Formulary Drug Reviews: Glecaprevir/ Pibrentasvir

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Abstract

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Generic Name: Glecaprevir/Pibrentasvir

Proprietary Name: Mavyret (AbbVie)

Approval Rating: 1P

Therapeutic Class: Hepatitis C Virus Direct-Acting Antivirals

Similar Drugs: Sofosbuvir/Velpatasvir (Epclusa)

Sound- or Look-Alike Names: Grazoprevir

Indications

Glecaprevir/pibrentasvir is Food and Drug Administration (FDA) approved for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A), and for the treatment of patients with HCV genotype 1 infection who have been previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.¹

Indications for available pangenotypic, fixed-dose combination products are compared in Table 1.¹⁻³

Clinical Pharmacology

Glecaprevir is an HCV NS3/4A protease inhibitor. In assays, glecaprevir inhibited proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a.¹ Pibrentasvir is an HCV NS5A inhibitor that has demonstrated activity against laboratory and clinical isolates from subtypes 1a, 1b, 2a, 2b, 3a, 4a, 4b, 4d, 5a, 6a, 6e, and 6p.¹

In cell culture, resistance has been observed with some amino acid substitutions known to reduce antiviral susceptibility, and some combinations of amino acid substitutions were associated with greater reductions in susceptibility. In clinical trials, virologic failure was observed in small numbers of patients with HCV genotype 1, 2, or 3 infection; 2 treatment-naïve

patients with genotype 1 infection and 18 treatment-naïve patients with HCV genotype 3 infection developed treatment-emergent amino acid substitutions in NS3 and/or NS5A. Treatment-emergent substitutions were also observed in several treatment-experienced patients who experienced virologic failure while receiving glecaprevir/pibrentasvir. Not all patients with virologic failure demonstrated treatment-emergent substitutions.¹ Baseline HCV polymorphisms in genotypes 1, 2, 4, 5, and 6 had no impact on treatment outcome; a lower response rate was observed in patients with genotype 3 HCV infection and baseline NS5A A30K polymorphism.¹ Pibrentasvir has been observed to retain some activity against some common resistance-conferring substitutions in HCV genotypes 1, 2, 3, 4, 5, or 6 that have been identified for other NS5A inhibitors, including those at key amino acid positions 28, 30, 31, or 93. Genotype 3a Y93H, which confers 200-fold or greater resistance to other NS5A inhibitors, conferred a 2.3-fold change in susceptibility to pibrentasvir.⁴

Pharmacokinetics

Following oral administration of the individual components of glecaprevir/pibrentasvir in healthy subjects, peak glecaprevir and pibrentasvir concentrations are both reached in 5 hours. Relative to fasting, administration with a moderate- to high-fat meal raises glecaprevir exposure by 83% to 163% and raises pibrentasvir exposure by 40% to 53%. Following administration of combination glecaprevir/pibrentasvir in

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Table 1. Comparison of Indications for Pangenotypic, Fixed-Dose Combination Products.^{1,2,3}

Indication	Glecaprevir/ Pibrentasvir (<i>Mavyret</i>)	Sofosbuvir/ Velpatasvir (<i>Epclusa</i>)	Sofosbuvir/Velpatasvir/ Voxilaprevir (<i>Vosevi</i>)
Chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis	X ^a	X	
Chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection with decompensated cirrhosis in combination with ribavirin		X	
HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis in patients previously treated with interferon, peginterferon, ribavirin, and/or sofosbuvir, but not with an NS3/4A protease inhibitor or NS5A inhibitor	^b		
HCV genotype 1 infection without cirrhosis or with compensated cirrhosis in patients previously treated with an HCV NS5A inhibitor or NS3/4A protease inhibitor, but not both	X		
HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis in patients previously treated with peginterferon alfa-ribavirin with or without an NS3/4A protease inhibitor		^b	
HCV genotype 1, 2, 3, 4, 5, or 6 infection with decompensated cirrhosis in combination with ribavirin in patients previously treated with peginterferon alfa-ribavirin with or without an NS3/4A protease inhibitor		^b	
HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis in patients previously treated with an HCV NS5A inhibitor			X
HCV genotype 1a or 3 infection without cirrhosis or with compensated cirrhosis and previously treated with sofosbuvir without an NS5A inhibitor			X

Note. NS3/4A protease inhibitors: boceprevir, glecaprevir, grazoprevir, paritaprevir, simeprevir, telaprevir, and voxilaprevir. NS5A inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, and velpatasvir. HCV = hepatitis C virus; FDA = Food and Drug Administration.

^aX = FDA-approved use.

