CLINICAL UPDATE

Brand Name	Epclusa®
Generic Name	sofosbuvir and velpatasvir
Drug Manufacturer	Gilead Sciences, Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

Clinical Update - New strength (200-50 mg) and updated indication to include pediatrics

FDA APPROVAL DATE

March 19, 2020

LAUNCH DATE

October 22, 2020

REVIEW DESIGNATION

Not available

TYPE OF REVIEW

Type N/A; New Drug Application (NDA): 208341

DISPENSING RESTRICTIONS

Specialty

Overview

INDICATION(S) FOR USE

Epclusa® is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult and pediatric patients 6 years of age and older or weighing at least 17 kg with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection:

- without cirrhosis or with compensated cirrhosis
- with decompensated cirrhosis for use in combination with ribavirin.

MECHANISMS OF ACTION

Epclusa® is a fixed-dose combination of sofosbuvir and velpatasvir, which are directacting antiviral agents against the hepatitis C virus.

Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC50 value ranging from 0.36 to 3.3 micromolar. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

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Velpatasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 400 mg of sofosbuvir and 100 mg of velpatasvir; 200 mg of sofosbuvir and 50 mg of velpatasvir.

DOSE & ADMINISTRATION

- Adults: 1 tablet (400 mg of sofosbuvir/100 mg of velpatasvir) taken orally once daily with or without food.
- Pediatrics, age ≥ 6 years or weight ≥ 17 kg:

Table 2 Dosing for Pediatric Patients 6 Years and Older or Weighing at Least 17 kg with Genotype 1, 2, 3, 4, 5, or 6 HCV

Body Weight (kg)	Dosing of EPCLUSA	EPCLUSA Daily Dose
at least 30	one 400 mg/100 mg tablet once daily or two 200 mg/50 mg tablets once daily	400 mg/100 mg per day
17 to less than 30	one 200 mg/50 mg tablet once daily	200 mg/50 mg per day

Table 3 Recommended Dosing for Ribavirin in Combination Therapy with EPCLUSA for Pediatric Patients 6 Years and Older

Body Weight (kg)	Oral Ribavirin Daily Dosage[a]
less than 47	15 mg per kg per day (divided dose AM and PM)
47–49	600 mg per day (1 x 200 mg AM, 2 x 200 mg PM)
50–65	800 mg per day (2 x 200 mg AM, 2 x 200 mg PM)
66–80	1,000 mg per day (2 x 200 mg AM, 3 x 200 mg PM)
greater than 80	1,200 mg per day (3 x 200 mg AM, 3 x 200 mg PM)

a. The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food.

- HCV/HIV-1 coinfection: See below table.

Patient Population	Regimen and Duration
Treatment-naïve and treatment-experienced[a], without cirrhosis and with compensated cirrhosis (Child-Pugh A)	EPCLUSA 12 weeks
Treatment-naïve and treatment-experienced[a], with decompensated cirrhosis (Child-Pugh B and C)	EPCLUSA + ribavirin 12 weeks

a. In clinical trials, regimens contained peginterferon alfa/ribavirin with or without an HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir).

- For treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis or with compensated cirrhosis (ChildPugh A), the recommended regimen is Epclusa® once daily for 12 weeks.
- If used in combination with ribavirin, follow the recommendations for ribavirin dosing and dosage modifications.
- For patients with renal impairment including end stage renal disease on dialysis, follow the dosage recommendations in the table above.

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EFFICACY

The approval of Epclusa® for the expanded indication was based on an open-label study in 173 genotype 1, 2, 3, 4, or 6 HCV treatment-naïve (N=147) or treatment-experienced (N=26) pediatric patients 6 years of age and older without cirrhosis or with compensated cirrhosis. The primary endpoint was the cure rate, as measured by the sustained virologic response (SVR) 12 weeks after the cessation of treatment.

- In patients 12 years to < 18 years of age, the SVR rate was 93% (71/76) in patients with genotype 1 HCV infection and 100% in patients with genotype 2 (6/6), genotype 3 (12/12), genotype 4 (2/2), and genotype 6 (6/6) HCV infection.
- In patients 6 years to < 12 years of age, the SVR rate was 93% (50/54) in patients with genotype 1 HCV infection, 91% (10/11) in patients with genotype 3 HCV infection, and 100% in patients with genotype 2 (2/2), and genotype 4 (4/4) HCV infection.

Effectiveness: The cure rates are from 97% to 100% in those without cirrhosis or with compensated cirrhosis.