Brand Name: Zepatier
Generic Name: Elbasvir/grazoprevir
Manufacturer: Merck Sharp & Dohme Corp.[2]
Drug Class: Elbasvir is an HCV NS5A inhibitor and grazoprevir is an HCV NS3/4A protease inhibitor[2,3,4,5,6]

Uses: [2,3,4,5,6]

Labeled: Chronic hepatitis C virus (HCV) genotypes 1a, 1b, or 4 as monotherapy or in combination with additional antiviral agents with or without co-infection of HIV
Off-Label: None

Mechanism of Action: [2,3,4,5,6]

Elbasvir prevents viral RNA replication and virion assembly by inhibiting HCV NS5A protein. Grazoprevir inhibits the proteolytic activity of the NS3/4A protease which is responsible for the cleavage of HCV encoded polyproteins for viral replication.

Pharmacokinetics: [2,3,4,5,6]

	Elbasvir	**Grazoprevir**
T_{max}	3-6 hrs	0.5-3 hrs
V_d	680 L	1250 L
$t_{½}$	24 hrs	31 hrs
Clearance	Not reported	Not reported
Protein Binding	99.9%	98.8%
Bioavailability	Not reported	Not reported

Metabolism: Hepatic, primarily via CYP3A and partially via oxidative metabolism. Grazoprevir is also a substrate of OATP1B1/3 and a weak inhibitor of CYP3A.
Elimination: Primarily through fecal route (90%) and less than 1% vial renal elimination.

Efficacy:
Buti M, Gordon SC, Zuckerman B, Lawitz E, Calleja JL, Hofer H, 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(1): 32-6.

Study Design: international, open-label, phase 2 trial
Description: *Methods:* Seventy-nine patients with chronic HCV genotype 1 infection who had previously failed four or more weeks of pegylated interferon with ribavirin (PR) combined with boceprevir, telaprevir, or simeprevir were administered grazoprevir 100 mg orally once daily, elbasvir 50 mg orally once daily, and ribavirin orally twice daily (total daily dose of 800-1400 mg based on weight) for 12 weeks. All patients were to be followed for 24 weeks after cessation of

therapy. Plasma HCV RNA measurements were performed at post-therapy follow-up weeks 4, 8, 12, and 24 using the COBAS Taq-Man version 2.0 assay. NS3 and NS5A genes were amplified using reverse transcriptase PCR at baseline and time of virologic failure. The primary efficacy endpoint was unquantifiable HCV RNA measured 12 weeks after the end of treatment (SVR_{12}). Descriptive statistics were used to assess response rates out to post-therapy follow-up week 24 (SVR_{24}). *Outcome Results:* At the end of therapy, HCV RNA was undetectable in 78 of 79 patients (98.7%). The SVR_{12} rate was 96.2% (95% CI, 89.3%-99.2%) with 3 out of the 79 patients relapsing within the first 8 weeks after cessation of therapy. The SVR24 rate was also 96.2% (95% CI, 89.3%-99.2%) because zero relapses occurred after follow-up week 8.

Limitations: The study was funded by Merck & Co, Inc. who was developing grazoprevir and elbasvir for treatment of hepatitis C virus infection at the time the study was performed. Also, all authors were investigators for Merck at some point. Several authors are employees of and hold stock in Merck and have been paid consultants of various pharmaceutical companies. The study was relatively small in number of subjects and was an open label design lacking a control group. The study lacked treatment naïve patients and had specific inclusion/exclusion criteria so extrapolations to other populations cannot be made confidently.

Conclusion: The results of this study show that elbasvir/grazoprevir plus ribavirin is an effective treatment option for patients with chronic hepatitis C genotype 1 who have failed previous combination of PR and an earlier-generation protease inhibitor. However, more studies need to be performed on various other patient populations.

Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour H, et al. Grazoprevir plus elbasvir in treatment-naïve 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.