^bUse evaluated in clinical trials.

noncirrhotic HCV-infected subjects, the peak concentration of glecaprevir was reduced by 51% relative to healthy subjects, but overall exposure was not altered. Peak concentration of pibrentasvir was reduced by 63% and overall exposure was 34% lower relative to healthy subjects.¹

Glecaprevir and pibrentasvir are both highly plasma protein bound (97.5% and greater than 99%, respectively).¹

The elimination half-life of glecaprevir is 6 hours, while that of pibrentasvir is 13 hours. Both are primarily eliminated via the biliary-fecal route, with greater than 90% of the dose excreted in the feces. Metabolism via cytochrome P450 (CYP-450) 3A is a secondary means of elimination for glecaprevir. Less than 1% of the dose of either component is excreted in the urine.¹ Glecaprevir has been shown to dose-dependently increase pibrentasvir exposure, while pibrentasvir does not significantly alter glecaprevir exposure.⁵

Glecaprevir and pibrentasvir area under the curve values were increased up to 56% in non-HCV-infected subjects with mild, moderate, severe, or end-stage renal impairment not on dialysis compared with subjects with normal renal

function. Exposure to both agents was also similar with and without dialysis in dialysis-dependent non-HCV-infected subjects. In HCV-infected subjects with end-stage renal disease (with or without dialysis), glecaprevir exposure was 86% higher and pibrentasvir exposure was 54% higher than in subjects with normal renal function. No dose adjustment is necessary in patients with mild, moderate, or severe renal impairment, including those on dialysis.¹

In HCV-infected patients with mild hepatic impairment (Child-Pugh A) and compensated cirrhosis, glecaprevir exposure was increased approximately 2-fold while pibrentasvir exposure was similar to that of noncirrhotic HCV-infected subjects. In non-HCV-infected subjects with moderate hepatic impairment (Child-Pugh B), glecaprevir exposure was 100% higher than in subjects with normal hepatic function, while pibrentasvir exposure was 26% higher. In patients with severe hepatic impairment (Child-Pugh C), glecaprevir exposure was 11-fold higher than in subjects with normal hepatic function, while pibrentasvir exposure was 114% higher. No dose adjustment is necessary in patients with mild hepatic impairment. Use is not recommended

in patients with moderate hepatic impairment, and use is contraindicated in patients with severe hepatic impairment.¹

Clinically significant differences in the pharmacokinetics of either agent were not observed based on age (18 to 88 years), gender, race/ethnicity, or body weight.^{1,6}

Comparative Efficacy

Indication: Infection With Hepatitis C Virus Genotypes 1 Through 6 Without Cirrhosis or With Compensated Cirrhosis

Guidelines

Guidelines: HCV guidance: Recommendations for testing, managing, and treating hepatitis C

Reference: American Association for the Study of Liver Diseases/Infectious Diseases Society of America/International Antiviral Society-USA (AASLD/IDSA/IAS-USA)⁷

Comments: The recommended therapies for treating HCV infections (genotypes 1 through 6) are listed below according to HCV genotype, cirrhosis status, and prior treatment exposure. Glecaprevir/pibrentasvir has not yet been incorporated into these guidelines.

Treatment-naïve.

Genotype 1a

- Without cirrhosis: Elbasvir/grazoprevir; glecaprevir/pibrentasvir; ledipasvir/sofosbuvir; or sofosbuvir/velpatasvir. Alternative regimens are paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD) with ribavirin; simeprevir plus sofosbuvir; daclatasvir plus sofosbuvir; or elbasvir/grazoprevir with ribavirin.
- With compensated cirrhosis: Elbasvir/grazoprevir; glecaprevir/pibrentasvir; ledipasvir/sofosbuvir; or sofosbuvir/velpatasvir. Alternative regimen is elbasvir/grazoprevir with ribavirin.

Genotype 1b

- Without cirrhosis: Elbasvir/grazoprevir; glecaprevir/pibrentasvir; ledipasvir/sofosbuvir; or sofosbuvir/velpatasvir. Alternative regimens are PrOD; simeprevir plus sofosbuvir; or daclatasvir plus sofosbuvir.
- With compensated cirrhosis: Elbasvir/grazoprevir; glecaprevir/pibrentasvir; ledipasvir/sofosbuvir; or sofosbuvir/velpatasvir. Alternative regimen is PrOD.

Genotype 2

- With or without compensated cirrhosis: Glecaprevir/pibrentasvir or sofosbuvir/velpatasvir. Alternative regimen is daclatasvir plus sofosbuvir.

