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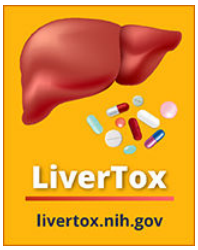


Zepatier

Updated: March 22, 2018.

OVERVIEW

Introduction

Zepatier is an oral, fixed combination of antiviral agents that is used to treat chronic hepatitis C, genotypes 1 and 4. This combination has been associated with low rate of transient serum enzyme elevations during therapy, but has not been implicated in cases of clinically apparent liver injury with jaundice.

Background

Zepatier is the commercial name for a combination of antiviral agents used to treat chronic hepatitis C associated with HCV genotypes 1 and 4. The hepatitis C virus (HCV) encodes several nonstructural (NS) polypeptides that are essential for its replication, NS3/4 that has protease and helicase activities, NS5A that is a membrane bound polypeptide of uncertain purpose and NS5B an HCV specific, RNA-dependent, RNA polymerase. These polypeptides are effective targets for antiviral therapy of hepatitis C. Zepatier is a fixed dose combination of grazoprevir (graz oh' pre vir) which is a potent HCV NS3/4 protease inhibitor and elbasvir (elb' as vir) an NS5A inhibitor. In cell culture and in humans infected with HCV, each of these agents has potent activity against HCV, but antiviral resistance arises rapidly with continued exposure. The combination of several direct acting agents with different molecular targets allows for a sustained viral suppression while avoiding antiviral resistance. The combination of these two agents with and without the ribavirin (an antiviral nucleoside analogue with activity against HCV) was shown to be very effective in suppressing HCV replication in patients infected with HCV genotypes 1 and 4, and to result in sustained virological responses and eradication of HCV in more than 95% of patients when given for 12 weeks or more. Zepatier was approved for use in the United States in 2016, the third all-oral antiviral combination to receive approval for chronic hepatitis C. It is available as tablets with the fixed dose combination of 100 mg of grazoprevir and 50 mg of elbasvir. The recommended dose in adults is 1 tablet daily for 12 weeks. The addition of ribavirin for 12 weeks and prolongation of therapy to 16 weeks is recommended for some groups of HCV infected patients, such as those with previous non-response to antiviral therapy and those with preexisting resistance associated viral variants. Current indications are limited to patients with HCV genotypes 1 and 4. Side effects are uncommon, but are generally mild and can include fatigue, headache and nausea.

Hepatotoxicity

In large randomized controlled trials, serum aminotransferase elevations more than 5 times the upper limit of normal (ULN) occurred in 1% of Zepatier treated patients, but were infrequent in placebo recipients. The elevations were generally asymptomatic and short-lived, often arising after the first 4 weeks of therapy and resolving with or without dose modification and only rarely requiring early discontinuation. In some instances,

ALT levels rose above 10 times the upper limit of normal, but these elevations were not accompanied by symptoms or jaundice and were invariably self-limited. In the many preregistration trials, Zepatier was not associated with instances of clinically apparent liver injury.

However, two forms of liver injury have been associated with direct-acting antiviral agents used to treat chronic hepatitis C, and these reactions appear to occur with all regimens. The first is acute decompensation of HCV-related cirrhosis. The liver injury usually arises within 2 to 6 weeks of starting antiviral therapy, but can occur later and even after discontinuation. The injury is marked by worsening jaundice and appearance of signs of hepatic failure such as ascites or hepatic encephalopathy, often with little or no change in serum aminotransferase levels. Lactic acidosis may be present early. The course is variable but calls for prompt discontinuation of treatment despite successful suppression of HCV RNA levels. Some instances have led to death or need for emergency liver transplantation. For this reason, patients with cirrhosis undergoing antiviral therapy with potent direct acting agents, such as Zepatier, should be monitored carefully, particularly during the first few weeks of treatment. This syndrome has not been clearly linked to therapy with grazoprevir and elbasvir, but this regimen has not been evaluated in patients with advanced cirrhosis due to hepatitis C.

