Elbasvir/Grazoprevir (Zepatier)

National Drug Monograph

February 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel,
VISN Pharmacist Executives and Office of Public Health

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]

Description/ Mechanism of Action	Elbasvir/grazoprevir is a fixed-dose combination of two direct acting antivirals that have different mechanisms of action. Elbasvir is a NS5A inhibitor and grazoprevir is a NS3/4A protease inhibitor.
Indication(s) under Review in this document	Elbasvir/grazoprevir is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults.
Dosage Form(s) Under Review	Elbasvir 50mg/grazoprevir 100mg fixed-dose combination tablet
REMS	NO REMS
Pregnancy Rating	- If elbasvir/grazoprevir is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. - If elbasvir/grazoprevir is administered without ribavirin, no adequate human data are available to establish whether or not it poses a risk to pregnancy outcomes.

Executive Summary[1-6]

Efficacy	• The FDA approval of elbasvir/grazoprevir with or without ribavirin was primarily based upon 6 clinical trials (Refer to Table 1).[1] These trials evaluated HCV genotype 1 and 4 patients with compensated liver disease with and without cirrhosis for treatment durations of 12 or 16 weeks. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment. The FDA approved regimens for elbasvir/grazoprevir with or without ribavirin achieved SVRs in the range of 94-97%. Because of lower SVRs in GT1a patients with baseline NS5A polymorphisms, these patients should receive elbasvir/grazoprevir plus ribavirin for 16 weeks.
Safety	• In patients receiving elbasvir/grazoprevir without co-administration of ribavirin for 12 weeks, the most common adverse reactions (≥5%) were fatigue, headache and nausea. In patients receiving elbasvir/grazoprevir co-administered with ribavirin for 16 weeks, the most common adverse reactions of moderate and severe intensity (≥5%) were anemia and headache. • Due to the potential for ALT elevations, the prescribing information recommends performing hepatic laboratory testing prior to therapy, at 8 weeks, 12 weeks (if receiving 16 weeks of therapy) and as clinically indicated. If ALT levels remain elevated >10 times the upper limit of normal or is accompanied by clinical symptoms, follow the recommendations in prescribing information.
Potential Impact	• Elbasvir/grazoprevir is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. For HCV Genotype 1a patients, the prescribing information recommends baseline testing for the presence of virus with NS5A resistance-associated polymorphisms (RAPs) to guide the regimen. Elbasvir/grazoprevir is available as a fixed-dose combination that is administered once daily for 12 or 16 weeks with or without ribavirin depending on the presence of RAPs and patient characteristics. Because of lower SVRs in GT1a patients with baseline NS5A polymorphisms, these patients should receive elbasvir/grazoprevir plus ribavirin for 16 weeks. No dosage adjustment is required in patients receiving elbasvir/grazoprevir with mild, moderate or severe renal impairment including hemodialysis.

	Elbasvir/grazoprevir has the potential for drug-interactions; therefore, the patient should be assessed for drug-interactions at baseline and throughout therapy.

Background

Purpose for review

The purpose of the review is to evaluate the efficacy and safety of elbasvir/ grazoprevir for HCV GT1 and GT4 (FDA approved Jan 2016).

Other therapeutic options

Formulary Alternatives for interferon free regimens for HCV Genotype 1 or 4 Patients	Other Considerations
Ledipasvir/sofosbuvir (Harvoni)	Fixed-dose combination product: One tablet once daily Minimal drug interactions except PPIs and H2 blockers FDA approved for HCV GT1, 4, 5 and 6 Sofosbuvir was not studied in patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis. The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30 mL/min/1.73m^2.
Ombitasvir, paritaprevir/ritonavir plus dasabuvir (Viekira Pak) for HCV GT1 or Ombitasvir, paritaprevir/ritonavir (Technivie) for HCV GT4	Viekira Pak and Technivie contains ritonavir; thus, potential for significant drug-drug interactions including antiretrovirals Technivie only FDA approved for HCV GT4 patients without cirrhosis
Sofosbuvir plus simeprevir	2 pills once a day (i.e., not a fixed-dose combination product) FDA approved for HCV GT1

Efficacy (FDA Approved Indications)[1-6]

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2016) using the search terms elbasvir (EBR) and grazoprevir (GZR). The search was limited to studies performed in humans and published in the English language. Four of the pivotal clinical trials contributing to assessment of efficacy in genotype 1 or 4 in published in peer-reviewed journals were included (C-EDGE-TN , C-EDGE-COINFECTION, C-SALVAGE, C-SURFER).[2-5] Two additional studies included in the FDA labeling were not published at the time of FDA approval and were only available as abstracts (C-EDGE-TE, C-SCAPE).