Genotype 3

- Without cirrhosis: Glecaprevir/pibrentasvir or sofosbuvir/velpatasvir. Alternative regimen is daclatasvir plus sofosbuvir.
- With compensated cirrhosis: Glecaprevir/pibrentasvir or sofosbuvir/velpatasvir. Alternative regimens are sofosbuvir/velpatasvir/voxilaprevir or daclatasvir plus sofosbuvir with or without ribavirin.

Genotype 4

- With or without compensated cirrhosis: Glecaprevir/pibrentasvir; sofosbuvir/velpatasvir; elbasvir/grazoprevir; or ledipasvir/sofosbuvir. Alternative regimen is paritaprevir/ritonavir/ombitasvir with ribavirin.

Genotype 5 or 6

- With or without compensated cirrhosis: Glecaprevir/pibrentasvir; sofosbuvir/velpatasvir; or ledipasvir/sofosbuvir.

Treatment-experienced

- Recommendations are dependent on what agents were previously used. Some drug regimens include the addition of ribavirin and/or peginterferon, and/or require a longer duration of therapy.

Studies

Drug: Glecaprevir/Pibrentasvir versus Sofosbuvir plus Daclatasvir

Reference: Foster GR, et al, 2017 (ENDURANCE-3 trial)⁸

Study Design: Phase 3, randomized, open-label, multicenter study

Study Funding: AbbVie

Patients: 505 treatment-naïve patients with HCV genotype 3 infection without cirrhosis. Approximately half of the sample was male (52%).

Intervention: Patients were randomized (2:1) to receive glecaprevir 300 mg/pibrentasvir 120 mg once daily or sofosbuvir 400 mg plus daclatasvir 60 mg once daily for 12 weeks. Subsequently, an additional treatment arm in which patients received glecaprevir 300 mg/pibrentasvir 120 mg once daily for 8 weeks was added.

Results

Primary End Point(s)

- Sustained virologic response at posttreatment week 12 (SVR12) was achieved in 222 of 233 patients (95%; 95% confidence interval [CI], 93%-98%) treated with glecaprevir/pibrentasvir for 12 weeks, in 111 of 115 (97%; 95% CI, 91%-9%) treated with sofosbuvir plus daclatasvir for 12 weeks, and in 149 of 157 (95%; 95%

CI, 92%-98%) treated with glecaprevir/pibrentasvir for 8 weeks. The 8-week glecaprevir/pibrentasvir regimen was noninferior to the 12-week regimen with the same agents. The 12-week glecaprevir/pibrentasvir regimen was noninferior to the 12-week sofosbuvir plus daclatasvir regimen, which is a guideline-recommended therapy for genotype 3 infection without cirrhosis.

Secondary End Point(s)

- Posttreatment virologic relapse occurred in 1% of patients in each of the 12-week treatment arms and in 3% in the 8-week treatment arm.
- Nonvirologic failure occurred in 7 patients treated with glecaprevir/pibrentasvir for 12 weeks, in 3 patients treated with sofosbuvir plus daclatasvir for 12 weeks, and in 2 patients treated with glecaprevir/pibrentasvir for 8 weeks.

Comments: The study was conducted in Australia, Canada, France, New Zealand, the United Kingdom, and the United States.

Limitations: Results have only been presented in a meeting abstract.

Drug: Glecaprevir/Pibrentasvir

Reference: Zeuzem S, et al, 2016 (ENDURANCE-1 trial)⁹

Study Design: Phase 3, randomized, open-label, multicenter study

Study Funding: AbbVie

Patients: 703 patients with chronic HCV genotype 1 without cirrhosis and with or without HIV-1 coinfection. Enrolled patients were treatment naive or previously treated with interferon or peginterferon with or without ribavirin, or with sofosbuvir plus ribavirin with or without peginterferon. Approximately half of the patients were male (49%) and the majority were white (84%); 62% were treatment naive; and 42% were infected with genotype 1a;. Only 5% were coinfecting with HIV-1. Among HCV treatment-experienced patients, 99% had received an interferon-based regimen, and the remaining 1% had received a sofosbuvir-based regimen. Patients with HIV and patients previously treated with sofosbuvir were excluded from the analysis of the primary end points.

Intervention: Patients received glecaprevir 300 mg/pibrentasvir 120 mg orally once daily for either 8 weeks or 12 weeks.

Results

Primary End Point(s)

- SVR12 was achieved in 331 of 332 patients (99.7%) in the 12-week treatment arm.
- SVR12 was achieved in 332 of 335 patients (99.1%) in the 8-week treatment arm; this result was noninferior to the SVR12 rate in the 12-week treatment arm.

