The Hepatitis C treatment landscape is changing in Pakistan

A new dawn has emerged in access to HCV Cure

- In partnership with Gilead Sciences, Ferozsons made the Breakthrough all-oral Hepatitis C treatment Sovaldi® available to patients in Pakistan in August 2014, within months of its approval by FDA in the United States.
- Pakistan became the first country in the world where patients began to receive Sovaldi® treatment at a fraction of the international cost under a special Access Program.
- Over 50,000 Hepatitis C patients benefited from treatment and access to cure within a year of availability.
- Many more patients are in need of a more affordable yet quality-assured treatment.

Ferozsons is heralding the change in the Hepatitis C landscape of Pakistan

Introducing

Savera

(Sofosbuvir) 400mg Tablets

A new dawn in access to HCV Cure in Pakistan

The first authorized generic of Sofosbuvir produced in Pakistan under license from Gilead Sciences.

In an exemplary partnership to bring breakthrough medical treatments to the patients of Pakistan, we are committed to expanding access to cure in critical diseases at all levels.

Savera
(Sofosbuvir) 400mg Tablets

Cure for All

INDICATION:[1]

Sofosbuvir (SAVERA) is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) as a component of a combination antiviral treatment regimen.

Sofosbuvir (SAVERA) efficacy has been established in subjects with HCV genotype 1, 2, 3, 4, 5 or 6 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection

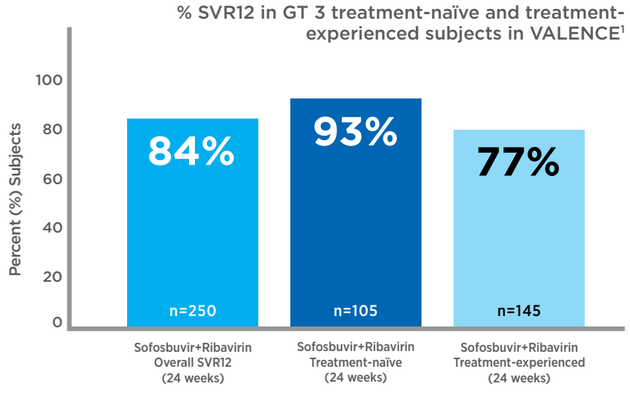
PRESCRIBING CONSIDERATIONS:[1]

- Monotherapy of Sofosbuvir (SAVERA) is not recommended.
- Treatment regimen and duration are dependent on both viral genotype and patient population.
- Treatment response varies based on baseline host and viral factors.

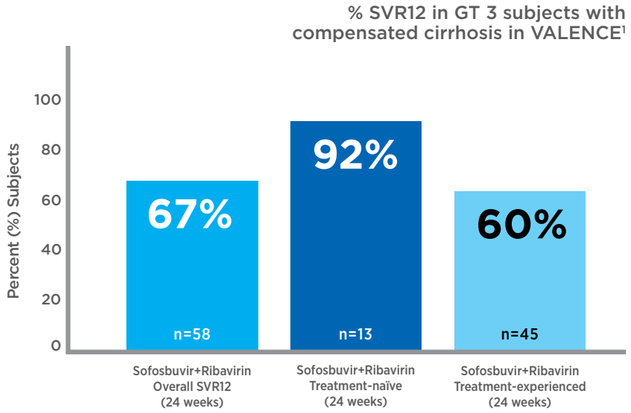
References: 1. Sofosbuvir Summary of Product Characteristics (Europe) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf

The first all-oral, IFN-free regimen for HCV GT 3 patients[1]

In VALENCE, Sofosbuvir + Ribavirin delivered high cure (SVR) rates in treatment-naïve and experienced GT 3 subjects[1,a]



GT 3 subjects with compensated cirrhosis in VALENCE achieved SVR12 with an all-oral regimen of Sofosbuvir + Ribavirin[1,b]

