Treatment of Hepatitis C with glecaprevir/pibrentasvir (Mavyret™)

Policy # 00593
Original Effective Date: 11/15/2017
Current Effective Date: 11/13/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Treatment of Hepatitis C with Dual Therapy (Ribavirin Plus Pegylated Interferon Alfa) is addressed separately in medical policy 00374.

Note: Pegylated Interferons (Pegasys®, PegIntron®) for Other (Non-Hepatitis C) Uses is addressed separately in medical policy 00375.

Note: Treatment of Hepatitis C with a sofosbuvir (Sovaldi®) Based Regimen is addressed separately in medical policy 00397.

Note: Treatment of Hepatitis C with sofosbuvir/ledipasvir (Harvoni®, Authorized Generic) is addressed separately in medical policy 00455.

Note: Treatment of Hepatitis C with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak™) is addressed separately in medical policy 00462.

Note: Treatment of Hepatitis C with elbasvir and grazoprevir (Zepatier™) is addressed separately in medical policy 00509.

Note: Treatment of Hepatitis C with sofosbuvir/velpatasvir (Epclusa®, Authorized Generic) is addressed separately in medical policy 00514.

Note: Treatment of Hepatitis C with sofosbuvir/velpatasvir/voxilaprevir (Vosevi™) is addressed separately in medical policy 00594

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When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider glecaprevir/pibrentasvir (Mavyret™)‡ for the treatment of individuals with chronic hepatitis C virus (HCV) to be **eligible for coverage.****

Patient Selection Criteria

Based on review of available data, the Company may consider glecaprevir/pibrentasvir (Mavyret) when the following criteria are met:

- Patient has a diagnosis of chronic hepatitis C virus (HCV) genotypes 1, 2, 3, 4, 5, or 6; AND
- Patient does NOT have decompensated cirrhosis (Child-Pugh B/C); AND
- There is clinical evidence or patient history that suggests the use of the clinically applicable preferred products [i.e., sofosbuvir/velpatasvir (Epclusa®)‡, sofosbuvir/ledipasvir (Harvoni®)‡, sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)‡], noted in the charts below, will be ineffective or cause an adverse reaction to the patient; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient meets the criteria in the chart below (including failure of certain treatment regimens) and adheres to the timeframes for treatment:

Treatment Naïve:	**Length of Therapy**		**Preferred Agent(s)**
Genotype	**No Cirrhosis**	**Compensated Cirrhosis (Child-Pugh A)**	
1, 2, 3, 4, 5, or 6	8 weeks	8 weeks	Genotypes 1, 4, 5, or 6: Epclusa, Harvoni Genotypes 2 or 3: Epclusa

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Treatment Experienced:	**Length of Therapy**			**Preferred Agent(s)**
Genotype	**Previous Regimen**	**No Cirrhosis**	**Compensated Cirrhosis (Child-Pugh A)**	
1	An NS5A inhibitor[1] withOUT prior treatment with an NS3/4A protease inhibitor	16 weeks	16 weeks	Age 18 years and older: Vosevi Age 3 years to 17 years: N/A (may use Mavyret)
1	As NS3/4A protease inhibitor[2] withOUT prior treatment with an NS5A inhibitor	12 weeks	12 weeks	Epclusa, Harvoni
1, 2, 4, 5, or 6	PRS[3]	8 weeks	12 weeks	Genotype 1a and patient is 3 to 17 years of age and if Sovaldi was included in the failed regimen: N/A (Mavyret may be used) Genotype 1a and patient is 18 years of age or older and if Sovaldi was included in the failed regimen: Vosevi Genotypes 1a, 1b, 4, 5, or 6 if there was no Sovaldi in the failed regimen: Epclusa, Harvoni

				Genotypes 1b, 4, 5, or 6 if Sovaldi was included in the failed regimen: N/A (Mavyret may be used) Genotype 2 if there was no Sovaldi in the failed regimen: Epclusa Genotype 2 if Sovaldi was included in the failed regimen: N/A (Mavyret may be used)
3	PRS[3]	16 weeks	16 weeks	If Sovaldi was included in the failed regimen and patient is 3 to 17 years of age: N/A (Mavyret may be used) If Sovaldi was included in the failed regimen and patient is 18 years of age or older: Vosevi If there was no Sovaldi in the failed regimen: Epclusa