Secondary End Point(s)

- SVR12 in patients with HIV-1 coinfection was achieved in 15 of 15 patients (100%) treated for 8 weeks and in 18 of 18 patients (100%) treated for 12 weeks.
- SVR12 was achieved in the 3 patients with prior sofosbuvir treatment experience.
- On-treatment virologic failure occurred at day 29 in 1 patient with genotype 1a infection in the 8-week treatment arm.
- Posttreatment relapse was not observed in any patient.

Comments: In part 1 of the similar MAGELLAN-1 study, which enrolled 50 patients 18 to 70 years of age with HCV genotype 1 infection without cirrhosis but with prior virologic failure or relapse following HCV direct-acting antiviral therapy, SVR12 was achieved in 6 of 6 patients (100%; 95% CI, 61%-100%) treated with glecaprevir 200 mg/pibrentasvir 80 mg, in 21 of 22 (95%; 95% CI, 78%-99%) treated with glecaprevir 300 mg/pibrentasvir 120 mg plus ribavirin, and in 19 of 22 (86%; 95% CI, 67%-95%) treated with glecaprevir 300 mg/pibrentasvir 120 mg for 12 weeks.¹⁰ The phase 2 SURVEYOR-I and SURVEYOR-II studies enrolled a total of 449 patients 18 to 70 years of age with HCV genotypes 1, 2, 3, 4, 5, or 6 without cirrhosis who were either treatment naive or had previously been treated with peginterferon-ribavirin. In these 2 dose-ranging studies using 8- and 12-week treatment periods, SVR12 was achieved in 92% to 100% of patients.¹¹ In a subsequent part 4 to the SURVEYOR-II study in patients treated with glecaprevir 300 mg/pibrentasvir 120 mg once daily for 8 weeks, sustained virologic response at posttreatment week 4 (SVR4) was achieved in 141 of 145 (97%) patients with genotype 2 infection, in 45 of 46 (98%) with genotype 4 infection, in 2 of 2 (100%) with genotype 5 infection, and in 10 of 10 (100%) with genotype 6 infection.¹² In a similar study (ENDURANCE-4) including 121 treatment-naïve or treatment-experienced (interferon- or sofosbuvir-based regimen) patients with chronic HCV infection genotype 4, 5, or 6 treated with glecaprevir 300 mg/pibrentasvir 120 mg once daily for 12 weeks, SVR12 was achieved in 120 of 121 patients (99%); treatment failure occurred in one patient who discontinued treatment on day 12).¹³

Limitations: ENDURANCE-1 was a large study comparing 8-week and 12-week treatment durations in patients infected with HCV genotype 1, but numbers of patients with HIV coinfection or experience with sofosbuvir therapy were insufficient to draw any conclusions for those groups. Results have only been reported in a meeting abstract/presentation. As a postmarketing requirement, AbbVie will conduct an additional study evaluating the efficacy of glecaprevir/pibrentasvir in HCV genotype 1-infected patients previously treated with an NS5A inhibitor plus sofosbuvir.¹⁴

Reference: Forns X, et al, 2017 (EXPEDITION-1 trial)¹⁵

Study Design: Open-label, single-arm, multicenter, phase 3 study

Study Funding: AbbVie

Patients: 146 patients (18 years and older) with chronic HCV infection and with compensated cirrhosis. Patients were either treatment naive or had not responded to treatment with interferon or peginterferon with or without ribavirin, or to treatment with sofosbuvir plus ribavirin with or without peginterferon; all patients were NS3/4A and NS5A inhibitor-naïve. Enrolled patients were infected with HCV genotype 1a (33%), 1b (27%), 2 (23%), 4 (11%), 5 (1%), or 6 (5%). Mean age was 60 years (range, 26 to 88 years); 62% of patients were male, and 82% were white. The majority (75%) were treatment naive.

Intervention: Patients received glecaprevir 300 mg/pibrentasvir 120 mg administered orally once daily for 12 weeks.

Results

Primary End Point(s)

- SVR12 was achieved in 145 patients (99%; 95% CI, 98%-100%).

Secondary End Point(s)

- No patients experienced on-treatment virologic failure.
- The proportion of patients with posttreatment virologic relapse was 1%. Relapse occurred in one patient with genotype 1a infection at posttreatment week 8. This patient had no baseline polymorphisms or treatment-emergent substitutions in NS3; however, in NS5A, Q30R-H58D was present at the time of failure, and Y93N was present at baseline and at the time of failure.

