PDL DRUG REVIEW

Proprietary Name: Epclusa®
Common Name: velpatasvir & sofosbuvir
PDL Category: Hepatitis C Agents

Comparable Products	Preferred Drug List Status
Daklinza	Non-Preferred with Conditions
Sovaldi	Preferred with Conditions

Summary

Pharmacology/Usage: Epclusa® is a fixed-dose combination tablet containing velpatasvir (an NS5A inhibitor) and sofosbuvir (a nucleotide analog hepatitis C virus (HCV) NS5B polymerase inhibitor). These are both direct-acting 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. Velpatasvir is an inhibitor of the HCV NS5A protein, which is also required for viral replication.

Indications: For the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections

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

The risk summary for this product indicates that if it is used in combination with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. No adequate human data are available to determine whether or not Epclusa® poses a risk to pregnancy outcomes. There was no evidence of adverse developmental outcomes in animal reproduction studies at exposures greater than those in humans at the recommended human dose. The safety and efficacy of use in the pediatric population has not been established.

Dosage Forms: Film-coated Tablets: 100mg velpatasvir/400mg sofosbuvir

Recommended Dosage: Take one tablet PO QD, with or without food. See the table below.

Patient Population	Treatment Regimen & Duration
Patients without cirrhosis & Patients with compensated cirrhosis (Child-Pugh A)	Epclusa® X12W
Patients with decompensated cirrhosis (Child-Pugh B or C)	Epclusa® + Ribavirin X12W*

*When ribavirin is administered, the recommended dose is based on weight; the starting dosage & on-treatment dosage of ribavirin can be decreased based on hemoglobin & creatinine clearance.

Dose adjustments are not required for those with hepatic impairment. Clinical and hepatic lab monitoring, as clinically indicated, is recommended for those with decompensated cirrhosis receiving Epclusa® and ribavirin. While dose adjustments are not required for patients with mild or moderate renal impairment, the safety and efficacy of use in those with severe renal impairment or end-stage renal disease requiring hemodialysis have not been established. Thus, dosage recommendations cannot be given for this patient population.

Drug Interactions: Sofosbuvir and velpatasvir are substrates of drug transporters p-gp and breast cancer resistance protein (BCRP). In vitro, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was seen. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. rifampin, St. John's wort, carbamazepine) may decrease levels of sofosbuvir and/or velpatasvir, thus leading to reduced therapeutic effects of Epclusa®. The use of these agents with Epclusa® is not recommended; however, Epclusa® may be administered with P-gp, BCRP, and CYP inhibitors.

The co-administration of the following drugs with Epclusa® is not recommended: topotecan, anticonvulsants (carbamazepine, phenytoin, phenobarbital, and oxcarbazepine), antimycobacterials (rifabutin, rifampin, and rifapentine), efavirenz, tipranavir/ritonavir, and St. John's wort. The co-administration of Epclusa® with amiodarone is not recommended; however, if concomitant use is required, cardiac monitoring is recommended. The concomitant use of omeprazole or other PPIs is not recommended. If it is medically necessary to co-administer, Epclusa® should be taken with food and taken 4 hours before omeprazole 20mg. Use with other PPIs has not been studied.

Rosuvastatin may be co-administered with Epclusa®, but at a dose that does not exceed 10mg. With atorvastatin, it is recommended to closely monitor for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis. Antacids should be separated from Epclusa® by 4 hours. While H2-receptor antagonists may be used simultaneously with Epclusa®, the dose should not exceed doses comparable to famotidine 40mg BID. Therapeutic monitoring is recommended if use Epclusa® with digoxin, and adjust the digoxin dose as needed. Last, it is recommended to monitor for tenofovir-associated adverse reactions if use concomitantly with Epclusa®.

Common Adverse Drug Reactions: *There was no specific placebo data available to compare with all the reported adverse events.* The most frequently reported adverse events included headache and fatigue (both reported by at least 10% of subjects treated with Epclusa® for 12 weeks). Adverse reactions observed in ≥5% of subjects included headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). Lab abnormalities include asymptomatic lipase elevations >3 times upper limit of normal (UNL; 3% Epclusa® vs 1% placebo), asymptomatic creatine kinase elevations ≥10 times ULN (1% Epclusa® vs 0% placebo), and increases in indirect bilirubin up to 3mg/dl above baseline.

There have been postmarketing reports of cases of symptomatic bradycardia and cases requiring pacemaker intervention when amiodarone is co-administered with sofosbuvir in combination with daclatasvir or simeprevir. Bradycardia generally occurred within hours to days, but cases have been seen up to 2 weeks after starting HCV treatment. Patients also taking beta blockers or those with underlying cardiac co-morbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with administration of amiodarone. Thus, the coadministration of amiodarone with Epclusa® is not recommended. If there are no other alternative viable treatment options and co-administration is required, then it is recommended to counsel patients about the risk of symptomatic bradycardia AND cardiac monitoring in an in-patient setting for the first 48 hours of co-administration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Contraindications: Epclusa® and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated

Manufacturer: Gilead Sciences, Inc

Analysis: There were several trials that assessed the safety and efficacy of Epclusa®. The table below, adapted from the prescribing information, includes some details of the trial.

