var drug_url = "glecaprevir-pibrentasvir";

Glecaprevir-Pibrentasvir *(Mavyret)*

Other Names: **GLE-PIB**

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Drug Summary

Glecaprevir-pibrentasvir is the first pangenotypic NS3/4A protease inhibitor-NS5A inhibitor combination to be approved that offers a potent ribavirin-free option for the vast majority of patients with chronic hepatitis C, including a potential 8-week option for non-cirrhotic patients with renal disease or HIV coinfection. This drug is not an option for patients with decompensated cirrhosis (Child B/C) given the presence of the protease inhibitor. In main registration trials, sustained virologic response rates for 8 or 12 weeks of glecaprevir-pibrentasvir for genotypes 1, 2, 5 or 6 were in the range of 98-100% with very few if any on-treatment virologic breakthroughs or post-treatment relapses. Despite earning an 8-week FDA indication for all genotypes (treatment-naïve) without cirrhosis, the efficacy of 8 weeks of glecaprevir-pibrentasvir was numerically lower for genotype 3 and 4 at 95% and 93% respectively. Glecaprevir-pibrentasvir is by far the least expensive of all DAAs, priced at $26,400 for an 8-week course (less than half the wholesale acquisition cost of 8 weeks of ledipasvir-sofosbuvir), and it is anticipated to expand and transform the treatment landscape worldwide.

Class and Mechanism

Glecaprevir (GLE, formerly ABT-493) is an NS3/4A protease inhibitor that prevents the cleavage of the HCV polyprotein. It has potent in vitro activity (on the order of less than or equal to 5 nanomolar), across the HCV genotypes including common HCV genotype 1 variants that have substitutions (at Q80, R155 and D168) conferring resistance to older-generation HCV protease inhibitors. Pibrentasvir (PIB, formerly ABT-530) is a next-generation NS5A inhibitor with pangenotypic activity in vitro; it maintains potent antiviral activity against common HCV NS5A single-position variants that confer resistance to first-generation NS5A inhibitors, including daclatasvir, ledipasvir, and ombitasvir.

Manufacturer for United States

The fixed dose medication glecaprevir-pibrentasvir (*Mavyret*) (Figure 1) is manufactured by AbbVie Inc.

Cost and Medication Access

The wholesale acquisition cost (WAC) for a 8-week course of glecaprevir-pibrentasvir is $26,400. The 8-week course of glecaprevir-pibrentasvir is indicated for treatment-naïve noncirrhotic patients with genotypes 1-6 HCV; this 8-week treatment course makes glecaprevir-pibrentasvir by far the least expensive option among all of the recommended treatment options for non-cirrhotic treatment-naïve patients. The 12-week treatment course has a cost of $39,600 and this duration is indicated for treatment-naive patients with compensated cirrhosis (Child-Pugh A) and some treatment experienced patients. The 16-week treatment course is $52,800 and is indicated for some subsets of treatment-experienced patients.

Adverse Effects

The most common adverse effects, observed in at least 10% of phase 3 trial participants, were headache and fatigue.

Key Drug Interactions

For complete information on glecaprevir-pibrentasvir-related drug interactions, see the Drug Interactions section in the Glecaprevir-Pibrentasvir (*Mavyret*) Prescribing Information.

Clinical Trials

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ENDURANCE-1

In this phase 3 open-label trial, 703 noncirrhotic adults with genotype 1 HCV infection were randomized to receive either 8 or 12 weeks of glecaprevir-pibrentasvir; 38% were treatment-experienced (3 were sofosbuvir experienced and the remainder interferon experienced). Among those enrollled 33 were coninfected with HIV. The sustained virologic response rate (SVR12) was 99% for the 8-week arm and 99.7% for the 12-week arm, and the SVR rate remained high in persons

with HIV-coinfection, prior treatment experience, and baseline resistance-associated substitutions.