Review of Efficacy

The FDA approval of elbasvir/grazoprevir was based on two double-blind placebo controlled studies (C-EDGE-TN, C-SURFER) and four open-labeled trials (C-EDGE-COINFECTION, C-EDGE-TE, C-SALVAGE, and C-SCAPE). These trials evaluated HCV genotype 1 and 4 patients with compensated liver disease with and without cirrhosis for treatment durations of 12 or 16 weeks. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment defined as HCV RNA < lower limit of quantification (LLOQ) at 12 weeks post-treatment. Refer to Table 1 for SVRs according to data provided in the prescribing information.[1]

Table 1. Summary of Clinical Trials supporting FDA indications for HCV Genotype 1 and 4 infection[a]

Study	Population	Regimen	SVR12

C-EDGE-TN	Treatment-naïve HCV Genotype 1 patients with or without cirrhosis	EBR/GZR for 12 weeks	273/288 (95%)
C-EDGE-Coinfection	Treatment-naive HCV/HIV Genotype 1 patients with or without cirrhosis	EBR/GZR for 12 weeks	179/189 (95%)
C-EDGE-TE	Prior peginterferon/ribavirin treatment-experienced HCV Genotype 1 patients with or without cirrhosis	EBR/GZR for 12 weeks EBR/GZR +RBV for 16 weeks	90/96 (94%) 93/96 (97%)
C-SALVAGE	Prior peginterferon/ribavirin plus HCV protease inhibitor treatment-experienced HCV Genotype 1 patients with or without cirrhosis	EBR/GZR + RBV for 12 weeks	76/79 (96%)
C-SURFER	Treatment-naive and prior peginterferon/ribavirin treatment-experienced Genotype 1 patients with severe renal impairment, including hemodialysis	EBR/GZR for 12 weeks	115/122 (94%)
Pooled C-EDGE-TN, C-EDGE-Coinfection, C-SCAPE	Treatment-naïve HCV mono- and co-infected Genotype 4 patients with or without cirrhosis	EBR/GZR for 12 weeks	64/66 (97%)
C-EDGE-TE	Prior peginterferon/ribavirin treatment-experienced HCV Genotype 4 patients	EBR/GZR +RBV for 16 weeks	8/8 (100%)

[a]Data reported according to prescribing information[1]; p-values nor 95% CI were not reported; EBR/GZR: elbasvir/grazoprevir. Overall Quality of Evidence: High (Refer to Appendix A; note all pivotal clinical trials sponsored by Merck)

Treatment-naïve HCV Genotype 1 patients with or without cirrhosis

C-EDGE TN

-Double-blind, placebo-controlled trial, randomized in 3:1 ratio to receive EBR/GZR for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with EBR/GZR for 12 weeks (deferred treatment group).
-Demographics included median age was 55 years (range: 20 to 78); 56% male; 61% White; 20% Black or African American; 8% Hispanic or Latino; mean BMI 26 kg/m2; 72% had baseline HCV RNA > 800,000 IU per mL; 24% had cirrhosis; 67% had non-C/C IL28B alleles (CT or TT); 55% had genotype 1a and 45% had genotype 1b.
-SVR12 shown in Table 2.

C-EDGE-COINFECTION

-Open-label single arm trial, in HCV/HIV-1 co-infected patients receiving EBR/GZR for 12 weeks.
-Demographics included median age of 50 years (range: 21 to 71); 85% male; 75% White; 19% Black or African American; 6% Hispanic or Latino; mean BMI 25 kg per m2; 59% had baseline HCV RNA > 800,000 IU per mL; 16% had cirrhosis; 65% had non-C/C IL28B alleles (CT or TT); 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-other HCV infection.
-SVR12 shown in Table 2.

