ELBASVIR/GRAZOPREVIR

Generic	Brand	HICL	GCN	Exception/Other
ELBASVIR/GRAZOPREVIR	ZEPATIER	43030		

***********Customer Service/PAC Alert************
(For Internal Use Only)

THIS IS A HIGH-IMPACT MEDICATION. DO NOT OVERRIDE OR APPROVE WITHOUT SUBMITTING FOR PHARMACIST REVIEW.

GUIDELINES FOR USE

1. Does the patient have a diagnosis of chronic hepatitis C, with genotype 1 or genotype 4 and meet **ALL** the following criteria?
   - The patient have a recent HCV infection documented by one detectable HCV RNA level within the last 6 months
   - The patient at least 18 years old
   - The patient currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (e.g., a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model

   If yes, continue to #2.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

2. Does the patient meet at least **ONE** of the following criteria?
   - The patient has a limited life expectancy (less than 12 months) due to non-liver related comorbid conditions (via physician attestation)
   - Zepatier will be taken concurrently with Sovaldi (sofosbuvir)
   - The patient has moderate or severe hepatitis impairment (Child-Pugh B or C)
   - Patient is currently taking any of the following medications: phenytoin, carbamazepine, rifampin, efavirenz (e.g., Atripla, Sustiva), atazanavir (e.g., Evotaz, Reyataz), darunavir (e.g., Prezcobix, Prezista), lopinavir, saquinavir, tipranavir, cyclosporine, nafcillin, ketoconazole, modafinil, bosentan, etravirine, elvitegravir/cobicistat/emtricitabine/tenofovir (e.g., Stribild, Genvoya), atorvastatin at doses higher than 20mg daily, or rosuvastatin at doses greater than 10mg daily

   If yes, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.
   If no, continue to #3.

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ELBASVIR/GRAZOPREVIR

GUIDELINES FOR USE (CONTINUED)

3. Does the patient have **ONE** of the following?
   - The patient has a contraindication to Epclusa, Harvoni **AND** Mavyret
   - The patient has previously failed a short trial with Epclusa, Harvoni, or Mavyret (e.g., inability to tolerate, adverse effect early in therapy); [**NOTE:** An individual who has completed a full course of therapy with Harvoni, Mavyret or Epclusa that did not achieve SVR will not be approved.]
   - Patient has stage 4 or 5 chronic kidney disease (CKD) **AND** has previously failed a short trial of or has contraindication to Mavyret

   If yes, continue to #3.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

4. Is the patient **ONE** of the following?
   - Genotype 1a infection, treatment naïve, and **NO** baseline NS5A polymorphisms
   - Genotype 1a infection, previously treated with peginterferon/ribavirin, and **NO** baseline NS5A polymorphisms
   - Genotype 1b infection, treatment naïve
   - Genotype 1b infection, previously treated with peginterferon/ribavirin
   - Genotype 4 infection, treatment naïve

   If yes, **approve for 12 weeks by HICL for #1 tablet per day.**
   If no, continue to #5.

5. Is the requested medication being used with ribavirin and the patient meets **ONE** of the following criteria?
   - Genotype 1a infection, previously treated with HCV protease inhibitor triple therapy (HCV protease inhibitor (e.g., Victrelis, Incivek, Olysio) plus peginterferon/ribavirin)
   - Genotype 1b infection, previously treated with HCV protease inhibitor triple therapy (HCV protease inhibitor (e.g., Victrelis, Incivek, Olysio) plus peginterferon/ribavirin)

   If yes, **approve for 12 weeks by HICL for #1 tablet per day.**
   If no, continue to #6.