Trial	Design	Population	Treatment regimens
Astral-1	Randomized, double-blind, placebo-controlled	Genotype 1, 2, 4, 5, and 6 TN & TE without cirrhosis or with compensated cirrhosis	Epclusa® X12W (N=624) Placebo X12W (N=116)

Trial	Design	Population	Treatment regimens
Astral-2	Randomized, open-label	Genotype 2 TN & TE without cirrhosis or with compensated cirrhosis	Epclusa® X12W (N=134) Sofosbuvir + ribavirin X12W (N=132)
Astral-3	Randomized, open-label	Genotype 3 TN & TE without cirrhosis or with compensated cirrhosis	Epclusa® X12W (N=277) Sofosbuvir + ribavirin X24W (N=275)
Astral-4	Randomized, open-label	Genotype 1, 2, 3, 4, 5, and 6 TN & TE with Child-Pugh class B decompensated cirrhosis	Epclusa® X12W (N=90) Epclusa® + ribavirin X12W (N=87) Epclusa® X24W (N=90)

TE- treatment experienced (including if failed on PEG+ribavirin w/ or w/out an HCV protease inhibitor TN- treatment naive

The primary endpoint in all studies was the sustained virologic response (SVR12), defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment. Relapse was defined as HCV RNA ≥LLOQ during the post-treatment period after having achieved HCV RNA <LLOQ at the end of treatment.

Astral-1: In this study, there were no subjects in the placebo group who achieved SVR12. The table below, adapted from the prescribing information, illustrates the results for those taking Epclusa®.

	Total (all GTs)	GT1		GT 2	GT 4	GT 5	GT 6
		GT-1a	GT-1b				
SVR12	99% (N=618/624)	98% (N=206/210)	99% (N=117/118)	100% (N=104/104)	100% (N=116/116)	97% (N=34/35)	100% (N=41/41)
Outcomes for subjects without SVR							
On-treatment virologic failure	0/624	0%	0%	0%	0%	0%	0%
Relapse	<1% (N=2/623)	<1% (1/209)	1% (N=1/118)	0%	0%	0%	0%
Other	1% (N=4/624)	1% (N=3/210)	0%	0%	0%	3% (N=1/35)	0%

Astral-2: The following table, adapted from the prescribing information, illustrates the results of this study.

	Epclusa® X12W (N=134)	Sofosbuvir + ribavirin X12W (N=132)
SVR12	99% (N=133/134)	94% (N=124/132)
Outcome for subjects without SVR		
On-treatment virologic failure	0%	0%
Relapse	0%	5% (N=6/132)
Other	1% (N=1/134)	2% (N=2/132)

Astral-3: The following table, adapted from the prescribing information, illustrates the results of this study. Table 1 includes subjects without cirrhosis or with compensated cirrhosis with genotype 3.

Table 1	Epclusa® X12W (N=277)	Sofosbuvir + ribavirin X24W (N=275)
SVR12	95% (N=264/277)	80% (N=221/275)
Outcome for subjects without SVR		
On-treatment virologic failure	0%	<1% (N=1/275)
Relapse	4% (N=11/276)	14% (N=38/272)
Other	1% (N=2/277)	5% (N=15/275)

Table 2 includes results of SVR12 by prior treatment and presence/absence of compensated cirrhosis in subjects with genotype 3.

Table 2	Epclusa® X12W (N=277)		Sofosbuvir + ribavirin X24W (N=275)	
	TN (N=206)	TE (N=71)	TN (N=201)	TE (N=69)
Without cirrhosis	98% (N=160/163)	94% (N=31/33)	90% (N=141/156)	71% (N=22/31)
With compensated cirrhosis	93% (N=40/43)	89% (N=33/37)	73% (N=33/45)	58% (N=22/38)

Astral-4: Treatment with Epclusa® with ribavirin for 12 weeks resulted in numerically higher SVR12 rates as compared with treatment with Epclusa® for 12 or 24 weeks. All patients with genotype 2 (N=4) and genotype 4 (N=2) HCV infection treated with Epclusa® plus ribavirin achieved SVR12. The following table, adapted from the prescribing information, includes the SVR12 for subjects treated with Epclusa® with ribavirin for 12 weeks. There were no subjects with genotype 5 or 6 HCV treated with Epclusa® with ribavirin for 12 weeks.

	Epclusa® + ribavirin X12W	
	SVR12	Virologic failure (Relapse & on-treatment failure)
Overall SVR12	94% (N=82/87)	3% (N=3/87)
Genotype 1	96% (N=65/68)	1% (N=1/68)
Genotype 1a	94% (N=51/54)	2% (N=1/54)
Genotype 1b	100% (N=14/14)	0%
Genotype 3	85% (N=11/13)	15% (N=2/13)

Place in Therapy: Epclusa® is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections: without cirrhosis or with compensated cirrhosis AND with decompensated cirrhosis for use in combination with ribavirin. Significant drug interactions need to be monitored while on this product. The evidence-based IDSA/AASLD Hepatitis C guidelines[2] are frequently updated and include several recommended regimens. Hepatitis C treatment is a rapidly changing therapeutic area and the recommendation for treatment for specific genotypes and clinical situations are continuing to evolve.

The studies discussed above do suggest potent antiviral activity for all HCV genotypes (1-6) and the drug is cost effective for certain clinical scenarios. Combination with ribavirin is required in some instances. It is recommended that this drug be preferred and require prior authorization to confirm appropriate use.

PDL Placement:

- ☐ **Preferred**
- ☐ **Non-Preferred**
- ☒ **Preferred with Conditions**

References

[1] Epclusa [package insert]. Foster City, CA: Gilead Sciences, Inc; 2016.

[2] American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. (2016) Recommendations for Testing, Managing, and Treating Hepatitis C. Available at http://www.hcvguidelines.org/. Accessed 2016.

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