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Liver or Kidney Transplant Recipient (Treatment Experienced or Treatment Naïve)			
Genotype	**Scenario**	**Length of Therapy**	**Preferred Agent(s)**
1	Treatment experienced with an NS5A inhibitor[1] withOUT prior treatment with an NS3/4A protease inhibitor	16 weeks	Kidney or Liver Transplant: N/A (Mavyret may be used)
3	Treatment experienced with PRS[3]	16 weeks	Kidney Transplant: N/A (Mavyret may be used) Liver Transplant: If Sovaldi was included in the failed regimen: N/A (Mavyret may be used) If Sovaldi was not included in the failed regimen: Epclusa
All others (1, 2, 3, 4, 5, or 6)	All others not meeting above scenarios	12 weeks	Kidney Transplant: N/A (Mavyret may be used) Liver Transplant: Genotypes 1, 4, 5, or 6: Epclusa, Harvoni Genotypes 2 or 3: Epclusa

[1]Patients in trials were treated with Harvoni Or Daklinza with pegylated interferon and ribavirin.
[2]Patients in trials were treated with prior regimens containing Olysio plus Sovaldi OR Olsyio, Incivek, or Victrelis plus pegylated interferon and ribavirin.
[3]Patients in trials were treated with regimens containing interferon, pegylated interferon, ribavirin, and/or Sovaldi, but no prior treatment with an HCV NS3/4A protease inhibitor (Olysio, Incivek, Victrelis) or NS5A inhibitor (Harvoni)

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of glecaprevir/pibrentasvir (Mavyret) when there is no clinical evidence or patient history that suggests the use of the clinically applicable preferred products [i.e., sofosbuvir/velpatasvir (Epclusa), sofosbuvir/ledipasvir (Harvoni), sofosbuvir/velpatasvir/voxilaprevir (Vosevi)], noted in the charts above, will be ineffective or cause an adverse reaction to the patient to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of glecaprevir/pibrentasvir (Mavyret) when the patient selection criteria are not met (with the exception of failing to use the preferred agents, where applicable, which is considered **not medically necessary****) to be **investigational.***

Background/Overview

Mavyret is indicated for the treatment of adult and pediatric patients 3 years and older with chronic HCV genotypes 1, 2, 3, 4, 5, or 6 infection with compensated cirrhosis or without cirrhosis. Mavyret is also indicated for the treatment of adult and pediatric patients 3 years and older with HCV genotype 1 infection who have previously been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both. Mavyret is recommended in patients 3 years and older who are liver or kidney transplant recipients. Mavyret is a fixed dose combination of glecaprevir (NS3/4A PI) and pibrentasvir (NS5A inhibitor) and is available in both tablets and oral pellets. The tablets contain 100 mg of glecaprevir and 40 mg of pibrentasvir. The dosage of Mavyret in adults and pediatric patients 12 years of age and older weighing at least 45 kg is three tablets taken once daily with food. Dosing for pediatric patients 3 to less than 12 years of age is based on weight. Mavyret pellets contain 50 mg of glecaprevir and 20 mg of pibrentasvir. For more information on pediatric dosing, please refer to the product's package insert. The lengths of therapy for treatment vary including 8, 12, or 16 week regimens.

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Hepatitis C
Hepatitis C is the most common blood borne pathogen. In the US, there are approximately 3.2 million people chronically infected with hepatitis C. Hepatitis C, a single-stranded RNA virus, is genetically complex with several recognized genotypes. Genotypes 1, 2, and 3 are the most frequently encountered genotypes worldwide. Type 1a is most frequently found in Northern Europe and North America, while 1b is most common in Japan and Southern and Eastern Europe. Genotypes 4 and 5 are most commonly found in Africa, while genotype 6 is common in Asia.