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ELBASVIR/GRAZOPREVIR

GUIDELINES FOR USE (CONTINUED)

6. Is the requested medication being used with ribavirin and the patient meets **ONE** of the following criteria?
   - Genotype 1a infection, treatment naïve, and has baseline NS5A polymorphisms
   - Genotype 1a infection, previously treated with peginterferon/ribavirin, and has baseline NS5A polymorphisms
   - Genotype 4 infection, previously treated with peginterferon/ribavirin

   If yes, **approve for 16 weeks by HICL for #1 tablet per day.**
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

   DENIAL TEXT: The guideline for **ELBASVIR/GRAZOPREVIR (Zepatier)** requires a diagnosis of hepatitis C. The following criteria must also be met:
   - Patient has genotype 1 or genotype 4 hepatitis C
   - Patient is at least 18 years old
   - Patient must have a trial of Epclusa, Harvoni or Mavyret OR contraindication to Epclusa, Harvoni AND Mavyret prior to approval (patient with previous failure of a full treatment of Epclusa, Harvoni or Mavyret will not be approved)
   - Patient is currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (e.g., a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model
   - Documentation of HCV infection (e.g., at least one detectable HCV RNA level within the last 6 months)
   - Testing for baseline NS5A polymorphisms is required for patients with genotype 1a infection
   - Ribavirin use is required for certain treatment-experienced patients or for treatment naïve patients with genotype 1a infection and baseline NS5A polymorphisms (per product labeling)
   - Treatment experienced patients will be approved per product labeling (previous failure of peginterferon/ribavirin for genotype 1a, 1b or 4; previous failure of HCV protease inhibitor triple therapy regimen for genotype 1a or 1b infection)

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ELBASVIR/GRAZOPREVIR

GUIDELINES FOR USE (CONTINUED)

Zepatier will not be approved for the following patients:

- Patients using any of the following interacting medications concurrently while on elbasvir/grazoprevir: phenytoin, carbamazepine, rifampin, efavirenz (e.g., Atripla, Sustiva), atazanavir (e.g., Evotaz, Reyataz), darunavir (e.g., Prezcobix, Prezista), lopinavir, saquinavir, tipranavir, cyclosporine, nafcillin, ketoconazole, modafinil, bosentan, etravirine, elvitegravir/cobicistat/emtricitabine/tenofovir (e.g., Stribild, Genvoya), atorvastatin at doses higher than 20mg daily, or rosuvastatin at doses greater than 10mg daily
- Patients taking Sovaldi (sofosbuvir) with Zepatier
- Patients with moderate or severe hepatic impairment (Child-Pugh B or C)
- Patients with limited life expectancy (less than 12 months) due to non-liver related comorbid conditions

RATIONALE

Ensure appropriate utilization of Zepatier.

FDA APPROVED INDICATIONS

Indicated with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) genotypes 1 and 4 infection in adults.

FDA APPROVED DOSAGE

- One tablet taken once daily with or without food.

Duration of therapy is as follows:

Patient type and infection type	Regimen	Duration
Genotype 1a: Treatment naïve or previous treatment with peginterferon/ribavirin without baseline NS5A polymorphisms	Zepatier	12 weeks
Genotype 1a: Treatment naïve or previous treatment with peginterferon/ribavirin with baseline NS5A polymorphisms	Zepatier plus ribavirin	16 weeks
Genotype 1b: Treatment naïve or previous treatment with peginterferon/ribavirin	Zepatier	12 weeks
Genotype 1a or 1b: Treatment experienced, HCV protease inhibitor triple therapy	Zepatier plus ribavirin	12 weeks
Genotype 4: Treatment naïve	Zepatier	12 weeks
Genotype 4: Treatment experienced, previous failure of peginterferon/ribavirin	Zepatier plus ribavirin	16 weeks

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OTHER INFORMATION
All patients should receive hepatic laboratory testing prior to starting Zepatier. Patients with genotype 1a should receive testing for NS5A resistance-associated polymorphisms.

