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A Review on: Harvoni and Hepatitis C

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ABSTRACT

Hepatitis C virus (HCV) is spreading at an alarming rate in world. In the past decade, clinical research in the field of new dosage regimens for HCV has been flourished based on direct acting antiviral agents (DAA's) with the motive to be safe and efficient in eliminating HCV, thus preventing life threatening complications. Hepatitis C virus is blood borne, circular and positive stranded virus. Resistance of Hepatitis C virus to DAA's is one of the major cause for therapeutic failure of treatment in people infected with HCV. Ribavirin with peg-INF was most relied and standard treatment therapy for HCV. But as peg-INF had many side effects and limited the treatment access due to contraindications in people's genotype, this developed the necessity for introducing new INF free DAA's combination treatment regimen which would be reliable, cost effective and efficacious. Ledipasvir is an inhibitor of the HCV NS5A protein, targets NS5A and ceases the virus from spreading in the body. Sofosbuvir - an inhibitor of the HCV NS5B RNA-dependent RNA polymerase which acts as chain terminator, which decreases the count of HCV in the body. This fixed dose combination (FDC) with multi genotypic activity and modest barrier to resistance and its viral potency has proved to be an ideal combination in treating Hepatitis C virus. This FDC has SVR rates more than 90% and minimum of adverse drug reactions for treating the patients with genotype 1, 2, 4, 5 & 6. This review deals with an overview of current treatment regimens for treating HCV.

INTRODUCTION:

Hepatitis C virus (HCV) is being the major threat to the human race. Hepatitis C virus infection has been infecting around 130-200 million people worldwide, which is equal to be 2-3% of world's population [1]. HCV has reported causing more than 3.5 lakhs death's each year due to liver cirrhosis, liver cancer and extra-hepatic manifestations [2]. Hepatitis C virus is small enveloped virus which belongs to the genus Hepacivirus and family Flaviviridae. The virus is one single strand positive sense RNA molecule of approximately 9.6 kb, diameter being 50 nm [3]. The virus is characterized by a remarkable genetic diversity in infected hosts [4]. Lack of specific cell systems permissive to HCV replication *in vitro* was a major obstacle for the development of antiviral drugs. The discovery of a specific cell system permissive to a strain of genotype 2 made possible the understanding of fundamental aspects of viral replication and host--virus interactions which boosted the development of antiviral drugs directed against specific targets, the so-called DAAs (direct-acting antivirals) [4]. A number of direct acting antiviral agents are under development for the treatment of chronic HCV infection. These agents block viral production by directly inhibiting one of several steps of HCV lifecycle [5] [see figure no1]. Before 2011, Peg-interferon and Ribavirin were considered to be the standard dose regimen in treating HCV [6] with sustained virological rate (SVR) being sub optimal; that is 45-50 % [7]. In 2011, launch of first DAA's, which are Boceprevir and Telaprevir, first generation protease inhibitors (PI's) in combination with Peg-interferon and Ribavirin(PR), was ideal combination regimen in HCV treatment [8]. But as Peg - interferon had many side effects, low SVR and limited treatment access due to patient's genotype and high pill burden of Boceprevir (12 tablets) and Telaprevir (6 tablets) daily, made it essential to introduce new peg-INF free fixed dose combinations regimen for treating HCV[2,9]. In the last quarter of 2014, two fixed dose combinations were approved by FDA and EMA. The first being Sofosbuvir and Ledipasvir, the second being Paritaprevir boosted by Ritonavir plus Ombitasvir[8]. Ledipasvir is an inhibitor of the HCV NS5A protein, targets NS5A and ceases the virus from spreading in the body. Sofosbuvir - an inhibitor of the HCV NS5B RNA- dependent RNA polymerase which acts as chain terminator, which decreases the count of HCV in the body [10, 11], and is effective across all Hepatitis C genotypes, and is a mainstay of interferon-free combination therapy. In Phase II and III studies, genotype 1 patients who took Sofosbuvir in combination with another DAA such as the NS3-4A protease inhibitor, Simeprevir, or the NS5A replication complex inhibitors, Ledipasvir or Daclatasvir, achieved a sustained virologic response rate of over 90%. Harvoni®, a combination tablet of

Sofosbuvir and Ledipasvir, dosed once daily is recommended for 24 weeks for treatment experienced genotype 1 patients with cirrhosis, but 12 weeks of therapy is sufficient for all other populations [12]. This FDC tablet approved by FDA, that excludes Peg-INF and Ribavirin, gives shorter duration of treatment, improved SVR, well tolerability should be administered orally with 90/400 mg of dose (Gilead Sciences) [13]. The purpose of this review is to summarize treatment data of Harvoni to treat Hepatitis C.