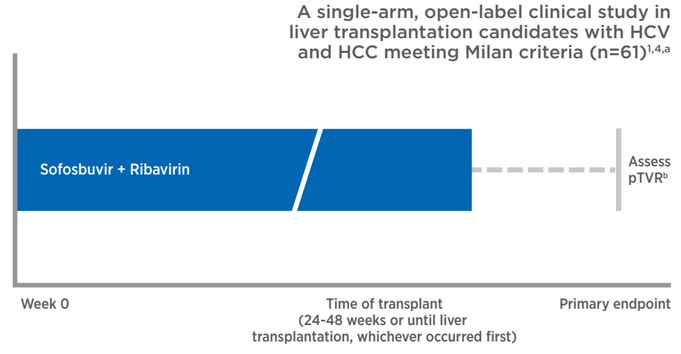


[a] Sustained virologic response (SVR) was the primary endpoint, which was defined as HCV RNA <25 IU per mL at 12 weeks after the end of treatment.[1] Achieving SVR is considered a virologic cure.[2]

[b] Cirrhosis was defined as any one of the following: a liver-biopsy sample showing cirrhosis; transient elastography (FibroScan®) showing cirrhosis or liver stiffness of more than 12.5 kPa; a serum FibroTest® score of more than 0.75 (on a scale of 0 to 1) plus a ratio of aspartate aminotransferase to platelets of more than 2 during screening.[3]

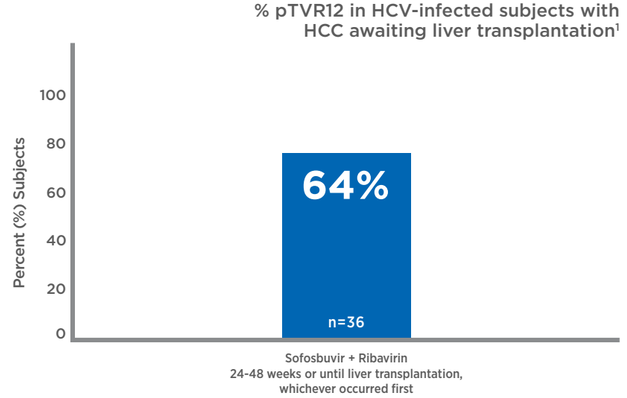
References: 1. Sofosbuvir Summary of Product Characteristics (Europe) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf **2.** Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54:1433-1444. doi:10.1002/hep.24641. **3.** Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368(20):1878-1887.

Patients awaiting liver transplantation: study design[1,4]



Sofosbuvir + Ribavirin was effective in HCC subjects awaiting liver transplantation to prevent post-transplant reinfection[1]

- 61 subjects diagnosed with hepatocellular carcinoma (HCC) awaiting liver transplantation received Sofosbuvir + Ribavirin for up to 48 weeks to prevent post-transplant HCV reinfection[1]
- Of these 61 subjects, 41 underwent liver transplantation, with 37 having HCV RNA <LLOQ at time of transplantation[1]
- pTVR was 64% among the 36 of these 37 subjects who were evaluable and who reached the 12-week post-transplant time point[1]



[a] Study included HCV-infected subjects, regardless of genotype, with HCC meeting the Milan criteria (defined as the presence of a tumor 5 cm or less in diameter in patients with single HCCs [hepatocellular carcinomas] and no more than 3 tumor nodules, each 3 cm or less in diameter in patients with multiple tumors and no extrahepatic manifestations of the cancer or evidence of vascular invasion of tumor). 45 subjects had HCV genotype 1; 44 subjects had a baseline CPT score less than 7; and all subjects had a baseline unadjusted MELD score ≤14.[1]

Subjects received 400 mg Sofosbuvir and weight based 1000-1200 mg RBV daily for 24-48 weeks or until the time of liver transplantation, whichever occurred first.[1]

[b] pTVR = post-transplant virologic response, defined as HCV RNA <LLOQ at 12 weeks post-transplant.

References: 1. Sofosbuvir Summary of Product Characteristics (Europe) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf **4.** Curry MP, Forns X, Chung R, Terrault N, et al. Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection After Liver Transplantation. Abstract presented at: 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1–5, 2013; Washington, DC.