Table 2: SVR12 in Treatment Naïve Patients

	C-EDGE-TN SVR12 N=288	**C-EDGE-COINFECTION SVR12 N=189**
Overall	273/288 (95%)	179/189 (95%)
Genotype		
Genotype 1a	144/157 (92%)	136/144 (94%)
Genotype 1b	129/131 (98%)	43/45 (96%)
Cirrhosis		
Without	207/220 (94%)	148/158 (94%)
With	66/68 (97%)	31/31 (100%)

P-values not provided in prescribing information

Treatment-experienced HCV Genotype 1 patients with or without cirrhosis

Prior peginterferon/ribavirin only experience: C-EDGE-TE

- Open-label trial of patients failing prior peginterferon/ribavirin treatment randomized in 1:1:1:1 ratio to receive EBR/GZR for 12 weeks, EBR/GZR + RBV for 12 weeks, EBR/GZR for 16 weeks, or EBR/GZR +RBV for 16 weeks.
- Demographics included median age 57 years (range: 19 to 77); 64% male; 67% White; 18% Black or African American; 9% Hispanic or Latino; mean BMI 28 kg/m2; 78% had baseline HCV RNA levels > 800,000 IU/mL; 34% had cirrhosis; 79% had non-C/C IL28B alleles (CT or TT); 60% had genotype 1a, 39% had genotype 1b, and 1% had genotype 1-other.
- SVR12 in Table 3. Only regimens recommended in FDA labeling for peginterferon-RBV experienced patients are included in the Table.

Prior peginterferon/ribavirin plus HCV Protease Inhibitor experience: C-SALVAGE

- Open-label single arm trial of patients failing prior boceprevir, simeprevir or telaprevir in combination with peginterferon/RBV who received EBR/GZR + RBV for 12 weeks.
- Demographics included median age 55 years (range: 23 to 75); 58% male; 97% White; 3% Black or African American; 15% Hispanic or Latino; mean BMI 28 kg/m2; 63% had baseline HCV RNA levels >800,000 IU/mL; 43% had cirrhosis; 97% had non-C/C IL28B alleles (CT or TT); 46% had baseline NS3 resistance-associated substitutions.
- SVR12 in Table 3.

Table 3: SVR12 in Treatment-Experienced Patients

	Prior PEG/RBV experience C-EDGE-TE		**Prior PEG/RBV/HCV PI experience C-SALVAGE**
Subgroups	**EBR/GZR 12 week regimen N=96**	**EBR/GZR +RBV 16 week regimen N=96**	**EBR/GZR + RBV 12 week regimen N=79**
Overall	90/96 (94%)	93/96 (97%)	76/79 (96%)
Genotype			
Genotype 1a	55/61 (90%)	55/58 (95%)	28/30 (93%)
Genotype 1b	35/35 (100%)	38/38 (100%)	47/48 (98%)
Cirrhosis			
Without	61/65 (94%)	61/64 (95%)	43/44 (98%)
With	29/31 (94%)	32/32 (100%)	32/34 (94%)
Response to prior therapy			
Relapse/breakthrough	33/33 (100%)	35/35 (100%)	NA
Nonresponder	57/63 (90%)	58/61 (95%)	NA

P-values not provided in prescribing information

Treatment of HCV Genotype 1 patients with Severe Renal Impairment including Hemodialysis

C-SURFER

- Double-blind, placebo-controlled trial, randomized in 1:1 ratio to receive EBR/GZR for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with EBR/GZR for 12 weeks (deferred treatment group).
- Included CKD Stage 4 (eGFR 15-29 mL/min/1.73 m2) or CKD Stage 5 (eGFR <15 mL/min/1.73 m2), including subjects on hemodialysis, who were treatment-naïve or who had failed prior therapy with peginterferon/RBV therapy.
- Demographics included median age of 58 years (range: 31 to 76); 75% male; 50% White; 45% Black or African American; 11% Hispanic or Latino; 57% had baseline HCV RNA levels > 800,000 IU/mL; 6% had cirrhosis; and 72% had non-C/C IL28B alleles (CT or TT).
-SVR in Table 4.

Table 4: SVR12 in Patients with Severe Renal Impairment

Subgroups	**EBR/GZR 12 week regimen N=122**
Overall	115/122 (94%)
Genotype	
Genotype 1a	61/63 (97%)
Genotype 1b	54/59 (92%)
Cirrhosis	

Without	109/115(95%)
With	6/7 (86%)
SVR by Prior Treatment	
Naïve	96/101 (95%)
Treatment -experienced	19/21 (90%)
Dialysis	
No	29/30 (97%)
Yes	86/92 (93%)
CKD Stage	
Stage 4	22/22 (100%)
Stage 5	93/100 (93%)

Effect of Baseline NS5A Resistance on SVR12 in GT1

-Baseline NS5A polymorphisms at resistance associated positions 28, 30, 31, or 93 were evaluated. Across all EBR/GZR Phase 2/3 studies, the prevalence of polymorphisms at any of these positions in genotype 1a patients in the US was 12% (37/309).). In clinical trials the effect of the following polymorphisms was most significant: M28A/G/T, Q30D/E/H/K/R, L31M/V, and Y93C/H/N.

