Drug Monograph

Drug/Drug Class:	**Zepatier® (elbasvir and grazoprevir) film coated tablet / Hepatitis C**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Zepatier® is available in a film-coated tablet containing 50 mg elbasvir and 100 mg grazoprevir respectively. Manufacturer: Merck & CO., Inc., Whitehouse Station, NJ 08889
Summary of Findings:	In treatment naïve patients, Zepatier achieved high SVR12 rates in cirrhotic and noncirrhotic patients with genotype 1, 4, or 6 infection. In treatment experienced patients, efficacy results showed a high level of efficacy in 12 week and 16 week study arms with and without ribavirin. Efficacy was marginally greater in the 16 week plus ribavirin arm. However, subgroup analyses, which excluded patients counted as non-virologic failures, found a stronger tendency towards greater efficacy in those randomized to 16 weeks plus ribavirin, except in prior relapsers.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Hepatitis C is a blood-borne virus that causes liver infection. Today, most people become infected with the virus by sharing needles or other equipment to inject drugs. Chronic Hepatitis C is a serious disease that can result in long-term health problems, even death. Hepatitis C is a slowly progressing disease. The majority of infected persons might not be aware of their infection because they are not clinically ill. Currently, there is not a vaccine for Hepatitis C. An estimated 2.7-3.9 million people in the United States have chronic hepatitis C. Chronic Hepatitis C can lead to cirrhosis and liver cancer.

Dosage Form(s) [1]

Zepatier® is available in a film-coated tablet containing 50 mg elbasvir and 100 mg grazoprevir respectively.

Manufacturer [1]

Merck & CO., Inc., Whitehouse Station, NJ 08889

Indication(s) [1]

Zepatier® is indicated with or without ribavirin for the treatment of chronic hepatitis C virus genotypes 1 or 4 infection in adults.

Clinical Efficacy [1,3] (mechanism of action/pharmacology, comparative efficacy)

Zepatier® is a fixed-dose combination tablet containing elbasvir and grazoprevir for oral administration. Elbasvir is an inhibitor of HCV NS5A, which is essential for viral replication and virion assembly. Grazoprevir is an inhibitor of HCV NS3/4A protease, necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.

Pharmacokinetics:

	Elbasvir	**Grazoprevir**
Metabolism	Liver, partial oxidative metabolism via CYP3A	Liver, partial oxidative metabolism via CYP3A
Half-life	~24 hours	~31 hours
Protein binding	> 99.9%	> 98.8%
Volume of distribution	680 L	1250 L
Excretion	> 90% feces < 1% urine	> 90% feces < 1% urine

C-EDGE TN

The objective is to evaluate the safety and efficacy of Zepatier in treatment-naïve patients.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, phase 3 trial.
INCLUSION CRITERIA	18 years and older treatment-naïve subjects with genotype 1 or 4 infections with or without cirrhosis.
EXCLUSION CRITERIA	Co-infection with hepatitis B or HIV, history of malignancy within past 5 years, clinically-relevant drug or alcohol abuse within 12 months of screening, pregnancy, breast feeding, expecting to conceive or donate eggs, organ transplant, history of gastric surgery or malabsorption disorder, evidence of history of chronic hepatitis not caused by HCV (including but not limited to nonalcoholic steatohepatitis, drug-induced hepatitis, and autoimmune hepatitis).
TREATMENT REGIMEN	Subjects were randomized in a 3:1 ratio to: Zepatier for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with Zepatier for 12 weeks (deferred treatment group).
RESULTS	Of 316 patients receiving immediate treatment, 299 or 316 (95%) achieved SVR12, including 144 of 157 (92%) with genotype 1a, 129 of 131 (99%) with genotype 1b, 18 of 18 (100%) with genotype 4, 68 or 70 (97%) with cirrhosis, and 231 of 246 (94%) without cirrhosis. Virologic failure occurred in 13 patients (4%), including 1 case of breakthrough infection and 12 relapses, and was associated with baseline NS5A polymorphisms and emergent NS3 or NS5A variants or both.
SAFETY	The most common adverse events in the active group were headache (17%), fatigue (16%), and nausea (9%).

C-EDGE TE

The objected was to evaluate the safety and efficacy of Zepatier in treatment-experienced patients.

STUDY DESIGN	Randomized, open-label comparative trial.
INCLUSION CRITERIA	Adults with genotype 1 or 4 infections, with or without cirrhosis, with or without HCV-HIV-1 co-infection, who had failed prior therapy with PegIFN + RBV therapy.
EXCLUSION	Not specified.

CRITERIA	
TREATMENT REGIMEN	Patients were randomized in a 1:1:1:1 ratio to one of the following treatment groups: Zepatier for 12 weeks, Zepatier + RBV for 12 weeks, Zepatier for 16 weeks, or Zepatier + RBV for 16 weeks.
RESULTS	Patients in the 12 week Zepatier group achieved 92% SVR, including 89% of the patients with cirrhosis, 90% with genotype 1a, 100% with genotype 1b, 78% with genotype 4, and 100% in those patients with co-infection. Patients in the 12 week + RBV group achieved 94% SVR12, including 88% of the patients with cirrhosis, 93% with genotype 1a, 96% with genotype 1b, 96% with genotype 4, and 100% in those patients with co-infection. Patients in the 16 week Zepatier group achieved 92% SVR12, including 92% of the patients with cirrhosis, 94% with genotype 1a, 96% with genotype 1b, 93% with genotype 4, and 83% in those patients with co-infection. Patient in the 16 week + RBV group achieved 97% SVR12, including 100% of those patients with cirrhosis, 95% with genotype 1a, 100% with genotype 1b, 100% with genotype 4, and 100% with co-infection.
SAFETY	Approximately 3% of participants in each study arm experienced a serious adverse event and a total of seven participants (5 in the 16 week +RBV group) discontinued study medication due to adverse events.