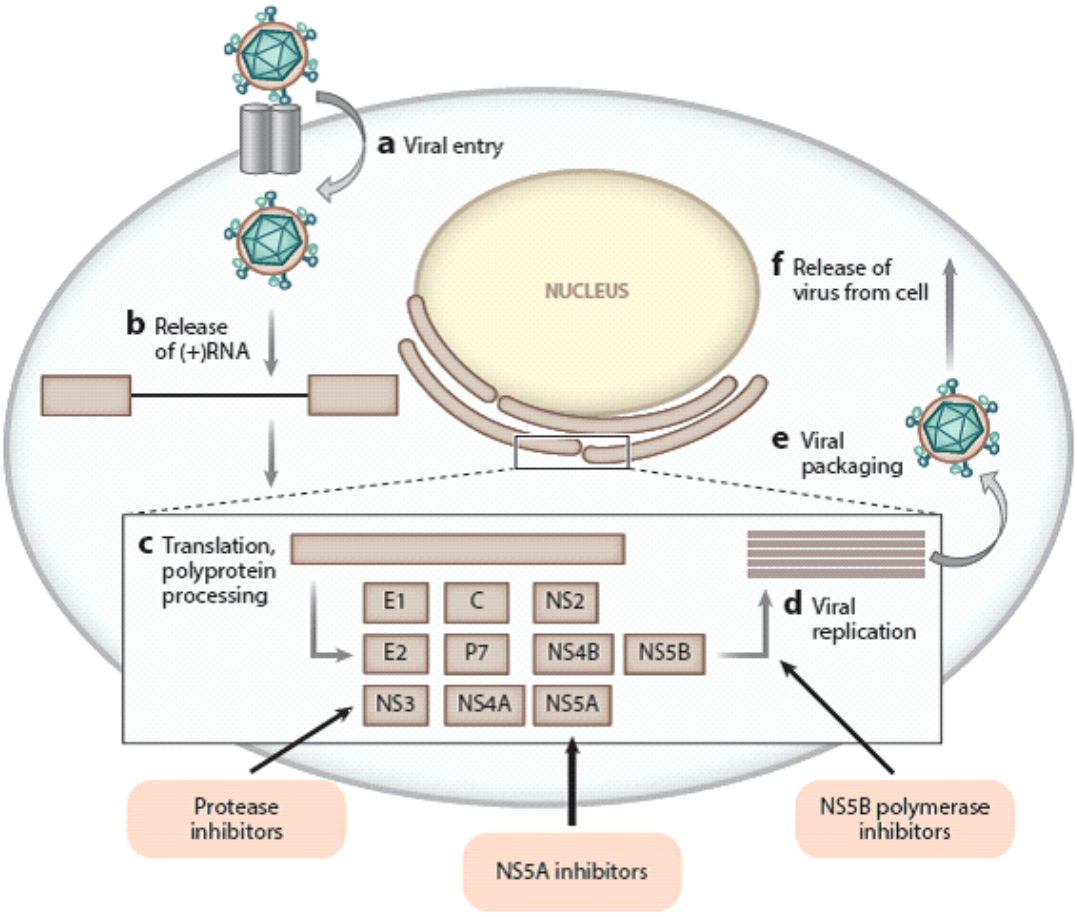


Figure 1

Life cycle of hepatitis C viral infection and targets for mechanism of action for direct-acting antivirals. (*a*) Virus particle–receptor binding and endocytosis; (*b*) cytoplasmic release and uncoating; (*c*) translation and polyprotein processing with structural and nonstructural proteins shown at the endoplasmic reticulum—the site for the mechanism of action of NS3/4 protease inhibitors; (*d*) RNA replication occurring in the membranous web—the site for the mechanism of action of the NS5A inhibitors and NS5B polymerase inhibitors; (*e*) virion packaging and assembly; and (*f*) virion maturation and release.

Figure no. 1: Life cycle of Hepatitis C viral infection and targets for mechanism of action for direct acting antivirals. [See ref no.14]

The old standard treatment used to treat Hepatitis C includes drugs like Interferons, Ribavirin, Boceprevir and Telaprevir. Their mechanism of action and side effects are shown in Table No.1

Table No 1: Historical drugs used to treat Hepatitis C.

