coinfected patients for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Healthcare professionals should initiate appropriate patient management for HBV infection as clinically indicated.

HBV reactivation has been reported in HBsAg positive patients and also in patients with serologic evidence of resolved HBV infection (ie, HBsAg negative and anti-HBc positive). The risk of HBV reactivation may be increased in patients receiving some immunosuppressant or chemotherapeutic agents. HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, ie, increases in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

ZEPATIER (elbasvir and grazoprevir) is not for use in patients with moderate or severe hepatic impairment (Child Pugh B or C). ZEPATIER is also not for use with inhibitors of organic anion transporting polypeptides 1B1/3 (OATP1B1/3) that are known or expected to significantly increase grazoprevir plasma concentrations (e.g., atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cyclosporine), strong cytochrome P450 3A (CYP3A) inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s Wort), and efavirenz. If ZEPATIER (elbasvir and grazoprevir) is administered with RBV, healthcare professionals should refer to the prescribing information for RBV as the contraindications, warnings and precautions, adverse reactions and dosing for RBV also apply to this combination regimen.

Elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 1% of subjects, generally at or after treatment week 8. These late ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Healthcare professionals should perform hepatic lab testing on patients prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic lab testing should be performed at treatment week 12.

Patients should be instructed to consult their healthcare professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces. Healthcare providers should consider discontinuing...
ZEPATIER (elbasvir and grazoprevir) if ALT levels remain persistently greater than 10 times ULN. ZEPATIER should be discontinued if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio.

The concomitant use of ZEPATIER with certain drugs may lead to adverse reactions or reduced therapeutic effect due to drug interactions. Certain strong CYP3A inhibitors may increase the plasma concentration of ZEPATIER, leading to possibly clinically significant adverse reactions. Moderate CYP3A inducers may decrease the plasma concentration of ZEPATIER, leading to reduced therapeutic effect and possible development of resistance. Coadministration of ZEPATIER with these drugs is not recommended. Physicians should consult the Prescribing Information for potential drug interactions.

In subjects receiving ZEPATIER for 12 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% in placebo-controlled trials) were fatigue, headache and nausea. In subjects receiving ZEPATIER with RBV for 16 weeks, the most commonly reported adverse reactions of moderate or severe intensity (greater than or equal to 5%) were anemia and headache.

**Selected Dosage and Administration Information for ZEPATIER ® (elbasvir and grazoprevir)**

ZEPATIER is a single tablet taken once daily. The recommended dosing is 12 or 16 weeks with or without RBV, depending on HCV genotype, prior treatment history and, for patients with genotype 1a infection, presence of certain baseline NS5A resistance-associated polymorphisms. See Prescribing Information for ZEPATIER for specific dosage regimens and durations. Refer to RBV prescribing information for RBV dosing and dosage modifications when ZEPATIER is given with RBV. To determine dosage regimen and duration of ZEPATIER for genotype 1a patients, testing for the presence of virus with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, or 93 is recommended prior to initiating treatment.

**About Merck**

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world’s most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer’s disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

**Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA**

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2016 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).


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