CLINICAL UPDATE

Brand Name	Mavyret®
Generic Name	glecaprevir and pibrentasvir
Drug Manufacturer	Abbvie Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New Formulation

FDA APPROVAL DATE

June 10, 2021

LAUNCH DATE

June 10, 2021

REVIEW DESIGNATION

Priority; Orphan

TYPE OF REVIEW

Type 3 - New Dosage Form; New Drug Application (NDA): 215110

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Mavyret® is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult and pediatric patients 3 years and older with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A).

Mavyret® is indicated for the treatment of adult and pediatric patients 3 years and older with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

MECHANISMS OF ACTION

Mavyret® is a fixed-dose combination of glecaprevir and pibrentasvir, which are direct-acting antiviral agents against the hepatitis C virus.

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 100 mg glecaprevir and 40 mg pibrentasvir.
Oral Pellets: 50 mg glecaprevir and 20 mg pibrentasvir.

DOSE & ADMINISTRATION

Recommended treatment duration for patients 3 years and older in tables.

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Treatment-Naïve Patients

HCV Genotype	Treatment Duration	
	No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1, 2, 3, 4, 5, or 6	8 weeks	8 weeks

Treatment-Experienced Patients

		Treatment Duration	
HCV Genotype	Patients Previously Treated With a Regimen Containing:	No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1	An NS5A inhibitor[1] without prior treatment with an NS3/4A protease inhibitor (PI)	16 weeks	16 weeks
	An NS3/4A PI[2] without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	PRS[3]	8 weeks	12 weeks
3	PRS[3]	16 weeks	16 weeks

1. Treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with (peg) interferon and ribavirin.
2. Treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with (peg) interferon and ribavirin.
3. PRS=Prior treatment experience with regimens containing (peg) interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

- Recommended dosage in adults: Three tablets taken at the same time orally once daily (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) with food.
- Recommended dosage in pediatric patients 3 years and older:
  - Pediatric Patients 3 Years to Less than 12 Years Old: Dosing is based on weight. Refer to Table 3 of the full prescribing information for specific dosing guidelines based on body weight. Instructions for Use should be followed for preparation and administration of Mavyret® oral pellets.
  - Pediatric Patients 12 Years of Age and Older, or Pediatric Patients Weighing at Least 45 kg: three tablets taken at the same time orally once daily (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) with food.
- HCV/HIV-1 co-infection and patients with any degree of renal impairment: Follow the dosage recommendations in the tables above.
- Liver or Kidney Transplant Recipients: Mavyret® is recommended for 12 weeks in patients 3 years and older who are liver or kidney transplant recipients. A 16-week treatment duration is recommended in genotype 1- infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A PI or in genotype 3-infected patients who are PRS treatment-experienced.

EFFICACY

The safety and efficacy of Mavyret® were evaluated during clinical trials enrolling approximately 2,300 adults with genotype 1, 2, 3, 4, 5 or 6 HCV infection without cirrhosis or with mild cirrhosis. Results of the trials demonstrated

that 92-100 percent of patients who received Mavyret® for eight, 12 or 16 weeks duration had no virus detected in the blood 12 weeks after finishing treatment, suggesting that patients' infection had been cured.

Treatment-Naïve or PRS Treatment-Experienced Adults with HCV Genotype 1, 2, 4, 5, or 6 Infection without Cirrhosis.

The efficacy of Mavyret® in subjects who were treatment-naïve or treatment-experienced to combinations of (peg)interferon, 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)].

ENDURANCE-1 was a randomized (1:1), open-label, multi-national trial comparing the efficacy of 8 weeks of treatment with Mavyret® versus 12 weeks of treatment in subjects without cirrhosis with genotype 1 infection with or without HIV-1 co-infection (n=33 co-infected).

ENDURANCE-1: Efficacy in Treatment-Naïve and PRS Treatment-Experienced Adults with HCV Genotype 1 Infection without Cirrhosis.

	MAVYRET 8 Weeks
	GT1 N=351
SVR12	99% (348/351)
Outcome for Subjects without SVR12	
On-treatment VF	<1% (1/351)
Relapse	0/349
Other*	<1% (2/351)

VF= virologic failure
* Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

The SVR12 data from the open-label trials SURVEYOR-2 (Parts 2 and 4) and ENDURANCE5,6 are pooled by genotype, where appropriate.

SURVEYOR-2 (Part 2 and Part 4) and ENDURANCE-5, 6: Efficacy in Treatment-Naïve and PRS Treatment-Experienced Adults with HCV Genotypes 2, 4, 5 or 6 Infection without Cirrhosis.