A second, liver complication of therapy of chronic hepatitis C is reactivation of hepatitis B. This occurs most frequently in patients who have HBsAg in serum but rare instances have arisen in subjects with anti-HBc without HBsAg. The cause of the reactivation of hepatitis B during antiviral therapy of hepatitis C is unknown, but may relate to the inhibition of HBV replication during HCV replication. For this reason, patients with hepatitis C who are to receive antiviral therapy should be screened for HBsAg and anti-HBc. Those with HBsAg are best managed by concurrent treatment with an antiviral agent active against HBV, such as entecavir or tenofovir. Subjects with anti-HBc without HBsAg rarely experience reactivation and can be managed by careful monitoring for HBV DNA levels during treatment and institution of therapy for HBV if levels appear de novo or rise significantly. Reactivation of hepatitis B has been described with many regimens, although not specifically with grazoprevir and elbasvir.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which elbasvir and grazoprevir might cause liver injury is not known. Both are metabolized in the liver largely via the cytochrome P450 system, predominantly CYP 1A2, and liver injury may be due to production of a toxic or immunogenic metabolite. Zepatier is also susceptible to drug-drug interactions with strong inducers or inhibitors of CYP 3A4.

Outcome and Management

While chronic therapy with grazoprevir and elbasvir can be associated with mild-to-moderate serum aminotransferase elevations, it has not been convincingly linked to cases of clinically apparent liver injury. Nevertheless, monitoring of serum aminotransferase levels monthly during the 12 weeks of therapy is recommended. Patients who develop aminotransferase elevations on therapy should be monitored more carefully, and Zepatier should be permanently discontinued if jaundice or symptoms of liver injury arise or if serum ALT or AST levels are persistently above 5 times the ULN. Patients with cirrhosis should be monitored for signs and symptoms of hepatic decompensation and therapy stopped promptly if these arise. All patients receiving antiviral therapy for hepatitis C should be screened for HBsAg and anti-HBc and either monitored carefully for evidence of reactivation or given prophylactis with agents active against hepatitis B during therapy and for several weeks thereafter.

Drug Class: Antiviral Agents, Hepatitis C Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Elbasvir, Grazoprevir – Zepatier®