Drug regimens have evolved quite a bit over the past few years in this class. It is beyond the scope of this policy to delve into the entire timeline of approvals, however a brief overview will provide an idea of the evolution of these drugs. The earlier regimens contained ribavirin and interferon/pegylated interferons. The next wave of products brought NS3/4A PIs to market such as Incivek®‡ and Victrelis®‡. After that, an NS5B polymerase inhibitor was approved (Sovaldi®)‡. Following the release of Sovaldi, a drug was approved that contained a combination NS5A inhibitor and NS5B polymerase inhibitor combination (Harvoni). Drugs approved up until that point in time mainly treated genotype 1 hepatitis C virus. After these drugs were approved, a multitude of other drugs were approved (Viekira/XR®‡, Zepatier™‡, Daklinza™‡, etc). As drugs continue to be FDA approved in this space, the range of genotypes that can be treated increases. The latest wave of drugs includes pangenotypic products such as Epclusa, Mavyret, and Vosevi. For more information on each individual drug, please see the product's package insert or refer to their respective medical policy.

Mavyret has been integrated into the American Association for the Study of Liver Diseases (AASLD) guidelines in various scenarios for the treatment of HCV, however it should be noted that these guidelines are receiving constant updates as new products are approved.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Mavyret was approved in late 2017 for the treatment of patients with chronic HCV genotypes 1, 2, 3, 4, 5, or 6 infection with compensated cirrhosis or without cirrhosis. Mavyret is also indicated 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 PI, but not both. In August of 2018,

information for the treatment of liver and kidney transplant recipients was added to the label. In 2021, the label was expanded to include pediatric patients 3 years of age and older.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Treatment naïve OR pegylated interferon, ribavirin and/or sofosbuvir (Sovaldi) experienced adults with HCV genotype 1, 2, 4, 5, or 6 without cirrhosis

The efficacy of Mavyret in subjects who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5 or 6 chronic HCV infection without cirrhosis was studied in three trials using an 8 week duration: ENDURANCE-1, ENDURANCE-5,6, and SURVEYOR-2 (Part 2 and Part 4). The SVR12 in ENDURANCE-1 was 99%. In SURVEYOR-2 (Part 2 and Part 4) and ENDURANCE-5,6, the SVR12s were 98% for genotype 2, 93% for genotype 4, 95% for genotype 5, and 100% for genotype 6.

Treatment-naïve adults with HCV Genotype 1-6 or pegylated interferon, ribavirin and/or sofosbuvir (Sovaldi) experienced adults with HCV Genotype 1, 2, 4, 5, or 6 Infection with compensated cirrhosis

The efficacy of Mavyret in treatment-naïve subjects with genotype 1, 2, 3, 4, 5 or 6 chronic HCV infection and compensated cirrhosis (Child-Pugh A) was studied in EXPEDITION-8, a single-arm, open-label trial in 343 subjects who received Mavyret for 8 weeks. The overall SVR12 for all genotypes was 98%. The SVR12 for Genotype 1 was 98%, Genotypes 2, 4, 5, and 6 were 100%, and Genotype 3 was 95%.

The efficacy of Mavyret in subjects who were treatment-naïve or treatment-experienced to combinations of PRS with genotype 1, 2, 4, 5 or 6 chronic HCV infection with compensated cirrhosis (Child-Pugh A) was studied in the EXPEDITION-1 trial, which included subjects treated with

Mavyret for 12 weeks. In this trial, total SVR12 for all genotypes was 99%. Genotype 1 was 99% and genotypes 2, 4, 5, and 6 were 100%.

Treatment-naïve or pegylated interferon, ribavirin and/or sofosbuvir (Sovaldi) experienced adults with HCV genotype 3 infection without cirrhosis or with compensated cirrhosis
The efficacy of Mavyret in subjects without cirrhosis or with compensated cirrhosis who were treatment-naïve or treatment-experienced to combinations of PRS with genotype 3 chronic HCV infection was studied in ENDURANCE-3 and in SURVEYOR-2 Part 3. In ENDURANCE-3, SVR12 was 94.9% in the 8 week treatment group and 95.3% in the Mavyret 12 week group. In SURVEYOR-2 Part 3, the SVR12 for those that were treatment naïve with compensated cirrhosis was 98%. The SVR12 in those who were treatment experienced with PRS without cirrhosis or with compensated cirrhosis that were treated for 16 weeks was 96%.