-The presence of one or more NS5A amino acid polymorphisms at position M28, Q30, L31, or Y93 in genotype 1a patients was associated with reduced efficacy of EBR/GZR for 12 weeks, regardless of prior treatment history or cirrhosis status (refer to Table 5).

Table 5. SVR12 in HCV GT1a patients with or without baseline NS5A polymorphisms

	EBR/GZR for 12 weeks SVR12	**EBR/GZR + RBV for 16 weeks SVR12**
No baseline NS5A polymorphisms (M28, Q30, L31, or Y93)	441/450 (98%)	49/49 (100%)
Presence of baseline NS5A polymorphism (M28, Q30, L31, or Y93)	39/56 (70%)	6/6 (100%)

-In genotype 1b patients SVR12 rates were 94% (48/51) and 99% (247/248) for those with and without one or more NS5A polymorphisms at position 28, 30, 31, or 93.

Treatment of HCV Genotype 4 patients with or without cirrhosis

Treatment-naïve

-Pooled data of 66 patients from three trials (C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION) who received EBR/GZR for 12 weeks.

- Demographics (from combined studies of GT4 patients) included 64% treatment-naïve; 66% male; 87% White; 10% Black or African American; 22% had cirrhosis; and 30% had HCV/HIV-1 co-infection.
- SVR12 was achieved in 64/66 (97%) of patients in these combined trials.

Treatment-experienced

-Total of 37 patients from C-EDGE-TE who received 12 or 16 week regimen of EBR/GZR±RBV. The distribution of patients with cirrhosis, HIV/HCV coinfection and prior treatment response within these treatment arms were not reported.

- SVR12 rates for the treatment groups were as follows: 78% (7/9) with EBR/GZR for 12 weeks, 93% (14/15) with EBR/GZR + RBV x 12 weeks, 60% (3/5) with EBR/GZR x 16 weeks, and 100% (8/8) with EBR/GZR + RBV x 16 weeks.

Baseline Resistance

In genotype 4 patients, SVR12 rates for subjects with baseline NS5A polymorphisms were 100% (28/28) and for those without baseline NS5A polymorphisms SVR12 rates were 95% (41/43).

Summary of efficacy

- EBR/GZR with or without ribavirin achieved SVRs in the range of 94-97%. Because of lower SVRs in GT1a patients with baseline NS5A polymorphisms, these patients should receive EBR/GZR plus ribavirin for 16 weeks. Any GT1 or GT4 patient with prior HCV protease inhibitor experience should receive ribavirin with EBR/GZR.

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

- Patients with HCV GT6

Safety (for more detailed information refer to the product package insert)[1]

	Comments
Boxed Warning	• None
Contraindications	• If co-administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. • Patients with moderate or severe hepatic impairment (Child-Pugh B or C) • Co-administration with drugs that are1) strong CYP3A inducers; 2) OATP1B1/3 inhibitors OR 3) efavirenz
Warnings/Precautions	• If co-administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen. • ALT elevations: Perform hepatic laboratory testing prior to therapy, at 8 weeks, 12 weeks (if receiving 16 weeks of therapy) and as clinically indicated. If ALT levels remain elevated >10 times the upper limit of normal or is accompanied by clinical symptoms, follow the recommendations in prescribing information.

Safety Considerations

The safety assessment was based on approximately 1700 subjects with chronic hepatitis C virus infection without or with cirrhosis (i.e, Child-Pugh A).

Adverse Reactions

Common adverse reactions	• In patients receiving elbasvir/grazoprevir without co-administration of ribavirin for 12 weeks, the most common adverse reactions (≥5%) were fatigue, headache and nausea. • In patients receiving elbasvir/grazoprevir co-administered with ribavirin for 16 weeks, the most common adverse reactions of moderate and severe intensity (≥5%) were anemia and headache.
Death/Serious adverse reactions	• Deaths were not addressed in the prescribing information. • In the C-EDGE TN clinical trial, no serious adverse reactions occurred in elbasvir/grazoprevir-treated patients. In C-EDGE TE clinical trial, no serious adverse reactions occurred in patients treated with elbasvir/grazoprevir without ribavirin for 12 weeks while serious adverse reactions occurred in 1% of patients that received elbasvir/grazoprevir plus ribavirin for 16 weeks.
Discontinuations due to adverse reactions	• In the C-EDGE TN, discontinuations due to adverse reactions occurred in 1% of elbasvir/grazoprevir-treated patients. • In the C-EDGE TE clinical trial, no discontinuations occurred in patients treated with elbasvir/grazoprevir without ribavirin for 12 weeks while 3% of patients discontinued treatment due to adverse reactions in patients that received elbasvir/grazoprevir plus ribavirin for 16 weeks.
ALT elevations	• In clinical trials, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the ULN, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in the following subpopulations: female sex (2% [10/608]), Asian race (2% [4/164]), and age 65 years or older (2% [3/177]).