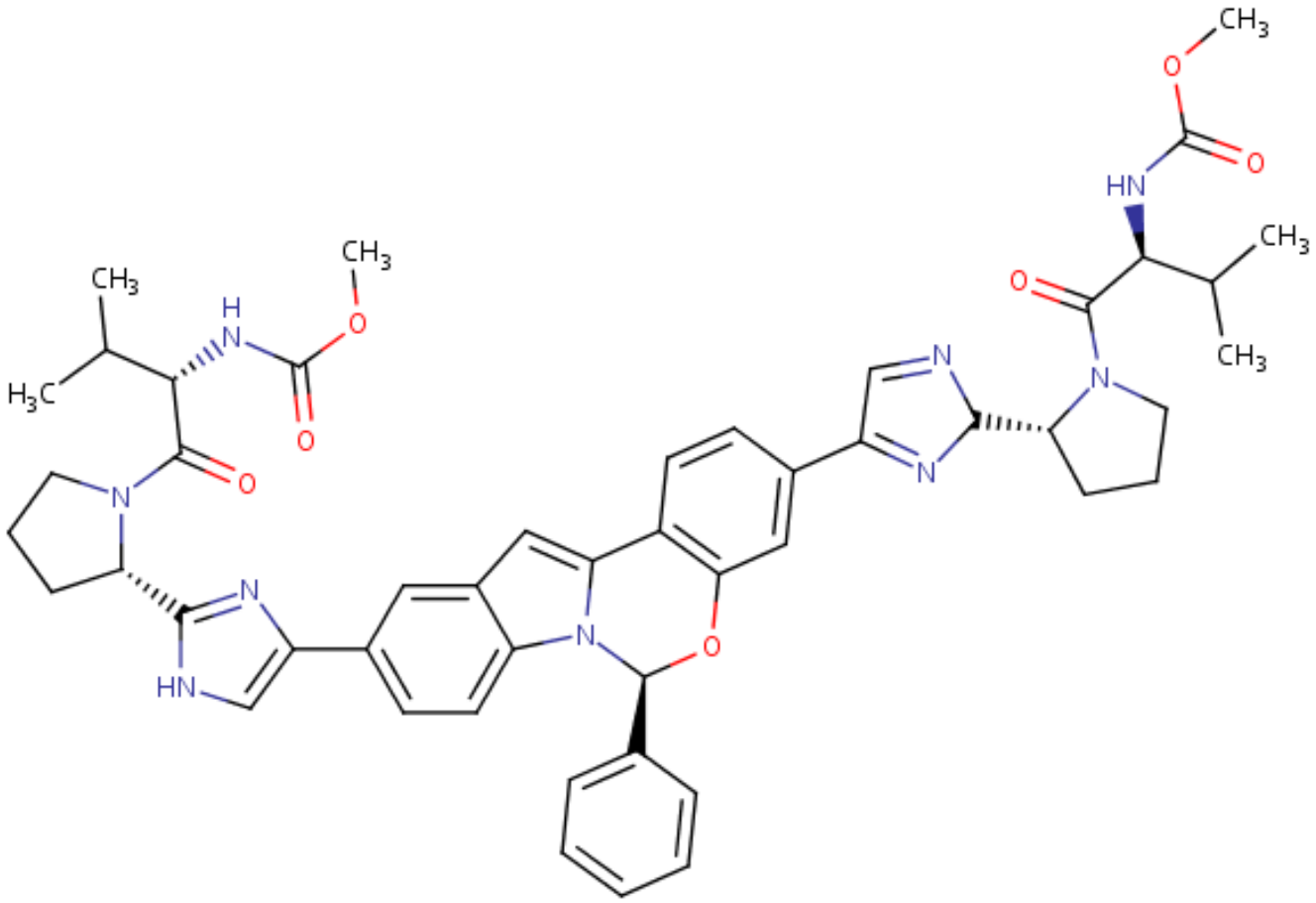
DRUG CLASS

Hepatitis C Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Elbasvir	1370468-36-2	C49-H55-N9-O7	

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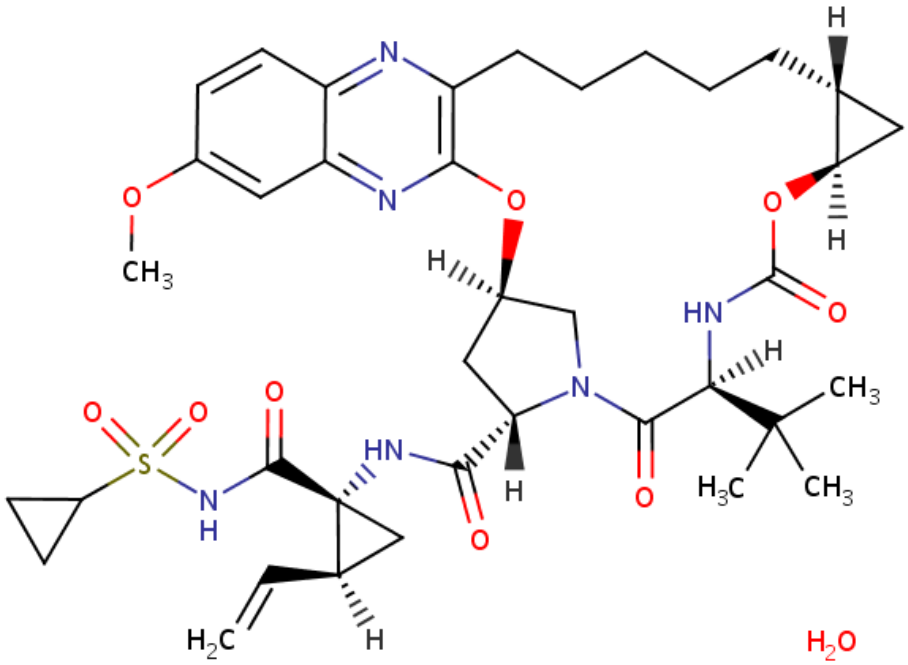
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Grazoprevir	1350462-55-3	C38-H50-N6-O9-S.H2-O	

ANNOTATED BIBLIOGRAPHY Zepatier, Elbasvir, Grazoprevir

References updated: 22 March 2018

Forns X, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, Gilbert C, et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. J Hepatol 2015; 63: 564-72. PubMed PMID: 25895428.