Comments: EXPEDITION-1 was conducted at 40 sites in Belgium, Canada, Germany, South Africa, Spain, and the United States. Similar results were achieved in the phase 2 SURVEYOR-I and SURVEYOR-II studies enrolling 27 patients with HCV genotype 1 and 55 patients with HCV genotype 3, all with compensated cirrhosis. Patients with genotype 1 received glecaprevir 300 mg plus pibrentasvir 120 mg for 12 weeks; patients with genotype 3 received glecaprevir 300 mg plus pibrentasvir 120 mg with or without ribavirin for 12 weeks. SVR12 was achieved in 26 of 27 patients (96%; 95% CI, 82%-99%) with genotype 1 infection, in 27 of 28 patients (96%; 95% CI, 82%-99%) with genotype 3 treated without ribavirin, and in 27 of 27 patients (100%; 95% CI, 88%-100%) with genotype 3 treated with ribavirin.¹⁶ Part 2 of the MAGELLAN-1 phase 2 study enrolled 91 patients (18 to 70 years of age) with HCV genotype 1 or genotype 4 infection with or without compensated cirrhosis, and with prior virologic

failure following HCV direct-acting antiviral therapy with NS5A and/or NS3/4A protease inhibitors. Patients were randomized to receive 12 or 16 weeks of glecaprevir 300 mg/pibrentasvir 120 mg. SVR12 was achieved in 39 of 44 patients (89%) treated for 12 weeks and in 43 of 47 patients (92%) treated for 16 weeks. In the subgroup of patients in whom previous regimens with telaprevir or boceprevir plus peginterferon-ribavirin, simeprevir plus sofosbuvir or peginterferon-ribavirin, or multiple protease inhibitors had failed, SVR12 was achieved at a rate of 100% (14 of 14 patients treated for 12 weeks and 13 of 13 patients treated for 16 weeks). In the subgroup in whom previous regimens with sofosbuvir/ledipasvir or daclatasvir plus peginterferon-ribavirin had failed, SVR12 was achieved in 14 of 16 patients (88%) treated for 12 weeks and in 17 of 18 (94%) treated for 16 weeks. In the subgroup of patients in whom previous regimens with ombitasvir/paritaprevir/ritonavir with or without dasabuvir, daclatasvir plus asunaprevir, or other combinations had failed, SVR12 was achieved in 11 of 14 patients (79%) treated for 12 weeks and in 13 of 16 (81%) treated for 16 weeks.¹⁷

Limitations: The small number of patients in some genotype groups, the limited number of treatment-experienced patients, and the lack of an active control arm were all limitations of the EXPEDITION-1 study.

Reference: Gane EJ, et al, 2016 (EXPEDITION-4 trial)¹⁸

Study Design: Open-label, multicenter study

Study Funding: AbbVie

Patients: 104 patients with renal impairment (estimated glomerular filtration rate less than 30 mL/min/1.73 m²) and HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis. Patients were treatment naive or previously treated with an interferon- or sofosbuvir-based regimen. Most patients were male (76%) and white (62%); 42% were treatment experienced, 19% had compensated cirrhosis, and 82% were on dialysis. All genotypes were represented, although most patients had genotype 1 infection (genotype 1: 52%, genotype 2: 16%, genotype 3: 11%, genotype 4: 19%, genotype 5 and 6: 1% each).

Intervention: Patients received glecaprevir 300 mg/pibrentasvir 120 mg orally once daily for 12 weeks.

Results

Primary End Point(s):

- SVR12 was achieved in 102 of 104 patients (98%) in the intention-to-treat analysis; 1 patient discontinued treatment early, and 1 patient was lost to follow-up.

Secondary End Point(s)

- SVR4 was achieved in 103 of 104 patients (99%). The patient not achieving SVR4 prematurely discontinued treatment.

Limitations: Results have only been reported in a meeting abstract/presentation.

Reference: Reau N, et al, 2017 (MAGELLAN-2 trial)¹⁹

Study Design: Phase 3, single-arm, open-label, multicenter study

Study Funding: AbbVie

Patients: 100 adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis who were at least 3 months post liver or renal transplant and on a stable immunosuppressive regimen (tacrolimus, sirolimus, everolimus, mycophenolate mofetil, azathioprine, cyclosporine, and/or mycophenolic acid). Patients were either treatment naïve or, excepting genotype 3–infected patients, could have received treatment with interferon, peginterferon with or without ribavirin, or sofosbuvir with ribavirin with or without peginterferon. Most patients were male (75%) and white (78%); 34% were treatment experienced; 80% had received a liver transplant, and 20% had received a kidney transplant. Most genotypes were represented, although the majority of patients had genotype 1 infection (genotype 1: 57%, genotype 2: 13%, genotype 3: 24%, genotype 4: 4%, genotype 5: 0%, and genotype 6: 2%). Ninety-nine patients were included in the modified intention-to-treat (mITT) analysis; one patient was lost to follow-up.

