Hepatitis C Virus (HCV) Direct Acting Antiviral (DAA)

Executive Summary

- Harvoni, Sovaldi, and Viekira Pak are DAAs indicated for the treatment of genotype 1 chronic HCV in adults. Sovaldi is additionally indicated for the treatment of adults with genotypes 2, 3, and 4 chronic HCV.
- There are no systematic reviews or studies comparing Harvoni, Sovaldi-Olysio, and Viekira Pak.
- In general, the rate of SVR12 across clinical trials in patients with genotype 1 chronic HCV treated with any of these products is > 90%; with Sovaldi-Olysio, Harvoni, and Viekira Pak treatments, the rates are > 95% in most instances.
- AEs occurred in 79% to 92% of patients and were generally mild to moderate in severity.
- The most frequent AEs were fatigue, headache, and nausea; these were more frequent in the SMV and Viekira treatment groups.
- AEs for Harvoni, Viekira, and SMV-SOF were mild to moderate and clinically manageable; few discontinued treatment due to the AEs.

Drugs in the class

- Boceprevir (Victrelis – Merck): to be withdrawn from market in December 2015
- Simeprevir (Olysio – Janssen)
- Ledipasvir/sofosbuvir (Harvoni – Gilead)
- Sofosbuvir (Sovaldi – Gilead)
- Ombitasvir/paritaprevir/ritonavir; dasabuvir tablets, co-packaged (Viekira Pak – AbbVie)

FDA indications and HCV Guidelines

Harvoni, Sovaldi, and Viekira Pak are DAAs with FDA indications for the treatment of genotype 1 chronic HCV in adults. Sovaldi is additionally indicated for the treatment of adults with genotypes 2, 3, and 4 chronic HCV. Guidelines by the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) for the management of hepatitis C recommend all-oral, interferon-free options whenever feasible for patients with HCV. Harvoni and Viekira Pak are prominently featured in guidelines as recommended regimens for patients with genotype 1 and 4 chronic HCV. Sovaldi in combination with Olysio is also a recommended regimen in patients with genotype 1 HCV; Sovaldi with ribavirin is recommended for patients with non-genotype 1 in most situations. Several recommended regimens are recognized as appropriate treatment options. In general, recommendations for Harvoni and Viekira Pak are similar where indicated. The guidelines are frequently updated and should be consulted for the most current information: www.HCVguidelines.org.

Table 1: Interferon-free Hepatitis C Genotype 1 Treatment Regimen Following FDA Indications and AASLD/IDSA HCV Guidelines

Patient population	Genotype	AbbVie Viekira ± RBV	Gilead Harvoni (SOF/LDV)	Janssen SMV/SOF
Treatment-naïve, non-cirrhotic	1a	RBV 12 wks	8/12 wks	12 wks
	1b	12 wks	8/12 wks	12 wks
Treatment-experienced, non-cirrhotic	1a	RBV 12 wks	12 wks	12 wks
	1b	12 wks	12 wks	12 wks
Treatment-naïve, cirrhotic	1a	RBV 12/24 wks	12 wks	24 wks
	1b	RBV 12 wks	12 wks	24 wks
Treatment-experienced, cirrhotic	1a	RBV 12/24 wks	24 wks	24 wks
	1b	RBV 12 wks	24 wks	24 wks
HCV/HIV co-infection	1a/1b	See above dosing	See above dosing*	Not indicated
Transplant recipients	1a/1b	RBV 24 wks	RBV 12 wks*	RBV 12 wks*

***** Not an FDA indication. Recommendation only in the AASLD/IDSA HCV guidelines.

Efficacy

There are no studies directly comparing Harvoni, Sovaldi, and Viekira Pak. All three drugs have been studied in patients with genotype 1 chronic HCV with and without cirrhosis. Harvoni is the only one of these three products that has been studied in patients previously treated with an HCV protease inhibitor-based regimen (i.e., telaprevir or boceprevir). Sovaldi and Viekira Pak have been studied in patients previously treated with interferon and ribavirin. When making indirect comparisons within similar patient populations (e.g., treatment-naïve, re-treatment, with or without cirrhosis) efficacy as assessed by SVR12 appears similar. Due to the rapidly evolving field of hepatitis C, the use of these products outside of their FDA-labeled indications is not uncommon. In general, the rate of SVR12 across clinical trials in patients with genotype 1 chronic HCV treated with any of these products is > 90%; with Harvoni and Viekira Pak, these rates are > 95% in most instances.