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ENDURANCE-2

This phase 3 randomized, double-blind placebo-controlled trial evaluated the safety and efficacy of 12 weeks of therapy with glecaprevir-pibrentasvir in patients with genotype 2 hepatitis C infection without cirrhosis. Thirty percent were treatment-experienced; most (91%) had received interferon-based while the remainder sofosbuvir-based therapy. Among DAA-naive patients who received glecaprevir-pibrentasvir, 195 (99%) of 196) achieved a sustained virologic response 12 (SVR12) by intent-to-treat analysis. There were no serious adverse events related to glecaprevir-pibrentasvir.

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ENDURANCE-3

In this phase 3 randomized study, investigators compared the efficacy and safety of 8 or 12 weeks of glecaprevir-pibrentasvir versus 12 weeks of sofosbuvir and daclatasvir in non-cirrhotic treatment-naive adults with genotype 3 hepatitis C infection; 348 patients were randomized in 2:1 ratio to 12 weeks of either glecaprevir-pibrentasvir or sofosbuvir plus daclatasvir while 157 were assigned to 8 weeks of glecaprevir-pibrentasvir. Sustained virologic response (SVR12) was achieved in 95% of patients in both the 8-week and 12-week glecaprevir-pibrentasvir arms by intent-to-treat analysis. The 12-week glecaprevir-pibrentasvir arm met non-inferiority criteria for SVR12 when compared with sofosbuvir plus daclatasvir. Glecaprevir-pibrentasvir was well tolerated with a low incidence (2%) of any serious adverse reactions.

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ENDURANCE-4

In this single-arm trial, 121 non-cirrhotic adults with genotype 4, 5 or 6 infection were assigned to 12 weeks of glecaprevir-pibrentasvir. Most of these patients (68%) were treatment-naive; 39% had prior interferon-based therapy. Nearly all (99%) achieved a sustained virologic response; the only individual who did not achieve SRV12 discontinued therapy after only 12 days.

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EXPEDITION-1

This phase 3 single-arm open-label trial evaluated the safety and efficacy of 12 weeks of glecaprevir-pibrentasvir in 146 adults with compensated cirrhosis and genotype 1, 2, 4, 5, or 6 hepatitis C infection. Sixty percent were genotype 1 patients; 25% were treatment-experienced—most (69%) had previously received interferon-based treatment and the remainder had received sofosbuvir-based therapy. The overall sustained virologic response rate was 99%; one patient with genotype 1a experienced a viral relapse at week 8 post-treatment, and had Y93N substitution detected at baseline and at time of failure.

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EXPEDITION-2

In this open-label, dual-arm phase 3 trial, 137 noncirrhotic adults with HCV (genotype 1-6) and HIV coinfection were assigned 8 weeks of glecaprevir-pibrentasvir and 16 coinfected patients with compensated cirrhosis received 12 weeks of glecaprevir-pibrentasvir. The majority (63%) of participants had genotype 1 infection; 19% were treatment-experienced (16% with interferon and 2% were sofosbuvir based). All but 10 patients were taking either raltegravir, dolutegravir or rilpivirine as the anchor drug for antiretroviral therapy. The overall sustained virologic response rate was 98%; one patient with genotype 3 with cirrhosis experienced on-treatment virologic breakthrough.

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EXPEDITION-4

This phase 3 single-arm open-label trial evaluated the safety and efficacy of 12 weeks of glecaprevir-pibrentasvir in 104 patients with genotype 1-6 hepatitis C infection and advanced renal insufficiency (estimated glomerular filtration rate less than 30 ml/min/1.73m^2); 88% had chronic kidney disease stage 5 and 82% were on hemodialysis. Fifty-two percent of patients had genotype 1 infection; 19% had compensated cirrhosis and 42% were treatment-experienced, all but two with prior interferon-based therapy. The overall sustained virologic response rate was 98% by intent-to-treat analysis. The rate of adverse events attributable to glecaprevir-pibrentasvir (pruritus 20%, fatigue 14%, nausea 12%) were comparable to those observed in the other glecaprevir-pibrentasvir trials.

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Figures

Figure 1 Glecaprevir-Pibrentasvir (*Mavyret*) Packaging

Note each daily packet contains 3 glecaprevir-pibrenatasvir fixed-dose tablets and each tablet consists of 100 mg of glecaprevir and 40 mg of pibrentasvir.

This photograph is courtesy of AbbVie

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