Intervention: Patients were treated with glecaprevir 300 mg/pibrentasvir 120 mg once daily for 12 weeks.

Results

Primary End Point(s)

- SVR12 was achieved in 98 of 99 patients (99%).

Secondary End Point(s)

- Posttreatment relapse occurred at posttreatment week 4 in one treatment-naïve, genotype 3a–infected patient.
- No patients experienced on-treatment virologic failure.

Limitations: Results have only been published in a meeting abstract.

Reference: Rockstroh J, et al, 2017 (EXPEDITION-2 trial)²⁰

Study Design: Phase 3, single-arm, open-label, multicenter study

Study Funding: AbbVie

Patients: 153 patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis, and with HIV-1 coinfection. Enrolled patients were HCV treatment naïve or previously treated

with interferon, peginterferon with or without ribavirin, or sofosbuvir plus ribavirin with or without peginterferon; previously treated genotype 3–infected patients were excluded. Patients also had to be on a stable antiretroviral regimen for at least 8 weeks prior to screening or be antiretroviral therapy naïve with a CD4+ count of at least 500 cells/mm³; nine patients were antiretroviral therapy naïve. Most patients were male (83% in patients without cirrhosis [8-week treatment group] and 94% in those with cirrhosis [12-week treatment group]), white (77% and 94%, respectively), and HCV treatment-naïve (81% and 87%, respectively); 10% had cirrhosis. Most genotypes were represented, although the majority of patients had genotype 1 infection (genotype 1: 61% and 63%, genotype 2: 9% and 6%, genotype 3: 16% and 25%, genotype 4: 12% and 6%, genotype 5: 0% and 0%, and genotype 6: 2% and 0%, respectively).

Intervention: Patients received glecaprevir 300 mg/pibrentasvir 120 mg once daily for 8 weeks in patients without cirrhosis (n=137) and for 12 weeks in patients with compensated cirrhosis (n=16).

Results

Primary End Point(s)

- SVR12 was achieved in 150 of 153 (98%) patients overall and in 150 of 151 (99%) patients included in the mITT analysis. One patient lost to follow-up at posttreatment week 12 returned at posttreatment week 24 and was found to have achieved sustained virologic response.²¹

Secondary End Point(s)

- Virologic failure at week 8 occurred in one HCV genotype 3–infected patient with cirrhosis, who reported 85% adherence to the treatment regimen.²¹

Comments: This study was conducted in Europe, Russia, and the United States.

Limitations: Results have only been reported in a meeting abstract/presentation.

Contraindications, Warnings, and Precautions

Contraindications

Glecaprevir/pibrentasvir is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and in patients receiving atazanavir or rifampin.¹

The contraindications, warnings, and precautions for glecaprevir/pibrentasvir and sofosbuvir/velpatasvir are compared in Table 2.^{1,2}

Table 2. Comparison of the Contraindications, Warnings, and Precautions Associated With Glecaprevir/Pibrentasvir and Sofosbuvir/Velpatasvir.^{1,2}

	Glecaprevir/pibrentasvir	Sofosbuvir/velpatasvir
Contraindications		
Coadministration of atazanavir	X	
Coadministration of rifampin	X	Not recommended
Contraindications associated with ribavirin, when used in conjunction with ribavirin		X
Severe hepatic impairment (Child-Pugh C)	X	
Warnings and precautions		
Bradycardia with concomitant use of amiodarone		X
Coadministration of inducers of P-glycoprotein and/or CYP enzymes (eg, carbamazepine, efavirenz, St. John's wort)	Not recommended	Not recommended
HBV reactivation	X	X
Moderate hepatic impairment (Child-Pugh B)	X	
Precautions associated with ribavirin, when used in conjunction with ribavirin		X

Note. CYP = cytochrome P; HBV = hepatitis B virus.