Sr. No.	Name of the drug	Mechanism of action	Side effects
1)	Interferons (low molecular weight glycoprotein cytokines)[15]	INF's activate JAK-STAT pathway and stimulate the transcription of specific genes, leading to synthesis of proteins contributes to viral resistance at different stages of viral infection. Inhibition of protein synthesis is the major effect [16].	Flu like symptoms Arthralgia Chill's Headaches Fever Myalgia Neurotoxicity Alopecia[16,17]
2)	Ribavirin (purine nucleoside analogue has broad spectrum antiviral activity)[15]	Interfere with the synthesis of gaunosine triphosphate, which inhibits capping of viral mRNA [18].	conjunctival irritation rashes haemolytic anemia pruritus[16,17,18]
3)	Boceprevir	Potent inhibition of the HCV NS3A protease[6]	Anemia Neutropenia Dysgeusia[19]
4)	Telaprevir	Potent inhibition of the HCV NS4A protease[6]	Anemia Rashes Anorectal discomfort[19]

Need for new drugs and their combinations therapy:

As HCV leads to serious liver disorders which can be classified as:

1) Acute or chronic hepatitis (inflammatory liver disease).

2) Hepatosis (noninflammatory liver disease).

3) Cirrhosis (degenerative disorder resulting in fibrosis of liver) [20].

Peg-interferon plus Ribavirin and first DAA's were the standard backbones of HCV treatment. But due to many side effects such as arthralgia, myalgia, vomiting, diarrhoea, fever and chill (in case of interferon) and conjunctival irritation, rashes, haemolytic anemia (in case of Ribavirin) [16, 17] and high pill burden (in case of Boceprevir 12 tabs and Telaprevir 6 tabs) [2]. It became evident to introduce newly fixed dose combination interferon free regimen to treat HCV infected patients, which would offer better tolerability, safety and efficacy.

The new drugs approved as single line treatment for Hepatitis C includes, Simeprevir, Ombitasvir, Paritaprevir, Ritonavir, Sofosbuvir, Ledipasvir, are given in table no.2 along with their mechanism of action and side effects.

Table no. 2: Approved new treatment drugs for the treatment of Hepatitis C.

Sr. No.	Name of the drug	Mechanism of action	Side effects
1)	Simeprevir	NS34A protease inhibitor[6]	Nausea Pruritis Rash Photosensitivity [21]
2)	Ombitasvir	HCV NS5A protein inhibitor[6]	Asthenia Fatigue Insomnia Pruritis[21]
3)	Paritaprevir	HCV NS3/4A protease inhibitor[6]	Asthenia Fatigue Insomnia Pruritis[21]
4)	Ritonavir	CYP450 3A4 inhibitor used as booster[6]	Asthenia Fatigue Insomnia Pruritis[21]
5)	Sofosbuvir	HCV NS5B RNA-dependent RNA polymerase inhibitor[10]	Fatigue Headache[21]
6)	Ledipasvir	HCV NS5A protein inhibitor[10]	Fatigue Headache[21]

Approved Combination therapy treatment for Hepatitis C includes drugs like, Epclusa, Zepatier, Harvoni, Viekira Pak, Sovaldi, Olysio, Daklinza are given in table no 3 as follows:

Table no 3: Combination therapy treatment guidelines for the treatment of Hepatitis C

[See reference no 21]

- **Genotype 1a**

Therapy of Choice	Patient History	Duration of Therapy
Epclusa® Sofosbuvir/Velpatasvir	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG interferon/Ribavirin Failure Without Cirrhosis With Compensated cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 12 weeks + ribavirin
Zepatier™ (elbasvir/grazoprevir)	No baseline high fold-change NS5A RAVs Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With baseline high fold-change NS5A RAVs Treatment naïve Without Cirrhosis PEG interferon + ribavirin failure ± cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 16 weeks
*Harvoni®(ledipasvir/sofosbuvir)	Treatment–Naïve Without Cirrhosis Treatment-Naïve With Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks + ribavirin 12 weeks + ribavirin (low initial dose, 600 mg,

		increase as tolerated)
Viekira Pak™ (ombitasvir/paritaprevir / ritonavir + dasabuvir) + ribavirin	Treatment-Naïve Without Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis	12 weeks 12 weeks
Sovaldi®(sofosbuvir) + Olysio®(simeprevir)	Treatment–Naïve Without Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis	12 weeks 12 weeks
*Daklinza™ (daclatasvir)) + Sovaldi® (sofosbuvir)	Treatment-Naïve Without Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks + ribavirin (low initial dose, 600 mg, increase as tolerated)

