Therapeutics Research • Education • AIDS Training
TREATASIA SNAPSHOTS
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Hepatitis C Treatment Snapshots: Ledipasvir + Sofosbuvir

Ledipasvir is a medication used to treat and cure infection caused by the hepatitis C virus (HCV). It is given in combination with sofosbuvir as a single, fixed-dose combination tablet of 90 mg of ledipasvir and 400 mg of sofosbuvir. The tablet is taken once a day, has few side effects, and can be used to treat HCV in people who are co-infected with HIV. The World Health Organization (WHO) has included it in its Model List of Essential Medicines.[1]

Acronyms:

HIV: Human immunodeficiency virus
Peg-IFN: Pegylated interferon

REGULATORY APPROVALS

The ledipasvir and sofosbuvir fixed-dose combination tablet was initially approved for use by the United States Food and Drug Administration (U.S. FDA) in October 2014, the European Commission (EC) in November 2014, and the Drug Controller General of India (DCGI) in December 2015. These approvals include treatment for genotypes 1, 3, 4, 5, and 6 of HCV and for co-infection with HIV.

U.S. FDA-approved indications for use

Genotype *	Population	Regimen	Duration**
1	Treatment-naïve with or without cirrhosis	Ledipasvir + sofosbuvir	12 weeks
1	Treatment-experienced without cirrhosis	Ledipasvir + sofosbuvir	12 weeks
1	Treatment-experienced with cirrhosis	Ledipasvir + sofosbuvir	24 weeks
4,5,6	Treatment-naïve and -experienced with or without cirrhosis	Ledipasvir + sofosbuvir	12 weeks

**Approval does not include infections with genotype 3.*
***Includes patients co-infected with HIV.*

EC-approved indications for use

Genotype	Population	Regimen	Duration*
1 and 4	Without cirrhosis	Ledipasvir + sofosbuvir	12 weeks
1 and 4	With compensated cirrhosis	Ledipasvir + sofosbuvir + ribavirin	12 weeks
		Ledipasvir + sofosbuvir	24 weeks
1 and 4	With compensated cirrhosis or after liver transplant without cirrhosis	Ledipasvir + sofosbuvir + ribavirin	12 weeks
1 and 4	Decompensated cirrhosis	Ledipasvir + sofosbuvir + ribavirin	12 weeks
3**	Cirrhosis and/or treatment failure	Ledipasvir + sofosbuvir + ribavirin	24 weeks

**Includes patients co-infected with HIV.*
***The clinical data to support the use of ledipasvir and sofosbuvir in patients with genotype 3 are limited.*

SAFETY AND EFFICACY

The drug's safety and efficacy were initially evaluated in three phase 3 clinical trials with a total of 1,952 participants who were chronically mono-infected with HCV genotype 1.

Clinical trials involving ledipasvir + sofosbuvir

Clinical trial	Regimen	Population	Cure rates*
ION-1[2]	Ledipasvir + sofosbuvir ± ribavirin	Genotype 1; treatment-naïve	G1/12 wks/99% G1/24 wks/98%
ION-2[3]	Ledipasvir + sofosbuvir ± ribavirin	Genotype 1; treatment-experienced	G1/12 wks/94% G1/24 wks/99%
ION-3[4]	Ledipasvir + sofosbuvir ± ribavirin	Genotype 1; treatment-naïve, non-cirrhotic	G1/8 wks/94% G1/12 wks/95%

**By genotype (G) and duration in weeks (wks). Cure rates for other patient groups are provided in the references.*

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INTERACTIONS WITH HIV MEDICINES

Ledipasvir can interact with some HIV medicines. Although no medicine adjustments are recommended, more frequent monitoring may be required.

HIV medicine	Interaction	Dose adjustments [5]
Tenofovir* + emtricitabine + atazanavir boosted with ritonavir	Increases tenofovir concentration Increases atazanavir concentration with risk of increased bilirubin	Use with caution with frequent renal monitoring
Tenofovir + emtricitabine + darunavir boosted with ritonavir	Increases tenofovir concentration	
Tenofovir + emtricitabine + lopinavir boosted with ritonavir		
Tenofovir + emtricitabine + elvitegravir		

**Tenofovir disoproxil fumarate*

CURRENT AVAILABILITY OF INDIAN GENERIC FORMULATIONS AND PRICING

As of January 2016, eight generic companies were distributing the co-formulated ledipasvir and sofosbuvir in India. The maximum retail price, according to the product packaging, is ~384 USD for a four-week supply (one bottle). At this price, a 12-week course would cost ~1,152 USD and a 24-week course would cost ~2,304 USD.

Cost comparison for combination HCV therapy in India using generic medicines

Regimen	Treatment duration	Cost*
Peg-IFN + ribavirin	48 weeks	10,032 USD
Sofosbuvir + peg-IFN + ribavirin	12 weeks	3,420 USD
Sofosbuvir + ribavirin	24 weeks	1,824 USD
Ledipasvir + sofosbuvir	12 weeks	1,152 USD

**Peg-IFN price calculated at 13,600 INR (~209 USD) per vial using the maximum retail price on Indian product packaging;*
Sofosbuvir price calculated at 19,800 INR (~304 USD) per bottle using the maximum retail price on Indian product packaging;
Ledipasvir + sofosbuvir price calculated at 25,000 INR (~384 USD) per bottle using the maximum retail price on Indian product packaging;
Indian generic companies provide ribavirin at no additional cost with the purchase of peg-IFN or sofosbuvir.

CONCLUSION

Combination therapy regimens with ledipasvir and sofosbuvir are associated with higher cure rates (up to 99%), fewer side effects, lower costs, and shorter treatment durations compared to regimens using peg-IFN and ribavirin alone (which have response rates of 46–77%).[6] Ledipasvir and sofosbuvir combination therapy also provides the opportunity for an all-oral treatment of HCV without the use of ribavirin, which is associated with more frequent side effects. A persistent concern is the lack of data showing efficacy against genotype 3 infections, which limits its usefulness in some Asian settings.

Indian generic companies currently only market their products in India. Generic companies need to expand regional drug distribution and access by proactively pursuing registration in more countries. To facilitate this process, fast-track registration should be allowed by national regulators. The current pricing of generic versions may still be too high for public health programs in low- and middle-income settings. Advocacy work to support rapid drug registrations and further price reductions remains an urgent priority.

1. World Health Organization, News release, WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers. May 2015. http://www.who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/.
2. N Afdhal, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection, *The New England Journal of Medicine*. April 2014, 370:1889-98.
3. N Afdhal, et al. Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection, *The New England Journal of Medicine*. April 2014, 370:1483-93.
4. KV Kowdley, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis, *The New England Journal of Medicine*. May 2014, 370:1879-88.
5. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003850/WC500177995.pdf
6. MW Fried, et al. Peginterferon alfa-2a Plus Ribavirin for Chronic Hepatitis C Virus Infection, *The New England Journal of Medicine*. September 2002, 347:975-982.

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