AASLD/IDSA Guidance for treatment of HCV infection (adapted from AASLD/IDSA HCV Guidance from July 2016, see hcvguidelines.org for most recent recommendations):

AASLD/IDSA Guidance - Initial Treatment of Patients Initiating Therapy for HCV infection (Treatment naïve or previous relapsers)	
Genotype	**Recommended Regimen**
1a	1. Zepatier daily for 12 weeks (no baseline high fold NS5A resistance associated variants (RAVs) for elbasvir detected) - **Rating 1A;** *Alternative regimen:* Zepatier with ribavirin for 16 weeks if genotype 1a AND baseline high fold NS5A RAVs) - **Rating IIa-B** 2. Harvoni daily for 12 wk, for treatment naïve patients with genotype 1a (with or without cirrhosis) **Rating 1A**; [Harvoni for 8 weeks is an option if pretreatment HCV RNA level < 6million, but should be done with caution and at the discretion of the prescriber] 3. Epclusa for 12 weeks (for patients with or without cirrhosis) - **Rating 1A** 4. Viekira with ribavirin for 12 wk (no cirrhosis) or *Alternative regimen:* Viekira Pak for 24 wk with ribavirin(with cirrhosis), for treatment naïve patients with genotype 1a - **Rating 1A** 5. Sovaldi + Olysio daily for 12 wk (no cirrhosis) - **Rating 1A** or *Alternative regimen:* Sovaldi + Olysio for 24 wk (cirrhosis) without the Q80K polymorphism), for treatment naïve patients with genotype 1a - **Rating II-B** Daklinza + Sovaldi for 12 weeks (no cirrhosis) - **Rating 1B** or Alternative regimen if cirrhosis: Daklinza + Sovaldi for **24 weeks with or without weight based ribavirin if cirrhosis present (Adjust Daklinza dose for drug interactions if needed), for treatment naïve patients with genotype 1a.** - **Rating IIa-B**
1b	1. Zepatier daily for 12 weeks (with or without cirrhosis) (no baseline high fold NS5A resistance associated variants (RAVs) for elbasvir detected) - **Rating 1A** 2. Harvoni daily for 12 weeks, for treatment naïve patients with genotype 1b (with or without cirrhosis) - **Rating 1A** 3. Epclusa for 12 weeks (for patients with or without cirrhosis) - **Rating 1A** 4. Viekira for 12 weeks for treatment naïve patients with genotype 1b (with or without cirrhosis) - **Rating 1A** 5. Sovaldi + Olysio daily for 12 weeks (no cirrhosis) - **Rating 1A**, *Alternative regimen,* if cirrhosis: Sovaldi plus Olysio for 24 weeks, with or without weight based ribavirin, for treatment naïve patients with genotype 1b - **Rating IIa-B** 6. Daklinza + Sovaldi for 12 weeks (no cirrhosis) - **Rating 1B** or *Alternative regimen,* if cirrhosis: Daklinza + Sovaldi for **24 weeks with or without weight based ribavirin (Adjust Daklinza dose for drug interactions if needed), for treatment naïve patients with genotype 1b. - **Rating IIa-B**
4	1. Epclusa for 12 weeks for treatment naïve patients with genotype 4 (for patients with or without cirrhosis) - **Rating 1A** 2. Technivie and ribavirin for 12 weeks, for treatment naïve patients (for patients with or without cirrhosis) - **Rating 1A**

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	3. Zepatier daily for 12 weeks(for patients with or without cirrhosis) - - **Rating IIa-B** Harvoni daily for 12 weeks, for treatment naïve patients with genotype 4 (for patients with or without cirrhosis) - **Rating IIa-B**