Contraindications [(1)]

- Hypersensitivity to elbasvir, grazoprevir, or any component of the formulation
- Moderate or severe hepatic impairment (Child-Pugh class B or C)
- Concurrent use with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors and strong inducers of CYP3A
- Concurrent drugs that are contraindicated include; atazanavir, carbamazepine, cyclosporine, darunavir, efavirenz, lopinavir, phenytoin, rifampin, saquinavir, St. John's wort, tipranavir.

Warnings and Precautions [(1)]

- ALT elevations (greater than 5 times upper limit) have been observed generally at week 8 or beyond.
- Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to treatment initiation to determine regimen and duration.
- Not indicated for treatment of HCV genotypes 2, 3, 5, and 6.
- If used with Ribavirin, refer to individual monographs for warnings regarding use.
- Potentially significant interactions may exist, requiring dose or frequency adjustments, additional monitoring, and/or selection of therapy.
- Use is contraindicated in moderate or severe hepatic impairment.

Adverse Effects [1]

C-EDGE TN

Most common	Zepatier (n=316)	Placebo (n=105)
Fatigue	11%	10%
Headache	10%	9%

C-EDGE TE

Most common	Zepatier (n=105) % at 12 weeks	Zepatier + Ribavirin (n=106) % at 16 weeks
Anemia	0%	8%
Headache	0%	6%
Fatigue	5%	4%
Dyspnea	0%	4%
Rash or Pruritus	0%	4%
Irritability	1%	3%
Abdominal pain	2%	2%
Depression	1%	2%
Arthralgia	0%	2%
Diarrhea	2%	0%

Drug Interactions [1]

- Aprepitant
- Aripiprazole
- Atazanavir
- Atorvastatin
- Cobicistat
- Conivaptan
- Cyclosporine
- CYP3A4 inducers
- CYP3A4 inhibitors
- Darunavir
- Dasatinib
- Deferasirox
- Dofetilide
- Efavirenz
- Flibanserin

- Fluvastatin
- Fosaprepitant
- Fusidic Acid
- Hydrocodone
- Idelalisib
- Ivacaftor
- Ketoconazole
- Lomitapide
- Lopinavir
- Lovastatin
- Luliconazole
- Mifepristone
- Netupitant
- Nimodipine
- OATP1B1/SLCO1B1 inhibitors
- Osimertinib
- Palbociclib
- Pazopanib
- Pimpozide
- Rifampin
- Rosuvastatin
- Saquinavir
- Siltuximab
- Simvastatin
- St. John's Wort
- Stiripentol
- Tacrolimus
- Tipranavir
- Tocilizumab
- Toptecan

Dosage and Administration [(1)]

Zepatier is a two-drug, fixed-dose combination product containing 50 mg of elbasvir and100 mg of grazoprevir in a single tablet. The recommended dosage is one tablet taken orally once daily with or without food. Zepatier is used in combination with ribavirin in certain patient populations.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST/ Month
Elbasvir/grazoprevir	Zepatier	Merck	50 mg/100 mg	1 tablet daily	$17,512.04*
Ledipasvir/sofosbuvir	Harvoni	Gilead	90 mg/400 mg	1 tablet daily	$30,309.00*
Ombitasvir/paritaprevir/ritonavir + dasabuvir	Viekira Pak	AbbVie	12.5 mg/75 mg/50 mg + 250 mg	2 tablets daily + 1 tablet BID	$26,723.18*

Sofosbuvir	Sovaldi	Gilead	400 mg	1 tablet daily	$26,941.60*
Daclatasvir	Daklinza	Bristol Myer Squibb	60 mg	1 tablet daily	$20,206.20*
Ombitasvir/paritaprevir/ritonavir	Technivie	AbbVie	12.5 mg/75 mg/50 mg	2 tablets daily	$24,585.17*

* Wholesale Acquisition Cost

Conclusion

Zepatier® is a two-drug fixed dose combination product containing 50 mg of elbasvir and 100 mg of grazoprevir in a single tablet. It is given once daily, with or without ribavirin for the treatment of chronic hepatitis C virus genotypes 1 or 4 infection in adults. In multiple clinical trials, patients taking Zepatier achieved high SVR12 rates with relatively few side effects. The most common side effects seen were headache and fatigue. This once daily, all oral, fixed-combination regimen represents a potent new therapeutic option for chronic HCV infection.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

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3. Alcorn, Keith. "Grazoprevir/elbasvir highly effective in treatment-experienced and HIV-coinfected hepatitis C patients." Retrieved 5/31/2016 from http://www.aidsmap.com

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