(Among 79 adults with previously treated chronic hepatitis C, genotype 1, who received grazoprevir, elbasvir and ribavirin for 12 weeks, the overall response rate was 96%, 5 had a serious adverse event, but none were hepatic and no patient had ALT elevations above baseline).

Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, Alric L, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2015; 385 (9973): 1075-86. PubMed PMID: 25467591.

(Among 253 patients with chronic hepatitis C genotype 1 treated with grazoprevir and elbasvir with or without ribavirin for 12 or 18 weeks, response rates averaged 95% [90-100%] and were independent of ribavirin or duration; serious adverse events occurred in 3% and late elevations in ALT in 6 [2%], which were self-limited in all and above 5 times ULN in only 1 patient).

Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, Kugelmas M, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2015; 385 (9973): 1087-97. PubMed PMID: 25467560.

(Among 218 patients with chronic hepatitis C, genotype 1 with or without HIV infection who were treated with grazoprevir and elbasvir with or without ribavirin in 5 different treatment groups, the overall response rate was 80% with 8 weeks and 87-96% with 12 weeks of treatment; late elevations in ALT or AST occurred in 3 patients, but all were less than 5 times ULN and did not result in dose modification or early discontinuations).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 12 were attributed to antiviral agents, but none for the oral direct acting agents used to treat chronic hepatitis C).

Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, Zhao Y, Brown DD, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med 2015; 163: 1-13. PubMed PMID: 25909356.

(Among 421 patients with chronic hepatitis C, genotypes 1, 4 and 6, treated with grazoprevir and elbasvir or placebo for 12 weeks, the overall response rate was 95% and serious adverse events occurred in 3% of both groups; late ALT or AST elevations above twice normal occurred in 7 patients and were above 5 times ULN in 4 [1.3%], leading to early discontinuation in 2 patients but not associated with elevations in bilirubin or symptoms).

Buti M, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, Gilbert C, et al. Grazoprevir, elbasvir, and ribavirin for chronic hepatitis C virus genotype 1 infection after failure of pegylated interferon and ribavirin

with an earlier-generation protease inhibitor: final 24-week results from C-SALVAGE. Clin Infect Dis 2016; 62: 32-6. PubMed PMID: 26371152.

(Among 79 patients with chronic hepatitis C, genotype 1, who had failed previous therapy with peginterferon, ribavirin and a protease inhibitor and who were treated with a 12 week course of grazoprevir, elbasvir and ribavirin, the overall response rate was 96%; no mention of adverse events [see Forns 2015]).

Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, Matthews GV, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV 2015; 2 (8): e319-27. PubMed PMID: 26423374.

(Among 218 patients with chronic hepatitis C, genotypes 1 and 4, and HIV coinfection treated with grazoprevir and elbasvir for 12 weeks, the overall response rate was 96%, 2 patients had unexplained elevations in ALT and AST above 5 times ULN, but both resolved without dose modification and without symptoms or jaundice).

Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour H Jr, Martin P, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet 2015; 386: 1537-45. PubMed PMID: 26456905.

(Among 224 patients with chronic hepatitis C, genotype 1, and renal insufficiency who were treated with grazoprevir and elbasvir or placebo for 12 weeks, the response rate to active therapy was 94% and adverse events were similar if not less among antiviral vs placebo treated patients, serious adverse events occurring in 14% vs 17%, deaths in 0.8% vs 2.7% and ALT elevations in 3% vs 38%).

European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015; 63: 199-236. PubMed PMID: 25911336.

(Guidelines for the antiviral therapy of chronic hepatitis C from the European liver disease research and academic society).

AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62: 932-54. PubMed PMID: 26111063.

(Guidelines for the antiviral therapy of chronic hepatitis C from the US liver and infectious diseases research and academic societies).

Elbasvir/grazoprevir (Zepatier) for hepatitis C. Med Lett Drugs Ther 2016; 58 (1489): 25-7. PubMed PMID: 26938699.

(Concise review of the mechanism of action, clinical efficacy, side effects and costs of the fixed combination of elbasvir and grazoprevir known as Zepatier, shortly after its approval for use in the United States, mentions minor side effects of fatigue, headache and nausea and that ALT elevations occurred in 1% of treated patients and that the agent is contraindicated in patients with cirrhosis).

Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, Luetkemeyer A, et al; C-EDGE CO-STAR Study Group. Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med 2016; 165: 625-34. PubMed PMID: 27537841.

(Among 301 adults with chronic hepatitis C [genotype 1, 4 or 6] who were receiving opioid agonist therapy and were treated with elbasvir and grazoprevir vs placebo for 12 weeks, the SVR rates were 91% vs 0%, and ALT elevations above 3 times baseline occurred in placebo recipients only [2%]).

Sperl J, Horvath G, Halota W, Ruiz-Tapiador JA, Streinu-Cercel A, Jancoriene L, Werling K, et al. Efficacy and safety of elbasvir/grazoprevir and sofosbuvir/pegylated interferon/ribavirin: A phase III randomized controlled trial. J Hepatol 2016; 65: 1112-9. PubMed PMID: 27542322.

(Concise summary of the efficacy, side effects, drug interactions and costs of grazoprevir and elbasvir shortly after the approval of Zepatier in the US mentions that ALT elevations occur in 1% of patients but are generally transient and asymptomatic, and that Zepatier is considered contraindicated in patients with advanced cirrhosis).

Brown A, Hézode C, Zuckerman E, Foster GR, Zekry A, Roberts SK, Lahser F, et al.; C-SCAPE Study Investigators. Efficacy and safety of 12 weeks of elbasvir ± grazoprevir ± ribavirin in participants with hepatitis C virus genotype 2, 4, 5 or 6 infection: The C-SCAPE study. J Viral Hepat 2017 Nov 20. [Epub ahead of print] PubMed PMID: 29152828.

(Among 98 adults with chronic hepatitis C with genotypes 2, 4, 5 and 6 treated with grazoprevir and elbasvir, two had late rises in ALT, but details were not provided).

Gane E, Nahass R, Luketic V, Asante-Appiah E, Hwang P, Robertson M, Wahl J, et al. Efficacy of 12 or 18 weeks of elbasvir plus grazoprevir with ribavirin in treatment-naïve, noncirrhotic HCV genotype 3-infected patients. J Viral Hepat 2017; 24: 895-9. PubMed PMID: 28470815.

(Among 41 patients with chronic hepatitis C, genotype 3, without cirrhosis who were treated with elbasvir, grazoprevir and ribavirin, SVR rates were 45% [12 weeks] and 57% [18 weeks of therapy], and there were no late rises in ALT or AST levels).

Boyd SD, Tracy L, Komatsu TE, Harrington PR, Viswanathan P, Murray J, Sherwat A. US FDA perspective on elbasvir/grazoprevir treatment for patients with chronic hepatitis C virus genotype 1 or 4 infection. Clin Drug Investig 2017; 37: 317-26. PubMed PMID: 28102520.

(Summary of data on efficacy of elbasvir and grazoprevir that supported their FDA approval as therapy of hepatitis C, mentions SVR rates of 92-94% for genotype 1a, 96-99% for genotype 1b, and 96-100% for genotype 4; no discussion of adverse events, ALT elevations or hepatic decompensation during therapy).

Zeuzem S, Serfaty L, Vierling J, Cheng W, George J, Sperl J, Strasser S, et al. The safety and efficacy of elbasvir and grazoprevir in participants with hepatitis C virus genotype 1b infection. J Gastroenterol 2018 Jan 17. [Epub ahead of print] PubMed PMID: 29344726.

(Among 1070 adults with chronic hepatitis C, genotype 1b, treated with elbasvir and grazoprevir for 12 weeks in 11 prelicensure studies, the overall SVR rate was 97%, and 12 patients [1%] had a late rise in ALT levels to above 5 times ULN, none of whom developed jaundice, but 2 had therapy discontinued early with peak ALT levels of 472 and 703 U/L).

Nassar AH, Abdul-Jawad BM, Barnes DS. Hepatic failure due to cholestatic hepatitis C in an immunosuppressed patient treated With elbasvir and grazeprevir. ACG Case Rep J 2018 Jan 17; 5: e6. PubMed PMID: 29392153.

(73 year old man with chronic inflammatory demyelinating polyneuropathy on prednisone and intravenous immunoglobulin therapy developed acute hepatitis C with a fulminant cholestatic course was started on elbasvir and grazoprevir, but continued to worsen and died 12 days later).