Warnings and Precautions

Hepatitis B virus (HBV) reactivation has occurred in patients coinfecting with HCV and HBV who were undergoing treatment with HCV direct-acting antivirals without HBV antiviral therapy. All patients should be tested for evidence of current or prior HBV infection before initiating treatment with glecaprevir/pibrentasvir. HCV/HBV coinfecting patients should be monitored for hepatitis flare or HBV reactivation during HCV treatment and during posttreatment follow-up. HBV treatment should be initiated as clinically indicated.¹

Plasma concentrations of glecaprevir and pibrentasvir may be reduced when glecaprevir/pibrentasvir is coadministered with carbamazepine, efavirenz, and St. John's wort, resulting in reduced therapeutic effect. The concomitant use of these agents with glecaprevir/pibrentasvir is not recommended.¹

Glecaprevir/pibrentasvir use is not recommended in patients with moderate hepatic impairment (Child-Pugh B).¹

There are no adequate and well-controlled studies of glecaprevir/pibrentasvir in pregnant women. Glecaprevir/pibrentasvir should be used during pregnancy only if clearly needed.¹

Caution should be used when administering glecaprevir/pibrentasvir to a breastfeeding woman. No studies have been conducted to assess the presence of glecaprevir or pibrentasvir in human milk or its effects on breastfeeding infants or human milk production.¹

Safety and effectiveness of glecaprevir/pibrentasvir have not been established in pediatric patients.¹

Adverse Reactions

The most frequently observed adverse reactions during glecaprevir/pibrentasvir clinical trials were headache (13%), fatigue (11%), and nausea (8%).¹

Table 3 includes the adverse reactions observed in treatment-naïve patients without cirrhosis treated with glecaprevir/pibrentasvir for 8 or 12 weeks or daclatasvir plus sofosbuvir for 12 weeks in a comparative trial.¹

Drug Interactions

Glecaprevir and pibrentasvir are inhibitors of P-gp, breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Coadministration with glecaprevir/pibrentasvir may increase plasma concentrations of drugs that are substrates of P-gp, BCRP, or OATP1B1 or OATP1B3. Glecaprevir and pibrentasvir are also weak inhibitors of CYP3A and 1A2, and of uridine glucuronosyltransferase (UGT) 1A1.¹

Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Coadministration of glecaprevir/pibrentasvir with drugs that inhibit P-gp, BCRP, or OATP1B1/3 may increase plasma concentrations of glecaprevir and/or pibrentasvir. Coadministration with drugs that induce P-gp or CYP3A may decrease glecaprevir and pibrentasvir plasma concentrations. Carbamazepine, efavirenz, and St. John's wort, all potent P-gp/CYP3A inducers, may significantly decrease glecaprevir and pibrentasvir plasma concentrations, leading to reduced therapeutic effect. Therefore, concomitant use of these agents with glecaprevir/pibrentasvir is not recommended. Table 4 summarizes clinically important drug interactions with glecaprevir/pibrentasvir.¹

Interactions are not anticipated when glecaprevir/pibrentasvir is coadministered with substrates of CYP3A, 1A2, 2C9, 2C19, or 2D6, or of UGT1A1 or UGT1A4. Clinically significant interactions have not been observed and no dose adjustment is required when glecaprevir/pibrentasvir is coadministered with the following drugs: abacavir,

Table 3. Glecaprevir/Pibrentasvir Adverse Reactions ($\geq 5\%$ Incidence) in Treatment-Naive HCV Patients Without Cirrhosis.¹

Adverse reaction	Glecaprevir/pibrentasvir 8 wk (n = 157)	Glecaprevir/pibrentasvir 12 wk (n = 233)	Daclatasvir + sofosbuvir 12 wk (n = 115)
Headache	16%	17%	15%
Fatigue	11%	14%	12%
Nausea	9%	12%	12%
Diarrhea	7%	3%	3%

Note. HCV = hepatitis C virus.