Sofosbuvir + Ribavirin is the first and only all-oral regimen for patients with HCC meeting the Milan criteria who are awaiting liver transplantation to prevent post-transplant reinfection[1]

- In patients with hepatocellular carcinoma (HCC) awaiting liver transplantation, Sofosbuvir in combination with ribavirin is recommended until the time of liver transplantation.[1]
- Sofosbuvir in combination in Ribavirin is recommended for 24 weeks in liver transplant reciepient also.[1]

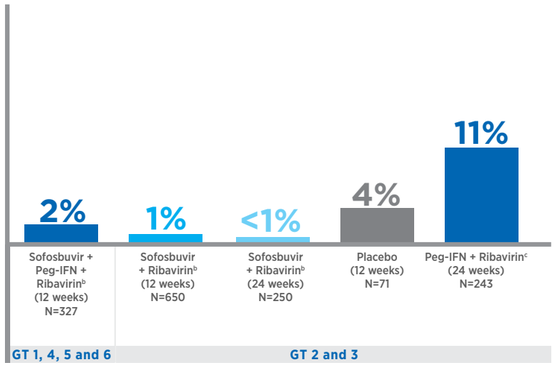
Recommended regimen and treatment duration for Sofosbuvir combination therapy in HCV-infected patients with HCC awaiting liver transplant[1]

Treatment Regimen	Duration
All Oral: Sofosbuvir 400 mg + Ribavirin[a]	until liver transplantation

- No response-guided therapy is required with Sofosbuvir.[1]

Sofosbuvir regimens had low discontinuation rates across clinical trials in HCV mono-infected subjects[1]

Discontinuation rates due to AEs by regimen across five Phase 3 Sofosbuvir clinical trials[1]



[a] Ribavirin dose is weight-based (<75 kg = 1000 mg; ≥75 kg = 1200 mg), administered daily in two divided doses taken orally with food. Patients with renal impairment (CrCl ≤50 mL/min) require Ribavirin dose reduction; refer to Ribavirin prescribing information.[1]

[b] Subjects received weight-based Ribavirin (1000 mg per day if weighing <75 kg or 1200 mg per day if weighing ≥75 kg).

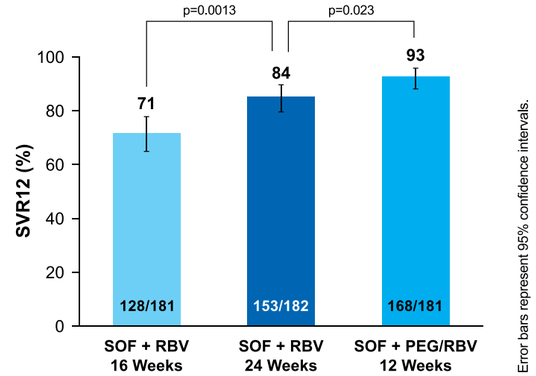
[c] Subjects received 800 mg Ribavirin per day regardless of weight.

Reference: 1. Sofosbuvir Summary of Product Characteristics (Europe) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf

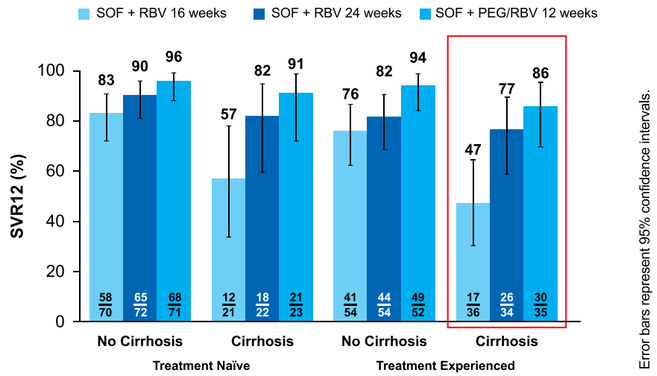
In BOSON, Sofosbuvir + Peginterferon/Ribavirin for 12 weeks delivered high cure rate (SVR) in genotype 3 HCV infected patients including treatment-experienced cirrhotic patients[5]