AASLD/IDSA Guidance - Retreatment of HCV infection (recommendations for patients in whom previous treatment has failed)		
GT	**Previous agent/regimen failed**	**Recommended Regimen**
1	Peginterferon/ribavirin regimen	1. Zepatier daily for 12 weeks (if genotype 1a, use 12-week regimen only if no baseline high fold-change NS5A resistance-associated variants (RAVs) for elbasvir), for patients with or without cirrhosis - **Rating 1A** Alternative regimen is Zepatier for 16 weeks with RBV for those with genotype 1a AND NS5A RAVs - **Rating IB/ IIa-B** 2. Epclusa for 12 weeks - **Rating 1A** 3. Harvoni daily for 12 weeks (no cirrhosis) – **Rating 1A** If cirrhosis: Harvoni and ribavirin for 12 weeks OR Alternative regimen is Harvoni for 24 weeks (cirrhosis) - **Rating 1A** 4. Viekira for 12 weeks with ribavirin (genotype 1a, no cirrhosis] Viekira for 12 weeks for genotype 1b [no ribavirin if genotype 1b] - **Rating 1A** Alternative regimen, if genotype 1a with cirrhosis: Viekira and ribavirin for 24 weeks, for those who have failed peginterferon/ribavirin - **Rating 1A** 5. Olysio + Sovaldi daily for 12 weeks if no cirrhosis - **Rating 1A** *Alternative regimen* for cirrhosis: Olysio plus Sovaldi with or without ribavirin, daily for 24 weeks - **Rating IIa-B** 6. Daklinza + Sovaldi for 12 weeks (if no cirrhosis), for treatment experienced, genotype 1 patients in whom peginterferon/ribavirin has failed (Adjust Daklinza dose for drug interactions if needed) - **Rating 1B** Alternative regimen, if cirrhosis: **Daklinza + Sovaldi for **24 weeks with or without ribavirin - **Rating IIa-B**
1	Sovaldi regimen (with ribavirin, and with or without peginterferon)	1. Harvoni with ribavirin for 12 weeks (no cirrhosis) - **Rating IIa-B,** or Harvoni with ribavirin for 24 weeks (cirrhosis) - **Rating IIa-B**
1	HCV protease inhibitor/peginterferon/ribavirin	1. Harvoni daily for 12 weeks for patients without cirrhosis. If cirrhosis: Harvoni plus ribavirin for 12 weeks OR Harvoni for 24 weeks - **Rating 1A** 2. Epclusa for 12 weeks - **Rating 1A** 3. Daklinza + Sovaldi daily for 12 weeks (no cirrhosis); or ** Daklinza and Sovaldi for 24 weeks (cirrhosis),

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AASLD/IDSA Guidance - Retreatment of HCV infection (recommendations for patients in whom previous treatment has failed)		
		with or without weight based ribavirin for those with cirrhosis - **Rating IIa-B** 4. Zepatier daily with ribavirin for 12 weeks (16 weeks if baseline NS5A RAVs for elbasvir) **Rating IIa-B**
1	Olysio + Sovaldi	If no cirrhosis, defer treatment if possible, if there are no reasons for urgent retreatment -Testing for RAVs that lead to decreased susceptibility for NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with compensated cirrhosis or have reasons for retreatment. -If retreating with sofosbuvir-based therapy with 2 drugs, a treatment of 24 weeks is recommended, and ribavirin should be added when possible, unless contraindicated. Consider triple or quadruple nucleotide-based (e.g., sofosbuvir) therapies if available, with treatment duration from 12 to 24 weeks and weight-based ribavirin, unless contraindicated.
1	NS5A inhibitors	If no cirrhosis, defer treatment if possible, if there are no reasons for urgent retreatment. Test for resistance associated variants for NS3 protease inhibitors or NS5A inhibitors. -If retreating with sofosbuvir-based therapy, use 24 week duration regimens when possible, and add ribavirin if tolerated. Consider triple or quadruple nucleotide-based (e.g., sofosbuvir) therapies if available, with treatment duration from 12 to 24 weeks and weight-based ribavirin, unless contraindicated.
4	Peginterferon/ribavirin regimen	1. Epclusa for 12 weeks - **Rating 1A** 2. Technivie with ribavirin for 12 weeks - **Rating 1A** 3. Zepatier daily for 12 weeks (use 16 weeks if previous on-treatment virologic failure after peg/RBV, add ribavirin for if previous failure to suppress or patient had breakthough) - **Rating IIa-B** 4. Harvoni daily for 12 weeks (add ribavirin if cirrhosis and patient is eligible for ribavirin), *Alternative,* if cirrhosis, is Harvoni for 24 weeks - **Rating IIa-B**

ELBASVIR/GRAZOPREVIR

FDA APPROVED INDICATIONS (CONTINUED)