Table 2: Phase 3 Trial Results (SVR) for HCV Genotype 1 Treatment Regimens

Trial	N	Patient type	GT	Cirrhosis	Duration (wk)	RBV	SVR12 (%)
SOVALDI + OLYSIO							
COSMOS	167	TN & TE	1	25%	12 12 24 24	- + - +	93 94.4 96.7 97.9*
HARVONI							
ION-1	865	TN	1	15.7%	12 12 24 24	- + - +	97.7 97.2 98 99
ION-2	440	TE	1	20%	12 12 24 24	- + - +	93.6 96.4 99.1 99.1
ION-3	647	TN	1	None	8 8 12	- + -	94 93.1 95.4
VIEKIRA PAK ± RBV							
SAPPHIRE-I	631	TN	1	None	12	+	95 (1a) 98 (1b)
SAPPHIRE-II	394	TE	1	None	12	+	96.0 (1a) 96.7 (1b)
PEARL-II	179	TE	1b	None	12	+ -	97 100
PEARL-III	419	TN	1b	None	12	+ -	99 99
PEARL-IV	305	TN	1a	None	12	+ -	97 90
TURQUOISE-II	380	TN/TE	1	100%	12 24	+ +	92 96

***Excludes non-virologic failures**

Table 3: Clinical Trial Results (SVR) for Treatment Regimens of Unique Populations for HCV Genotype 1

Trial	RX	N	Patient type	GT	Cirrhosis	Rx duration (wk)	RBV	SVR12 (%)
HIV Co-infections								
TURQUOISE-I	**Viekira**	63	TN & TE	1	19%	12	+	94%
						24	+	91%
ERADICATE	**Harvoni**	50 13 ARV – 37 ARV +	TN	1	None			98%
						12	-	100%
						12	-	97%
Post-Liver Transplantation Recipients								
CORAL-1	**Viekira**	34	TN	1	None	24	+	97%
SOLAR-1	**Harvoni**	223 (24% decomp cirrhosis)	TN & TE	1 & 4	50%	12	+	96%
						24	+	97%
						12	+	80%
						24	+	80%
Decompensated Cirrhosis								
ELECTRON-2	**Harvoni**	20	TN	1	100% (CTP B)	12	-	65%
SOLAR-1	**Harvoni**	108	TN & TE	1	100%	12	+	87%
						24	+	89%

Safety

- The AE profiles for Harvoni, Sovaldi, and Viekira Pak differ based on concomitantly administered medications as well as the individual components of each agent.
- AEs occurred in 79% to 92% of patients and were generally mild to moderate in severity.
- The most frequent AEs were fatigue, headache, and nausea. These were more frequent in the SMV and Viekira treatment groups.
- AEs for Harvoni, Viekira, and SMV-SOF were mild to moderate and clinically manageable; few discontinued treatment due to the AEs.
- In clinical trials across all three drugs, rates of discontinuation due to AEs were ≤ 2%.
- The most commonly reported AEs (occurring in ≥ 10% of patients) in clinical trials with Harvoni were fatigue and headache.
- The most commonly reported AEs (incidence ≥ 20%) with Sovaldi + RBV were fatigue and headache.
- In patients receiving Viekira Pak without ribavirin, the most commonly reported AEs (≥ 5%) were nausea, pruritus, and insomnia. The most commonly reported AEs (incidence > 10%) with Viekira Pak + RBV were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia.
- Anemia is associated with administration of both peginterferon and ribavirin. Less than 1% of patients treated with Viekira Pak + RBV had hemoglobin levels decrease to < 8.0 g/dL during treatment; ≤ 2% of patients discontinued therapy due to anemia across the clinical trials.
- Drug Safety Board Communication: Serious risk of symptomatic bradycardia with co-use of amiodarone with sofosbuvir in combination with another DAA. The mechanism of interaction is unknown. Fewer than five individuals in the DoD had concurrent use.

Conclusion

- There are no studies directly comparing Harvoni, Sovaldi, or Viekira Pak. In general, when making indirect comparisons across similar patient populations, efficacy (assessed as SVR12, the primary endpoint) appears similar among these products.

- Harvoni and Viekira Pak represent all-oral (interferon-free) therapies that have demonstrated with high rates of clinical cure (SVR12) in large populations across Phase III clinical trials.
- Sovaldi, when used with Olysio, represents an all-oral option for patients with genotype 1 chronic HCV; however, data are limited to one small Phase IIa study.
- In patients with non-genotype 1 chronic HCV, Sovaldi represents an important therapy allowing for interferon-free options for patients with genotypes 2 or 3 chronic HCV.
- In the absence of head-to-head trials, HCV treatment should be based on individual patient characteristics, likelihood of adherence, patient preferences, as well as cost.

References

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Abbreviations

AASLD/IDSA	– American Association for the Study of Liver Diseases/Infectious Diseases Society of America
AEs	– adverse events
ARV	– antiretroviral therapy
DAAs	– direct acting antiviral agents
HCV	– hepatitis c virus
SMV	– simeprevir
SMV-SOF	– simeprevir-sofosbuvir
SVR12	– sustained virologic response at 12 weeks (surrogate for clinical cure)
TE	– treatment experienced
TN	– treatment naïve
RBV	– ribavirin