Drug-Drug Interactions[1]

- Consult the prescribing information prior to use for potential drug interactions and on-going evaluation.
- Grazoprevir is a substrate of OATP1B1/3 transporters. Co-administration with drugs that inhibit OATP1B1/3 transporters may result in a significant increase in the plasma concentrations of grazoprevir.
- Elbasvir and grazoprevir are substrates of CYP3A and P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir appears to be minimal. Co-administration of moderate or strong inducers of CYP3A may decrease elbasvir and grazoprevir plasma concentrations leading to reduced therapeutic effect of elbasvir/grazoprevir. Co-administration with strong CYP3A inhibitors may increase elbasvir and grazoprevir concentrations.

- Co-administration of the following drugs is contraindicated: phenytoin, carbamazepine, rifampin, St. John's Wort, efavirenz, atazanavir, daruinavir, lopinavir, saquinavir, tipranvir, and cyclosporine.
- Co-administration of the following drugs is not recommended: naficillin, ketoconazole, bosentan, etravirine, elvitegravir/cobicistat/emtricitabine/tenofovir, modafinil
- Tacrolimus: Co-administration increases serum levels of tacrolimus; frequent monitoring of tacrolimus levels, and for tacrolimus-associated adverse events, is recommended.
- Statins: lowest necessary dose of fluvastatin, lovastatin or simvastatin should be utilized and statin-associated adverse should be closely monitored while max dose are recommended for atorvastatin (20mg max dose), rosuvastatin (10mg max dose).

Risk Evaluation

As of February 2016	Comments
Sentinel event advisories	• None for combination product
Look-alike/sound-alike error potentials	• Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List):

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Elbasvir-grazoprevir 50-100mg tab	None	None	None	Entecavir Elvitegravir Ledipasvir-sofosbuvir
Zepatier	None	None	None	Zemplar Zelapar Zetia

Other Considerations

- None

Dosing and Administration[1]

For HCV Genotype 1a patients, the prescribing information recommends baseline testing for the presence of virus with NS5A resistance-associated polymorphisms (RAPs) at the amino acid positions 28, 30, 31, or 93 to guide elbasvir/grazoprevir regimen.

Elbasvir/grazoprevir: One tablet taken orally once daily with or without food. For certain patient populations, co-administration with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day) is recommended. **Treatment regimen and duration are based upon patient characteristics as described in the Table below.**

Treatment Regimen and Duration for HCV Genotype 1 or 4 based upon patient characteristics

Population includes HCV monoinfection, HCV/HIV-1 co-infection, hepatocellular carcinoma (HCC) and patients with or without cirrhosis	Dosage Regimens	Total Treatment Duration
Genotype 1a: Treatment-naïve or treatment-experienced with PEG/RBV **without** baseline **NS5A** polymorphisms at the amino acid positions 28, 30, 31, or 93	Elbasvir/grazoprevir	12 weeks
Treatment-experienced with a first generation HCV protease inhibitor (e.g., telaprevir, boceprevir or simeprevir) in combination with PEG/RBV regimen **without** baseline **NS5A** polymorphisms at the amino acid positions 28, 30, 31, or 93	Elbasvir/grazoprevir plus RBV	12 weeks
Genotype 1a: Treatment-naïve or treatment-experienced (including prior	Elbasvir/grazoprevir plus RBV	16 weeks

PEG/RBV or first generation HCV protease inhibitor ,e.g, telaprevir, boceprevir or simeprevir, in combination with PEG/RBV) **with** baseline **NS5A** polymorphisms at the amino acid positions 28, 30, 31, or 93		
Genotype 1b: Treatment-naïve or treatment-experienced with PEG/RBV Treatment-experienced with a first generation HCV protease inhibitor (e.g., telaprevir, boceprevir or simeprevir) in combination with PEG/RBV regimen	Elbasvir/grazoprevir Elbasvir/grazoprevir plus RBV	12 weeks 12 weeks
Genotype 4: Treatment-naïve Treatment-experienced with PEG/RBV	Elbasvir/grazoprevir Elbasvir/grazoprevir plus RBV	12 weeks 16 weeks