Table 4. Glecaprevir/Pibrentasvir Drug Interactions.¹

Concomitant drug	Effect on concentration	Clinical comments
Antiarrhythmics Digoxin	↑ Digoxin	Measure serum digoxin concentrations before initiating glecaprevir/pibrentasvir. Reduce digoxin concentrations by decreasing the dose by approximately 50% or by modifying the dosing frequency and continue monitoring.
Anticoagulants Dabigatran etexilate	↑ Dabigatran	If glecaprevir/pibrentasvir and dabigatran etexilate are coadministered, refer to the dabigatran etexilate prescribing information for dabigatran etexilate dose modifications in combination with P-gp inhibitors in the setting of renal impairment.
Anticonvulsants Carbamazepine	↓ Glecaprevir ↓ Pibrentasvir	Coadministration may lead to reduced therapeutic effect of glecaprevir/pibrentasvir and is not recommended.
Antimycobacterials Rifampin	↓ Glecaprevir ↓ Pibrentasvir	Coadministration is contraindicated because of potential loss of therapeutic effect.
Ethinyl estradiol-containing products Ethinyl estradiol-containing medications such as combined oral contraceptives	↔ Glecaprevir ↔ Pibrentasvir	Coadministration of glecaprevir/pibrentasvir may increase the risk of ALT elevations and is not recommended.
Herbal products St. John's wort (<i>Hypericum perforatum</i>)	↓ Glecaprevir ↓ Pibrentasvir	Coadministration may lead to reduced therapeutic effect of glecaprevir/pibrentasvir and is not recommended.
HIV antiviral agents Atazanavir	↑ Glecaprevir ↑ Pibrentasvir	Coadministration is contraindicated due to increased risk of ALT elevations.
Darunavir Lopinavir Ritonavir Efavirenz	↑ Glecaprevir ↑ Pibrentasvir ↓ Glecaprevir ↓ Pibrentasvir	Coadministration is not recommended. Coadministration may lead to reduced therapeutic effect of glecaprevir/pibrentasvir and is not recommended.
HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin Pravastatin	↑ Atorvastatin ↑ Lovastatin ↑ Simvastatin ↑ Pravastatin	Coadministration may increase the concentration of atorvastatin, lovastatin, and simvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Coadministration with these statins is not recommended. Coadministration may increase the concentration of pravastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Reduce pravastatin dose by 50% when coadministered with glecaprevir/pibrentasvir.
Rosuvastatin	↑ Rosuvastatin	Coadministration may significantly increase the concentration of rosuvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with glecaprevir/pibrentasvir at a dose that does not exceed 10 mg.
Fluvastatin Pitavastatin	↑ Fluvastatin ↑ Pitavastatin	Coadministration may increase the concentrations of fluvastatin and pitavastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Use the lowest approved dose of fluvastatin or pitavastatin. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment.
Immunosuppressants Cyclosporine	↑ Glecaprevir ↑ Pibrentasvir	Glecaprevir/pibrentasvir is not recommended for use in patients requiring stable cyclosporine doses greater than 100 mg per day.

Note. ↑ = increased; ↓ = decreased; ↔ = no effect. ALT = alanine aminotransferase; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

Table 5. Treatment Duration for Glecaprevir/Pibrentasvir.¹

HCV genotype	Prior treatment	Treatment duration	
		No cirrhosis	Compensated cirrhosis (child-Pugh A)
1, 2, 3, 4, 5 or 6	None	8 wk	12 wk
1	NS5A inhibitor without an NS3/4A protease inhibitor	16 wk	16 wk
	NS3/4A protease inhibitor without an NS5A inhibitor	12 wk	12 wk
1, 2, 4, 5, or 6	Interferon, peginterferon, ribavirin, and/or sofosbuvir, but no NS3/4A protease inhibitor or NS5A inhibitor	8 wk	12 wk
3	Interferon, peginterferon, ribavirin, and/or sofosbuvir, but no NS3/4A protease inhibitor or NS5A inhibitor	16 wk	16 wk

Note. HCV = hepatitis C virus.

amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/cobicistat, emtricitabine, felodipine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.^{1,22,23}

Recommended Monitoring

Before initiating treatment with glecaprevir/pibrentasvir, patients should be tested for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).¹

Dosing

The recommended dosage is 3 tablets taken once daily with food (total daily dose, glecaprevir 300 mg/pibrentasvir 120 mg). Treatment duration varies from 8 weeks to 16 weeks, depending on previous treatment and the presence of cirrhosis (see Table 5).¹

No dosing adjustments are necessary for patients with mild, moderate, or severe renal impairment, including those on dialysis.¹ No dosing adjustments are necessary for patients with mild hepatic impairment (Child-Pugh A). Use in patients with moderate hepatic impairment (Child-Pugh B) is not recommended, and use is contraindicated in patients with severe hepatic impairment (Child-Pugh C).¹

Product Availability

Glecaprevir/pibrentasvir received FDA approval in August 2017.¹⁴ It is available as a fixed-dose combination tablet containing glecaprevir 100 mg and pibrentasvir 40 mg, and is supplied in 4-week or 8-week cartons. Each weekly carton contains 7 child-resistant daily dose wallets of 3 tablets each.¹ Tablets should be stored at or below 30°C (86°F) in the original blister package until administered.¹

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for glecaprevir/pibrentasvir.¹⁴

Conclusion

Glecaprevir/pibrentasvir is approved for treatment of patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A), and for the treatment of patients with HCV genotype 1 infection who have previously been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. In clinical trials of HCV patients, glecaprevir/pibrentasvir produced high SVR12 rates in treatment-naïve and treatment-experienced patients with renal impairment, prior renal and liver transplant, or coinfection with HIV-1. Glecaprevir/pibrentasvir has demonstrated good tolerability but is associated with drug interactions that may limit its use in certain patients.

Declaration of Conflicting Interests

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