Study Design: multicenter, phase 3, double-blind, randomized trial

Description: *Methods:* Two-hundred and twenty six patients were enrolled voluntarily. 11 patients were assigned to a cohort that was open-label and received grazoprevir 100 mg and elbasvir 50 mg once daily for 12 weeks and underwent intensive pharmacokinetic sampling. The rest of the patients were randomly assigned in a 1:1 fashion to receive double-blinded grazoprevir 100 mg and elbasvir 50 mg once daily for 12 weeks or placebo. At week 16, treatment groups were unmasked, and those assigned to the placebo group then received the study treatment for 12 weeks (deferred treatment group). This therapy is ongoing and results have not been published. The primary efficacy outcome was compared SVR12 for patients in the immediate treatment group versus historical control patients with a reference SVR12 of 45%. The primary safety outcome was comparison between the randomized groups. Safety events were rated either Tier 1 or 2 depending on severity. *Outcome Results:* 76% of the patients were on hemodialysis, 81% had stage 5 CKD, and 80% were HCV treatment-naïve. After 6 patients were excluded from analysis due to reasons other than virologic failure, 115 of 116 patients receiving treatment (in both immediate treatment group and pharmacokinetic group) 115 (99%) achieve SVR12 ($p<0.001$). 115 (94%) in the full

analysis set population achieved SVR12. Baseline NS3/4A or NS5A RAVs were detected in 32.1% in the immediate treatment group and 14.8% in the intensive PK population. Of these patients, SVR12 was 100% in the immediate treatment group and 94.1% in the PK group. Renal system adverse events were comparable between treatment group and placebo.

Limitations: The results of the pharmacokinetic part of the study are not published in this article. SVR24 for the immediate treatment group and SVR12 for the deferred treatment group are not reported in this article because they were not completed at the time of publishing. Merck Sharp & Dohme Corp. were involved in many aspects of the trial. Patients with decompensated liver disease and those receiving peritoneal dialysis were excluded and therefore the results cannot be extrapolated to that population. The reference historical SVR rate used was relatively low at 45%. There is no active treatment option that this was compared to.

Conclusion: The results of this study show that elbasvir/grazoprevir for 12 weeks is a safe and effective treatment option for patients with HCV genotype 1 infection and advanced stage 4-5 CKD, regardless of previous antiviral therapy. However, more studies need to be performed on various other patient populations.

KRockstroh J, Nelson M, Katlama C, Lalezari J, Mallolas J Bloch M, 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: e319-27.

Study Design: multicenter, phase 3, open-label, single-arm trial

Description: *Methods:* This study evaluated the efficacy, safety, and tolerability of grazoprevir plus elbasvir in patients with HCV and HIV co-infection. 218 patients with HCV genotypes 1, 4, or 6, baseline HCV RNA of ≥10000 IU/mL, and HIV co-infection were enrolled to received grazoprevir 100 mg plus elbasvir 50 mg once daily for 12 weeks. *Outcome Results:* 210 (96%) patients achieved SVR12 (95% CI, 92.9-98.4) which exceeds the historical reference of 70% (from the PHOTON-1 study). 75 patients (34%) experienced drug-related adverse events. Most commonly, patients experienced fatigue (5%), headache (7%), and nausea (5%), however, zero patients discontinued therapy due to adverse effects.

Limitations: Patients with decompensated liver disease, Child-Pugh class B or C, Child-Turcotte-Pugh score >6 points, hepatitis B co-infection, history of malignant disease, and evidence of hepatocellular carcinoma were excluded. This limits the ability to extrapolate the data to these populations.

Conclusion: The results of this study show that elbasvir/grazoprevir for 12 weeks is a safe and effective treatment option for patients with HCV genotype 1, 4, or 6 and HIV co-infection.

Contraindications: [2,3,4,5,6]

Moderate to severe hepatic impairment (Chid-Pugh B or C): patients with this degree of liver impairment can obtain grazoprevir plasma concentrations that are 5-12 fold greater than normal and are at increased risk for fluctuations in hepatic enzymes.

Use with OATPB1/3 inhibitors (e.g. cyclosporine, atazanavir, darunavir, lopinavir, saquinavir, tipranavir)
Use with strong CYP3A inducers
Use with efavirenz

Precautions: [2,3,4,5,6]

ALT Elevations: LFTs should be monitored prior to therapy, at treatment week 8, and as clinically indicated. If ALT levels persist >10 time ULN, consider discontinuing therapy.
Hepatitis B virus/HCV coinfection: safety and efficacy of use has not yet been established in this patient population. HBV reactivation has occurred in patients co-infected with HCV during treatment for HCV with direct-acting antiviral agents. All patients should be screen for HBV prior to initiation of therapy and should be monitor for signs of HBV infection during treatment.
Liver transplant recipients: safety and efficacy of use has not yet been established in this patient population
Use with moderate CYP3A inhibitors: not recommended
Use with strong CYP3A inhibitors: not recommended
Use with statins: recommended max daily dose of atorvastatin is 20 mg; recommended max daily dose of rosuvastatin is 10 mg

