יוני 2021

רופא/ה יקר/ה
רוקח/ת יקר/ה,

הנדון: **ZEPATIER® TABLETS**
זפטייר טבליות

Dosage form and Composition:
Elbasvir 50mg and Grazoprevir 100mg; Tablets

חברת מרק שארפ ודוהם (ישראל-1996) בע"מ, (MSD ישראל), מבקשת ליידע על עדכון בעלון לרופא ובעלון לצרכן של Zepatier Tablets כמפורט להלן.

ההתוויה המאושרת לתכשיר:
ZEPATIER is indicated for the treatment of chronic hepatitis C (CHC) genotypes 1 or 4 infection in adults.

עדכונים מהותיים שבוצעו בעלון לרופא (טקסט שהוסף לעלון לרופא מודגש בקו תחתון):

2 DOSAGE AND ADMINISTRATION

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2.4 Hepatic Impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation *[see Contraindications (4), Warning and Precautions (5.3), Use in Specific Populations (8.9), and Clinical Pharmacology (12.3)].*

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4 CONTRAINDICATIONS

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- ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of hepatic decompensation due to the risk of hepatic decompensation *[see Warnings and Precautions (5.3), Use in Specific Populations (8.9)].*

5 WARNING AND PRECAUTIONS

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5.3 Risk of Hepatic Decompensation/Failure in Patients with Evidence of Advanced Liver Disease

Postmarketing cases of hepatic decompensation/failure, including those with fatal outcomes, have been reported in patients treated with HCV NS3/4A protease inhibitor-containig regimens, including ZEPATIER.

Reported cases occurred in patients treated with HCV NS3/4A protease inhibitor-containing regimens with baseline cirrhosis with and without moderate or severe liver impairment (Child-Pugh B or C) as well as some patients without cirrhosis. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatic laboratory testing should be performed in all patients [see Warnings and Precautions (5.2)]. In patients with compensated cirrhosis (Child-Pugh A) or evidence of advanced liver disease, such as portal hypertension, more frequent hepatic laboratory testing may be warranted; and patients should be monitored for signs and symptoms of hepatic decompensation such as the presence of jaundice, ascites, hepatic encephalopathy, and variceal hemorrhage. Discontinue ZEPATIER in patients who develop evidence of hepatic decompensation/failure.

ZEPATIER is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation [see Contraindications (4), Adverse Reactions (6.1), Use in Specific Populations (8.9), and Clinical Pharmacology (12.3)].

6 ADVERSE REACTIONS

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6.2 Postmarketing Experience

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Hepatobiliary Disorders
Hepatic decompensation, hepatic failure [see Warnings and Precautions (5.3)]

7 DRUG INTERACTIONS

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7.2 Established and other Potentially Significant Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with ZEPATIER, doses should be readjusted after administration of ZEPATIER is completed.

Clearance of HCV infection with direct-acting antivirals may lead to changes in hepatic function, which may impact the safe and effective use of concomitant medications. For example, altered blood glucose control resulting in serious symptomatic hypoglycemia has been reported in diabetic patients in postmarketing case reports and published epidemiological studies. Management of hypoglycemia in these cases required either discontinuation or dose modification of concomitant medications used for diabetes treatment.

Frequent monitoring of relevant laboratory parameters (e.g., International Normalized Ratio [INR] in patients taking warfarin, blood glucose levels in diabetic patients) or drug concentrations of concomitant medications such as CYP450 substrates with a narrow therapeutic index (e.g., certain immunosuppressants) is recommended to ensure safe and effective use. Dose adjustments of concomitant medications may be necessary.

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8 USE IN SPECIFIC POPULATIONS

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8.9 Hepatic Impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in patients with severe hepatic impairment (Child-Pugh C) due to a 12-fold increase in grazoprevir exposure in non-HCV infected Child-Pugh C subjects. In addition, postmarketing cases of hepatic decompensation/failure have been reported in patients with advanced liver disease *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)].*

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12 CLINICAL PHARMACOLOGY

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12.4 Microbiology

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In Postmarketing Observational Studies

Effectiveness (SVR12 rates) in observational studies can be subject to certain biases and confounding factors that cannot be accounted for in the analyses, in part due to the nature of the study designs and populations under study.

Protocol 095

In Protocol 095, a sub-study of a prospective, observational comparative study, effectiveness of treatment with ZEPATIER plus ribavirin for 16 weeks was assessed in 29 HCV genotype 1a-infected patients with 1 or more baseline NS5A polymorphisms at amino acid positions M28, Q30, L31, and/or Y93. Overall, the SVR12 rate for patients with 1 or more baseline NS5A polymorphisms at any of the 4 amino acid positions was 93% (27/29). 23 patients had a NS5A polymorphism at a single amino acid position at baseline. The SVR12 rates for patients with a single polymorphism at amino acid position M28, Q30, L31, or Y93 were 100% (14/14), 100% (1/1), 33% (1/3), and 100% (5/5), respectively. Six patients had NS5A polymorphisms at more than 1 amino acid position (M28, Q30, L31, and/or Y93) at baseline. The SVR12 rate for these patients was 100% (6/6).

VA NS5A Cohort Study

In a retrospective Veterans Administration (VA) NS5A cohort study, effectiveness of treatment with ZEPATIER plus ribavirin for 16 weeks was assessed in 93 HCV genotype 1a-infected patients with 1 or more baseline NS5A polymorphisms at amino acid positions M28, Q30, L31, and/or Y93. Overall, the SVR12 rate for patients with 1 or more baseline NS5A polymorphisms at any of the 4 amino acid positions was 81% (75/93). 65 patients had a NS5A polymorphism at a single amino acid position at baseline. The SVR12 rates for patients with a single polymorphism at amino acid position M28, Q30, L31, or Y93 were 94% (16/17), 100% (8/8), 84% (16/19), and 81% (17/21), respectively. 28 patients had NS5A polymorphisms at more than 1 amino acid position (M28, Q30, L31, and/or Y93) at baseline. The SVR12 rate for these patients was 64% (18/28).

<u>עדכונים מהותיים שבוצעו בעלון לצרכן</u> (טקסט שהוסף לעלון לצרכן מודגש ב<u>קו תחתון</u>):

עדכונים בפרק: 4. תופעות לוואי

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סימנים של בעיות כבד. זפטייר עשוי לגרום לעליות בבדיקות דם הקשורות לכבד. הדבר יכול להיות סימן לבעיות כבד חמורות. הרופא שלך יבצע בדיקות דם על מנת לבדוק את הכבד שלך, לפני ובזמן נטילת **זפטייר**. ספר לרופא שלך מיד אם אתה מפתח כל אחד מהתסמינים הבאים או אם הם מחמירים במהלך הטיפול ב**זפטייר:**

- איבוד תיאבון
- בחילה והקאה
- תחושת עייפות או חולשה
- <u>בלבול</u>
- <u>ישנוניות</u>
- <u>הקאה דמית</u>
- הצהבה של העור או העיניים שלך
- שינויים בצבע הצואה <u>או השתן</u> שלך
- <u>דימום או חבורות ביתר קלות מהרגיל</u>
- <u>שלשול</u>
- <u>נפיחות באזור הבטן או כאב בצד ימין עליון של אזור הקיבה</u>

בעלונים לרופא ולצרכן בוצעו עדכונים נוספים שאינם נכללים בהודעה זו.

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, חברת MSD, בטלפון 09-9533333.
Zepatier tablets מופצת ע"י חברת נובולוג בע"מ.

בברכה,
שלי ישי
רוקחת ממונה
MSD ישראל

References:
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Zepatier_Tablets-PIL_HEB-06_2021