EFFICACY

The efficacy of Zepatier was studied in two placebo-controlled trials and four uncontrolled phase 2 and phase 3 clinical trials in 1401 study participants with genotype 1, 4, or 6 HCV infection with compensated liver disease (with or without cirrhosis). Table 2 below describes a total of six trials used for the assessment of efficacy for treatment of genotype 1 or 4 infection (Zepatier was not approved by

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the FDA for treatment of genotype 6 infection). All patients in the active treatment groups received Zepatier (grazoprevir 100mg/elbasvir 50mg) once daily. Those receiving ribavirin received weight-based dosing (800-1400mg per day), divided twice daily. The primary endpoint in all trials was sustained virologic response (SVR), defined as HCV RNA less than the lower limit of quantification at 12 weeks after ending treatment (SVR12).

Clinical trials for Zepatier (elbasvir/grazoprevir) *[From Zepatier prescribing information]*

Trial	Population	Study Groups and Duration (Number of Subjects Treated)
C-EDGE TN (double-blind)	GT 1, 4 TN with or without cirrhosis	• ZEPATIER for 12 weeks (N=306) • Placebo for 12 weeks (N=102)
C-EDGE COINFECTION (open-label)	GT 1, 4 TN with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER for 12 weeks (N=217)
C-SURFER (double-blind)	GT 1 TN or TE with or without cirrhosis Severe Renal Impairment including Hemodialysis	• EBR* + GZR* for 12 weeks (N=122) • Placebo for 12 weeks (N=113)
C-SCAPE (open-label)	GT 4 TN without cirrhosis	• EBR* + GZR* for 12 weeks (N=10) • EBR* + GZR* + RBV for 12 weeks (N=10)
C-EDGE TE (open-label)	GT 1, 4 TE with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER for 12 or 16 weeks (N=105, and 101, respectively) • ZEPATIER + RBV for 12 or 16 weeks (N=104 and 104, respectively)
C-SALVAGE (open-label)	GT 1 TE with HCV protease inhibitor regimen† with or without cirrhosis	• EBR* + GZR* + RBV for 12 weeks (N=79)

GT = Genotype
TN = Treatment-Naïve
TE = Treatment-Experienced (failed prior treatment with interferon [IFN] or peginterferon alfa [PegIFN] with or without ribavirin [RBV] or were intolerant to prior therapy).
*EBR = elbasvir 50 mg; GZR = grazoprevir 100 mg; EBR + GZR = co-administered as single agents.
† Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with PegIFN + RBV.

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ELBASVIR/GRAZOPREVIR

FDA APPROVED INDICATIONS (CONTINUED)

Efficacy - Treatment naïve patients with genotype 1 infection
C-EDGE TREATMENT NAÏVE (TN) study was a phase 3, multi-center, international, randomized, blinded, placebo-controlled, parallel group trial of treatment naïve cirrhotic and non-cirrhotic patients with chronic HCV genotype 1, genotype 4, or genotype 6 infection. In the initial treatment period, 316 patients received Zepatier and 105 patients received placebo once daily. The median age was 54 years (range: 20-78 years); other patient characteristics included: 46% female, 37% non-white, 91% with genotype 1 infections (50% of those with genotype 1 had genotype 1a), 22% with cirrhosis (28% of patients with cirrhosis had biopsy as evidence of cirrhosis), and 68% of patients had HCV RNA levels above 800,000 IU/mL.

C-EDGE COINFECTION was an uncontrolled, non-randomized, open-label, single arm study that enrolled 218 treatment naïve, HCV/HIV co-infected patients with genotype 1, 4, or 6 HCV infection. Patient characteristics included the following: mean age 50 years (age range 21-71 years); 85% male; 75% Caucasian, 19% of African descent, 6% Hispanic or Latino; mean body mass index (BMI) 25kg/m2; 16% had cirrhosis; 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-other infection; and patients were either naïve to HIV antiretroviral therapy (ART) or stable on ART for at least 8 weeks.