	MAVYRET 8 Weeks			
	GT2 N=197	GT4 N=46	GT5 N=22	GT6 N=65
SVR 12	98% (193/197)	93% (43/46)	95% (21/22)	100% (65/65)
Outcome for Subjects without SVR12				
On Treatment VF	0/197	0/46	0/22	0/65
Relapse	1% (2/195)	0/45	5% (1/22)	0/65
Other*	1% (2/197)	7% (3/46)	0/22	0/65

GT=genotype; VF= virologic failure * Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

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EXPEDITION-8: Efficacy in Treatment-Naïve Adults with HCV Genotype 1, 2, 3, 4, 5 or 6 Infection with Compensated Cirrhosis.

	MAVYRET 8 Weeks (N=343)						
	Total (all GTs) (N=343)	GT1 (N=231)	GT2 (N=26)	GT3 (N=63)	GT4 (N=13)	GT5 (N=1)	GT6 (N=9)
SVR12	98% (335/343)	98% (226/231)	100% (26/26)	95% (60/63)	100% (13/13)	100% (1/1)	100% (9/9)
Outcome for Subjects without SVR12							
On-treatment VF	0/343	0/231	0/26	0/63	0/13	0/1	0/9
Relapse	<1% (1/336)	0/225	0/26	2% (1/62)	0/13	0/1	0/9
Other*	2% (7/343)	2% (5/231)	0/26	3% (2/63)	0/13	0/1	0/9

GT = genotype; VF = virologic failure
* Includes subjects who discontinued due to lost to follow-up or subject withdrawal.

EXPEDITION-1 and ENDURANCE-5, 6: Efficacy in Treatment-Naïve and PRS Treatment-Experienced Adults with HCV Genotype 1, 2, 4, 5 or 6 Infection with Compensated Cirrhosis.

	MAVYRET 12 Weeks					
	Total (all GTs) (N=155)	GT1 (N=90)	GT2 (N=31)	GT4 (N=16)	GT5 (N=5)	GT6 (N=13)
SVR12	99% (153/155)	99% (89/90)	100% (31/31)	100% (16/16)	100% (5/5)	92% (12/13)
Outcome for Subjects without SVR12						
On-treatment VF	<1% (1/155)	0/90	0/31	0/16	0/5	8% (1/13)
Relapse	<1% (1/152)	1% (1/88)	0/31	0/16	0/5	0/12

GT = genotype; VF = virologic failure

ENDURANCE-3: Efficacy in Treatment-Naïve, HCV Genotype 3-Infected Adults without Cirrhosis.

	MAVYRET[1] 8 Weeks (N=157)	MAVYRET 12 Weeks* (N=233)	DCV+SOF 12 Weeks (N=115)
SVR12	95% (149/157)	95% (222/233)*	97% (111/115)
Outcome for Subjects without SVR12			
On-treatment VF	1% (1/157)	<1% (1/233)	0/115
Relapse	3% (5/150)	1% (3/222)	1% (1/114)
Other[2]	1% (2/157)	3% (7/233)	3% (3/115)

VF=virologic failure
[1] MAVYRET 8 weeks was a non-randomized treatment arm.
[2] Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
* Data for MAVYRET 12-week treatment is displayed to reflect the original randomized study design. The treatment difference (95% confidence interval) was -1.2% (-5.6, 3.1) between the randomized arms of MAVYRET 12 weeks and DCV + SOF 12 weeks.

SURVEYOR-2 Part 3: Efficacy in PRS Treatment-Experienced, HCV Genotype 3-Infected Adults without Cirrhosis or with Compensated Cirrhosis.

	PRS Treatment-Experienced without Cirrhosis or With Compensated Cirrhosis
	MAVYRET 16 Weeks (N=69)
SVR12	96% (66/69)
Outcome for Subjects without SVR12	
On-treatment VF	1% (1/69)
Relapse	3% (2/68)
Other*	0/69
SVR12 by Cirrhosis Status	
Without Cirrhosis	95% (21/22)
With Compensated Cirrhosis	96% (45/47)

VF=virologic failure
* Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Clinical Trial in Pediatric Subjects 3 Years and Older:

DORA Part 1

Forty-seven subjects were enrolled in DORA (Part 1) and received the adult dose of Mavyret® tablets. The median age was 14 years (range: 12 years to 17 years); the mean weight was 59 kg (range: 32 kg to 109 kg); 55% were female; 74% were White; 13% were Asian, and 9% were Black; 79% had HCV genotype 1, 6% had HCV genotype 2, 9% had HCV genotype 3, and 6% had HCV genotype 4; 77% were HCV TN; 23% were treatment-experienced to interferon; 4% had HIV-coinfection; none had cirrhosis. The overall SVR12 rate was 100% (47/47).

DORA Part 2

Eighty subjects aged 3 years to less than 12 years were enrolled in DORA (Part 2) and 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); 55% were female; 69% were White, 18% were Asian, and 4% were Black; 73% had HCV genotype 1, 3% Reference ID: 4864107 had HCV genotype 2, 23% had HCV genotype 3, and 3% had HCV genotype 4; 97.5% were HCV TN; 2.5% were treatment-experienced to interferon; 1% had HIV-coinfection; none had cirrhosis.