- **Genotype 1b**

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 12 weeks + ribavirin
Zepatier™ (elbasvir/grazoprevir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG-interferon/Ribavirin failure Without cirrhosis With Compensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks
*Harvoni® (ledipasvir/sofosbuvir)	Treatment–Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis	12 weeks 12 weeks

	PEG-interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	 12 weeks 12 weeks 12 weeks + ribavirin (low initial dose, 600 mg, increase as tolerated)
Viekira Pak™(ombitasvir/paritaprevir/ ritonavir + dasabuvir) + ribavirin	Treatment–Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG-interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks
Sovaldi® (sofosbuvir) + Olysio®(simeprivir)	Treatment–Naïve Without Cirrhosis PEG-interferon/Ribavirin failure Without Cirrhosis	12 weeks 12 weeks
Daklinza™ (daclatasvir) + Sovaldi® (sofosbuvir)	Treatment-Naïve Without Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks + ribavirin (low initial dose, 600 mg, increase as tolerated)

- **Genotype 2**

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 12 weeks + ribavirin
Daklinza™ (daclatasvir) + Sovaldi® (sofosbuvir)	With Decompensated Cirrhosis	12 weeks + ribavirin (initial low dose, 600 mg, increase as tolerated)

- **Genotype 3**

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 12 weeks + ribavirin
Daklinza™ (daclatasvir) + Sovaldi® (sofosbuvir)	Treatment–Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	12 weeks 24 weeks ± ribavirin 12 weeks 24 weeks 12 weeks + ribavirin (initial low dose, 600 mg, increase as tolerated)

- **Genotype 4**

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 12 weeks + ribavirin
Technivie™ (ombistasvir/ paritaprevir/ritonavir) + ribavirin	Treatment–Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG-interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks
Zepatier™(elbasvir/grazoprevir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG-interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis	12 weeks 12 weeks 12 weeks
Harvoni® (ledipasvir/sofosbuvir)	Treatment–Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG-interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 12 weeks + ribavirin (low initial dose, 600 mg, increase as tolerated)

Daklinza™ (daclatasvir) + Sovaldi®(sofosbuvir)	With Decompensated Cirrhosis	12 weeks + ribavirin (low initial dose, 600 mg, increase as tolerated)

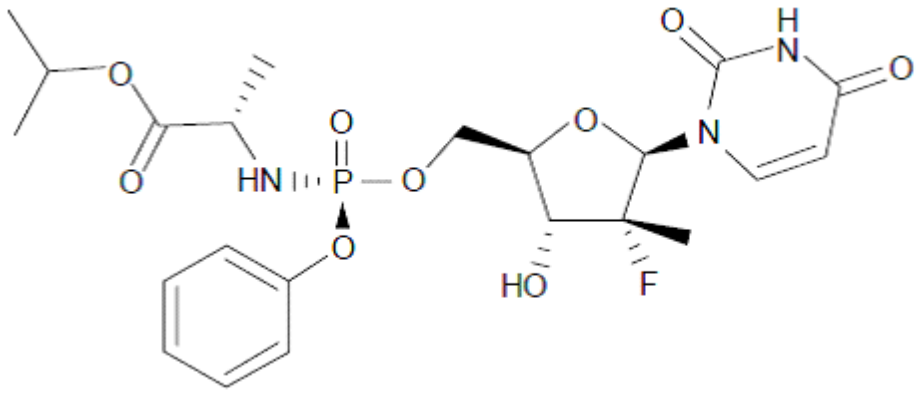
•**Genotype 5 or 6**

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve With and Without Cirrhosis PEG-interferon/ribavirin failure With or without Cirrhosis	12 weeks 12 weeks
Harvoni® (ledipasvir/sofosbuvir)	Treatment–naïve With and Without Cirrhosis PEG-interferon/ribavirin failure With or without Cirrhosis	12 weeks 12 weeks