Adverse Effects: [2,3,4,5,6]

Occurring in >10% of patients

Central Nervous System

Fatigue (5%-11%)
Headache (≤11%)

Gastrointestinal

Nausea (5%-11%)

Occurring in ≥1% to <10% of patients

Central Nervous System

Anxiety (1%)
Depression (1%)
Dizziness (2%-3%)
Insomnia (3%-5%)
Irritability (1%-2%)

Dermatologic

Alopecia (1%)
Night sweats (2%)
Pruritis (≤2%)

Gastrointestinal

Abdominal pain (2%)

Constipation (2%)
Decreased appetite (2%)
Diarrhea (2%-5%)
Dyspepsia (2%)
Flatulence (2%)
Upper abdominal pain (2%)
Vomiting (1%-2%)
Xerostomia (1%-2%)

Hepatic

Increased serum ALT (≤1%)
Increased serum Bilirubin (≤2%)

Neuromuscular/Skeletal

Arthralgia (≤2%)
Increased creatine phosphokinase (2%)
Myalgia (2%)
Weakness (4%)

Otic

Tinnitus (2%)

Drug Interactions: [2,3,4,5,6]

OATP1B1/3 inhibitors: **(**e.g. cyclosporine, atazanavir, darunavir, lopinavir, saquinavir, tipranavir)

Strong CYP3A inducers: **(**e.g. rifampin, carbamazepine, phenytoin, St. John's wort, efavirenz)

Moderate CYP3A inhibitors: **(**e.g. bosentan, etravirine, modafinil, nafcillin)

Strong CYP3A inhibitors: **(**e.g. cobicistat, ketoconazole)

Warfarin: grazoprevir is a weak CYP3A inhibitor. When given in combination with warfarin, plasma concentrations of warfarin may be elevated.

It is recommended to always check drug interactions when initiating Zepatier due to the many possible interactions, some not listed above.

Dosing/Administration: [2,3,4,5,6]

Usual Dosage:

1 tablet once daily (elbasvir 50 mg and grazoprevir 100 mg) without regard to meals

HCV with or without cirrhosis treatment regimen and duration:

Genotype 1a: Treatment-naive or peginterferon alfa/ribavirin-experienced without baseline NS5A polymorphisms

Elbasvir/grazoprevir for 12 weeks

Genotype 1a: Treatment-naive or peginterferon alfa/ribavirin-experienced with baseline NS5A polymorphisms

Elbasvir/grazoprevir + ribavirin for 16 weeks

Genotype 1b: Treatment-naive or peginterferon alfa/ribavirin-experienced

Elbasvir/grazoprevir for 12 weeks

Genotype 1a or 1b: Peginterferon alfa/ribavirin/PI-experienced

Elbasvir/grazoprevir + ribavirin for 12 weeks

Genotype 4: Treatment-naïve

Elbasvir/grazoprevir for 12 weeks

Genotype 4: Peginterferon alfa/ribavirin-experienced

Elbasvir/grazoprevir + ribavirin for 16 weeks

Cost:[1,5]

$5,460 per week

$65,520 for total of 12 weeks of treatment

$87,360 for total of 16 weeks of treatment

Comparison:[1,2,12,13,14,15]

	Cost (12 weeks)	Overall SVR	Genotype
Epclusa (2016)	$89712	83-94%	1, 2, 3, 4, 5, and 6
Zepatier (2016)	$65520	94%-97% (genotype 1) 97%-100% (genotype 4)	1 and 4
Harvoni (2014)	$113400	93%-97%	1, 4, 5, and 6

Conclusion:

Zepatier is a recommended regimen for patients with HCV genotypes 1 and 4 with or without cirrhosis in the AASLD/IDSA guidelines.[11] Zepatier is a great option for patients with HCV genotype 1 or 4 and severe renal impairment or end-stage renal disease. It can also be used in patients with HIV co-infection with select antivirals (abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir). Zepatier has impressive SVR rates comparable to other treatment regimens at a more affordable cost and with less adverse effects. In many clinical trials evaluating Zepatier, zero patients had to discontinue treatment due to adverse effects caused by the drug.

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