Special Populations (Adults)[1]

	Comments
Elderly	• Clinical trials included 187 patients aged 65 and over. In the elderly, higher elbasvir and grazoprevir plasma concentrations were observed as well as higher rate of late ALT elevations was observed in subjects aged 65 years.
Pregnancy	• If co-administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy. • If elbasvir/grazoprevir is administered without ribavirin, no adequate human data are available to establish whether or not it poses a risk to pregnancy outcomes.
Lactation	• It is not known is present in human milk, affects human milk production, or has effects on the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for therapy and any potential adverse effects on the breastfed child from therapy or from the underlying maternal condition. • If co-administered with ribavirin, the nursing mothers information for ribavirin applies to this combination regimen (see prescribing information for ribavirin).
Renal Impairment	• No dosage adjustment is required in patients receiving elbasvir/grazoprevir with mild, moderate or severe renal impairment including hemodialysis. However, ribavirin is known to be substantially excreted by the kidney, and the risks of adverse reactions are greater in patients with impaired renal function. The total daily dose of ribavirin should be reduced for patients with creatinine clearance less than or equal to 50 mL/min as follows: creatinine clearance between 30-50ml/min use alternating doses of 200mg and 400mg every other day; for creatinine clearance <30ml/min or for hemodialysis use 200mg daily.
Hepatic Impairment	• No dosage adjustment in patients with mild hepatic impairment (Child-Pugh A). Elbasvir/grazoprevir is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and contraindicated in patients with severe hepatic impairment (Child-Pugh C).
Pharmacogenetics/genomics	• No data identified in prescribing information.

Projected Place in Therapy

- VHA Population Health Services HCV Registry Reports indicate that there were 119,629 Veterans with HCV viremia in VHA care as of October 2015, approximately 80% of whom were HCV Genotype 1 and 1% of whom were HCV Genotype 4.[6-7]
- Elbasvir/grazoprevir is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. For HCV Genotype 1a patients, the prescribing information recommends baseline testing for the presence of virus with NS5A resistance-associated polymorphisms (RAPs) to guide the regimen. Elbasvir/grazoprevir is available as a fixed-dose combination that is administered once daily for 12 or 16 weeks with or without ribavirin depending on the presence of RAPs and patient characteristics. Because of lower SVRs in GT1a patients with baseline NS5A polymorphisms, these patients should receive EBR/GZR plus ribavirin for 16 weeks. No dosage adjustment is required in patients receiving elbasvir/grazoprevir with mild, moderate or severe renal impairment including hemodialysis. Elbasvir/grazoprevir has the potential for drug-interactions; therefore, the patient should be assessed for drug-interactions at baseline and throughout therapy.

References

1. Zepatier [package insert]. Merck & Co,. Inc., Whitehouse Station; January 2016.
2. Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ari ZB, Zhao Y, et al. Grazoprevir–Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 InfectionA Randomized TrialC-EDGE Treatment-Naive Trial of Grazoprevir–Elbasvir. Annals of Internal Medicine. 2015;163(1):1-13
3. Rockstroh JK, 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 Aug;2(8):e319-27. doi: 10.1016/S2352-3018(15)00114-9. Epub 2015 Jul 9.
4. Forns X, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, 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 Sep;63(3):564-72. doi: 10.1016/j.jhep.2015.04.009. Epub 2015 Apr 18.
5. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, 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 Oct 17;386(10003):1537-45. doi: 10.1016/S0140-6736(15)00349-9. Epub 2015 Oct 5
6. Population Health Services HCV Viremic Veterans in VHA Care in the Past 12 Months Awaiting Treatment for the Nation, by VISN and by Station. October 2, 2015. https://vaww.vha.vaco.portal.va.gov/sites/PublicHealth/pophealth/hcvantivirals/HCV%20Viremic/viremic-fib4.aspx
7. Office of Public Health HCV Genotype of HCV Viremic Veterans in VHA Care in 2014 for the Nation, by VISN and by Station. http://vaww.hepatitis.va.gov/data-reports/ccr2014/ClinTopic-HCVGTEverInCare-Jan15-HCVVir-2014-All.asp

Prepared February 2016; Contact person: Melinda Neuhauser, PharmD, MPH, PBM Services

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description

High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-19