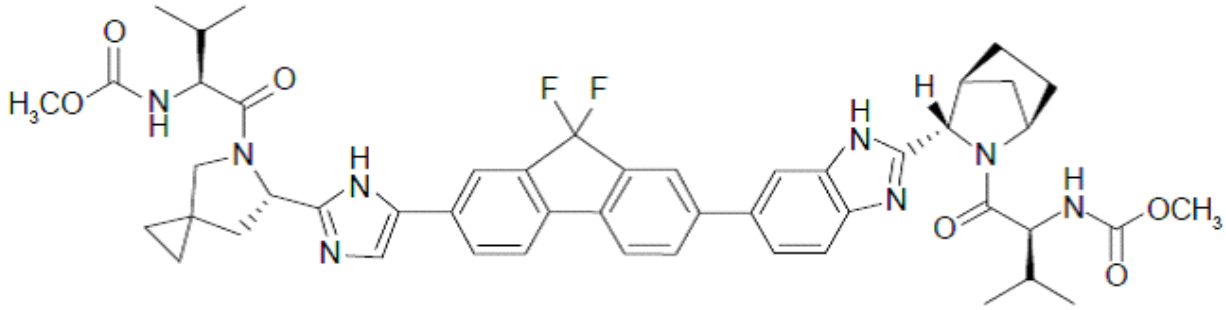
*Although not recommended in the ISDA/AASLD treatment guidelines, ledipasvir/sofosbuvir (Harvoni®) treatment for 8 weeks can be considered in patients who are treatment naïve, not cirrhotic, and have a pre-treatment viral load less than 6 million IU/mL.

Harvoni- fixed dose combination:

Sofosbuvir and Ledipasvir is a combination of two direct acting antiviral agents, which is a single fixed dose tablet (Harvoni @Gilead sciences) intended for oral use daily, which simplifies the dosage regimen and improves adherence of the therapy [22]. Sofosbuvir a nucleotide analogue of HCV NS5B polymerase inhibitors with similar *in vitro* activity against all genotypes [23]Sofosbuvir is phosphorylated to the active form (the nucleoside triphosphate), which competes with natural substrate leading to chain termination [24], while Ledipasvir is a potent NS5A inhibitor which is membrane anchored RNA binding protein, that inhibits apoptosis and promotes tumorigenesis [8].



Chemical structure of Sofosbuvir [see reference no.12]



Chemical structure of Ledipasvir. [See reference no.12]

Mechanism of action:

As, Harvoni is a combination of two drugs, Sofosbuvir and Ledipasvir, their mechanism of action also differs, which is as follows:

Sofosbuvir: it is a nucleotide prodrug which undergoes intracellular metabolism and gets converted to uridine analog triphosphate, which when incorporated into HCV RNA by the NS5B polymerase acts as chain terminator [25].

Ledipasvir: it is an inhibitor of the HCV NS5A protein, which is required for viral replication and ceases the spread of virus [26, 11].

Pharmacokinetics of Harvoni:

- The plasma peak concentration of the Ledipasvir and Sofosbuvir are 4 hours and 1 hour respectively [13].
- The plasma protein binding of the drugs, Ledipasvir is>99.8% and Sofosbuvir is 61-65% [10, 26].
- The half lives of the Sofosbuvir and Ledipasvir are 47 hours and ~1 hour respectively [10].
- The drugs Ledipasvir and Sofosbuvir are metabolised through liver and extrahepatic [7].
- The drugs Ledipasvir and Sofosbuvir are excreted through biliary and renal routes respectively [27].
- The sustained virological rates were found to be 93-99% after 12 weeks of therapy [6].

Drug interactions with Harvoni:

- Ledipasvir and Sofosbuvir, when co-administered with amiodarone, leads to bradycardia and cardiac arrest [21,29].

- Ledipasvir and Sofosbuvir are substrates of drug transporters P-gp and BRCP. P-gp inducers (eg: Rifampin, Phenytoin or St. John's wort) may decrease plasma concentrations, resulting in lowered therapeutic effect [26, 28].

- Acid reducing agents lower the concentrations of Ledipasvir and Sofosbuvir because solubility of Ledipasvir decreases as pH increases [21].

- Ledipasvir and Sofosbuvir are safe when co-administered with HIV medications, but administration with Tipranavir/Ritonavir may lower the concentrations [29].

- Antacids and Ledipasvir and Sofosbuvir combination should be separated by 4 hours gap [21].

CONCLUSION:

Based on all the information mentioned above and the references, we can conclude that the new fixed dose combination of Ledipasvir and Sofosbuvir approved by USFDA, is a single tablet dose regimen which is Interferon free regimen with potent efficacy in patients with all genotypes and decompensated cirrhosis, with minimal drug interactions and side effects, this FDC has outranked the old standards of treatment and commenced the new era of HCV treatment.

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