C-EDGE TN and C-EDGE COINFECTION: SVR12 in treatment naïve subjects with or without cirrhosis with genotype 1 HCV treated with Zepatier for 12 weeks *[From Zepatier prescribing information]*

	C-EDGE TN [Immediate treatment group] (n = 288)	C-EDGE CO-INFECTION [HCV/HIV co-infection] (n = 189)
Regimen	**Zepatier for 12 weeks**	**Zepatier for 12 weeks**
Overall SVR in genotype 1	95% (273/288)	95% (179/189)
SVR – genotype 1a	92% (144/157)	94% (136/144)
SVR – genotype 1b	98% (129/131)	96% (43/45)
SVR – no cirrhosis	94% (207/220)	94% (148/158)
SVR – cirrhosis	97% (66/68)	100% (31/31)
Relapse	3% (10/288)	3% (6/189)

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ELBASVIR/GRAZOPREVIR

FDA APPROVED INDICATIONS (CONTINUED)

Efficacy - Treatment experienced patients with genotype 1 infection
C-EDGE TE was a randomized, open-label study that enrolled patients with genotype 1 or 4 HCV infection, with or without cirrhosis, with or without HIV-1 co-infection, who had failed previous treatment with peginterferon/ribavirin. Participants were randomized to one of four treatment arms: 1) Zepatier for 12 weeks, 2) Zepatier and ribavirin for 12 weeks, 3) Zepatier for 16 weeks, or 4) Zepatier plus ribavirin for 16 weeks. Patient characteristics included the following: median age 57 years (range: 19-77 years); 64% male; 67% Caucasian, 18% of African descent, 9% Hispanic or Latino; mean BMI 28kg/m2; 78% with baseline HCV RNA levels above 800,000 IU/mL; 34% had cirrhosis; 60% had genotype 1a, 39% had genotype 1b, and 1% had genotype 1-other.

C-EDGE TE: SVR12 in treatment experienced subjects (previous trial of peginterferon/ribavirin) with or without cirrhosis with genotype 1 HCV treated with Zepatier *[From Zepatier prescribing information]*

	Zepatier for 12 weeks (n = 96)	Zepatier and ribavirin for 16 weeks (n = 96)
Overall SVR in genotype 1	94% (90/96)	97% (93/96)
SVR – genotype 1a	90% (55/61)	95% (55/58)
SVR – genotype 1b	100% (35/35)	100% (38/38)
SVR – no cirrhosis	94% (61/65)	95% (61/64)
SVR – cirrhosis	94% (29/31)	100% (32/32)
Relapse	100% (33/33)	100% (35/35)

C-SALVAGE was an open-label, single arm trial that enrolled participants with genotype 1 infection, with or without cirrhosis, who failed previous treatment with HCV protease inhibitor/peginterferon/ribavirin triple therapy. Protease inhibitors were one of the following: Victrelis (boceprevir), Incivek (telaprevir), or Olysio (simeprevir). Participants received Zepatier and ribavirin for 12 weeks. Patient characteristics included the following: median age 55 years (range 23 to 75); 58% male; 97% Caucasian, 3% of African descent, 15% Hispanic or Latino; mean BMI 28kg/m2; 63% had baseline HCV RNA levels greater than 800,000 IU/mL; 43% had cirrhosis; and 46% had baseline NS3 resistance-associated substitutions. The overall SVR was 96%, whereas 4% (3/79) were unable to attain SVR due to relapse.

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ELBASVIR/GRAZOPREVIR

FDA APPROVED INDICATIONS (CONTINUED)

Efficacy - Patients with severe renal impairment and genotype 1 infection
C-SURFER was a randomized, double-blind, placebo-controlled study in patients with genotype 1 infection, with or without cirrhosis, with CKD stage 4 or 5 (eGFR <30 mL/min/1.73m2). Approximately 52% had genotype 1a infection, and 48% had genotype 1b infection. Patients were treatment naïve (80.4%) or treatment experienced (19.6%). Stage 4 CKD was seen in 18.7% and stage 5 in 81.3%, with 76.2% currently receiving hemodialysis. The majority (94%) had no cirrhosis. The distribution of fibrosis stage at the start of the study was as follows: F0-F2: 69.4%, F3: 11.9%, F4: 6%, and 12.8% as other. Enrolled patients had a mean age 56 of years (18-70 years of age). More than half (57.4%) had baseline HCV RNA levels above 800,000 IU/mL.