Treatment-naïve and pegylated interferon, ribavirin and/or sofosbuvir (Sovaldi) experienced adults with chronic kidney disease (CKD) stage 4 and 5 and chronic HCV infection without cirrhosis or with compensated cirrhosis
EXPEDITION-4 studied the safety and efficacy in subjects with severe renal impairment (CKD Stages 4 and 5) with compensated liver disease (with and without Child-Pugh A cirrhosis). The overall SVR12 rate was 98% and no subjects experienced virologic failure. The presence of renal impairment did not affect efficacy; no dose-adjustments were required during the trial.

Adults who are NS5A inhibitor or NS3/4A-protease inhibitor - experienced, without cirrhosis or with compensated cirrhosis
MAGELLAN-1 included genotype 1 or 4 infected subjects who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A PI. The SVR12 in those that were PI experienced (and NS5A inhibitor naïve) was 92% with 12 weeks of Mavyret therapy. The SVR12 in those that were NS5A inhibitor experienced (PI naïve) was 94% with 16 weeks of therapy.

Liver or Kidney Transplant
MAGELLAN-2 was an open-label study in 100 post-liver or kidney transplant HCV genotypes 1, 2, 3, 4, or 6 infected subjects without cirrhosis who received Mavyret for 12 weeks. The study included subjects who were HCV treatment-naïve or treatment experienced to combinations of (peg)interferon, ribavirin, and/or sofosbuvir, with the exception of genotype 3-infected subjects who

were all treatment-naïve. The overall SVR12 rate in post-transplant subjects was 98% (98/100). There was one relapse and no on-treatment virologic failures.

Pediatric Subjects (12 years to less than 18 years)
DORA [Part 1]) evaluated adolescent subjects 12 years to less than 18 years without cirrhosis who received Mavyret for 8 or 16 weeks. Treatment duration was chosen to match approved adult durations based on HCV genotype and prior treatment experience. Forty-seven subjects were enrolled in DORA (Part 1). The median age was 14 years (range: 12 to 17); 79% had HCV genotype 1, 6% had HCV genotype 2, 9% had HCV genotype 3, 6% had HCV genotype 4; 77% were HCV treatment-naïve; 23% were treatment-experienced to interferon; 4% had HIV-coinfection; none had cirrhosis; the mean weight was 59 kg (range: 32 kg to 109 kg). The overall SVR12 rate was 100% (47/47).

DORA [Part 2]) evaluated subjects aged 3 years to less than 12 years who received weight-based dosing of Mavyret oral pellets for 8, 12, or 16 weeks. The median age was 7 years (range: 3 years to 11 years); the mean weight was 26 kg (range: 13 kg to 44 kg); 73% had HCV genotype 1, 3% had HCV genotype 2, 23% had HCV genotype 3, and 3% had HCV genotype 4; 97.5% were HCV treatment naive; 2.5% were treatment-experienced to interferon; 1% had HIV-coinfection; none had cirrhosis. Sixty-two subjects received the weight-based recommended dosage. Eighteen subjects received doses lower than the recommended weight-based dosage and were not included in the efficacy assessment. The overall SVR12 rate for the subjects who received the recommended dosage was 98.4% (61/62); the subject who did not achieve SVR12 discontinued treatment due to an adverse reaction.

References

1. Mavyret [package insert]. Abbvie, Inc. North Chicago, IL. Updated June 2021.
2. Recommendations for Testing, Managing, and Treating Hepatitis C. American Association for the Study of liver diseases. Updated January 2021.

Policy History

Original Effective Date: 11/15/2017
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11/02/2017 Medical Policy Committee review

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11/15/2017	Medical Policy Implementation Committee approval. New policy.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Added information and criteria regarding liver and kidney transplant patients.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Removed reference to policy 00457 as it is retired. Updated the treatment length from 12 weeks to 8 weeks for treatment naïve compensated cirrhotic patients to coincide with the updated FDA package insert.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/07/2021	Medical Policy Committee review
10/13/2021	Medical Policy Implementation Committee approval. Added a new requirement for the use of preferred hepatitis C treatments (Harvoni, Epclusa, Vosevi), where applicable. Updated policy with a new dosage form, pellets.
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2024

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.