Results from C-SURFER clinical trials for treatment naïve patients with genotype 1 HCV infection

	Grazoprevir/elbasvir immediate treatment group and pharmacokinetic population
SVR	
All patients	99% (115/116)
Intent-to-treat population	94% (115/122)
Genotype 1a	97% (61/63)
Genotype 1b	92% (54/59)
No cirrhosis	95% (109/115)
Patients with cirrhosis	86% (6/7)
Treatment naive	95% (96/101)
Treatment experienced	90% (19/21)
Hemodialysis	93% (86/92)
No hemodialysis	97% (29/30)
CKD stage 4	100% (22/22)
CKD stage 5	93% (93/100)
Relapse after treatment	
All patients	<1% (1/116)

Efficacy - Treatment naïve and treatment experienced patients with genotype 4 infection
Four trials (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SCAPE) evaluated the efficacy of Zepatier for treatment of genotype 4 infection. C-SCAPE randomized treatment naïve participants to 12 weeks of Zepatier with or without ribavirin. Study details for the other three studies are listed above. The combined genotype 4 study population from the four trials was 64% treatment naïve, 66% male, 87% Caucasian, 10% of African descent, 22% with cirrhosis, and 30% with HCV/HIV-1 co-infection. The overall SVR12 for the combined results of the four trials was 97% (64/66).

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ELBASVIR/GRAZOPREVIR

FDA APPROVED INDICATIONS (CONTINUED)

SAFETY
Contraindications for Zepatier include moderate or severe hepatic impairment (Child-Pugh B or C). As OATP1B1/3 inhibitors and CYP3A inhibitors may increase serum concentrations of Zepatier, the concurrent use of the following OATP1B1/3 inhibitors and strong CYP3A4 inhibitors with Zepatier is contraindicated: anticonvulsants (e.g., phenytoin, carbamazepine), antimycobacterials (e.g., rifampin), St. John's Wort, HIV medications (e.g., efavirenz, atazanavir, darunavir, lopinavir, saquinavir, tipranavir), and cyclosporine. When Zepatier is prescribed with ribavirin, prescribers must also consider contraindications, warnings, and precautions associated with ribavirin therapy.

For patients using a 12-week regimen of Zepatier, the most common adverse reactions reported in clinical trials include headache, nausea, and fatigue. Patients using Zepatier with ribavirin for 16 weeks most commonly experienced anemia (8%) and headache (6%). In clinical trials liver enzyme elevations occurred in approximately 1% of patients taking Zepatier, and were more common in female and Asian patients. Hepatic laboratory testing should be completed as clinically indicated, as well as prior to starting therapy, at treatment week 8, and at treatment week 12 for patients receiving 16 weeks of therapy.

No dose adjustments are necessary in patients with mild hepatic impairment (Child-Pugh A), but Zepatier is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C). No dose adjustment is required for patients with severe renal impairment or for those using hemodialysis.

The safety and efficacy of Zepatier have not been evaluated in the pediatric population. Clinical trials of Zepatier included 187 participants age of 65 and older; higher plasma concentrations of Zepatier and a higher rate of ALT elevations were noted in participants age 65 years and older than in those younger than age 65.

There are no human data on the safety of Zepatier use in pregnant humans; however, animal studies in rats and rabbits indicate that no adverse developmental effects were observed with Zepatier at 10-18 times the recommended human dose of elbasvir and 41-78 times the human dose of grazoprevir. While it is not known whether Zepatier is present in human breast milk, Zepatier was present in the milk of rats, but was not found to affect growth and development of nursing rat pups.

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ELBASVIR/GRAZOPREVIR

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