- In GT3 patients, including a large proportion of treatment-experienced patients with cirrhosis, Sofosbuvir + Peginterferon/Ribavirin for 12 weeks resulted in the highest SVR12 rates observed to date in a Phase 3 study.
- GT3 patients receiving 24 weeks of Sofosbuvir + Ribavirin had higher SVR12 rates than those receiving 16 weeks of treatment, confirming that 24 weeks is the optimal duration for this combination in GT3 patients.
- Sofosbuvir + Peginterferon/ Ribavirin for 12 weeks was well tolerated with a high rate of treatment completion.

SVR12 in GT 3



SVR12 in GT 3 by Treatment History and Cirrhosis Status



References: 5. Foster G R et al. Sofosbuvir + Peginterferon/Ribavirin For 12 Weeks vs Sofosbuvir + Ribavirin for 16 or 24 Weeks in Genotype 3 HCV infected patients and treatment-experienced cirrhotic patients with genotype 2 HCV: The Boson Study. J Hepatol. 2015; 62 (N2): S259–S260

Sofosbuvir drug interaction profile[1]

- Sofosbuvir is a substrate of intestinal drug transporter P-gp
- Sofosbuvir is cleared renally and is not metabolized by the CYP450 pathway

Sofosbuvir use with select medications[1,a]

Concomitant Drug Class: Drug Name[a]	Should not be used with Sofosbuvir[b]	Coadministration with Sofosbuvir not recommended[b]	No clinically significant interaction with Sofosbuvir[c]
Antimycobacterials: rifampin	✔		
Herbal Supplements: St. John's wort	✔		
Antiretrovirals: tipranavir/ritonavir		✔	
Antiarrhythmics: amiodarone (in combination with another DAA)		✔	
Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine		✔	
Antimycobacterials: rifabutin, rifapentine		✔	
Antiretrovirals: darunavir/ritonavir, emtricitabine, efavirenz, raltegravir, rilpivirine, tenofovir disoproxil fumarate			✔
Immunosuppressants: cyclosporine, tacrolimus			✔
Opioids: methadone			✔

Sofosbuvir offers simple dosing for patients with HCV genotypes 1, 2, 3, 4, 5 & 6[1]

- Sofosbuvir in combination with Ribavirin for 24 weeks can be considered for patients with genotype 1 infection who are Interferon ineligible.
- **Liver Transplant Patients**

  Sofosbuvir in combination with Ribavirin is recommended for 24 weeks in liver transplant recipients. A starting Ribavirin dose of 400 mg administered orally in two divided doses with food is recommended. If the starting dose of Ribavirin is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily.

Recommended regimens and treatment duration for combination therapy in HCV mono-infected and HCV/HIV-1 co-infected patients[1]

Genotype	Treatment Regimen	Duration
GT 1,4, 5 and 6	Sofosbuvir 400 mg + Peg-IFN alfa[d] + Ribavirin[e]	12 weeks[f]
GT 2	All oral: Sofosbuvir 400 mg + Ribavirin[e]	12 weeks[f]
GT 3	All oral: Sofosbuvir 400 mg + Ribavirin[e]	24 weeks
GT 3	Sofosbuvir 400 mg + Peg-IFN alfa[b] + Ribavirin[e]	12 weeks[f]
Patients with CHC awaiting liver transplantation	Sofosbuvir 400 mg + Ribavirin[e]	Until Liver[g] Transplatation

[a] This information is not all-inclusive.

[b] Decrease in concentration of Sofosbuvir, leading to a reduced therapeutic effect.

[c] No dosage adjustment for Sofosbuvir or concomitant medications is necessary.

[d] See Peginterferon Alfa prescribing information for dosage recommendation for patients with genotype 1,4, 5 & 6 HCV

[e] Dosage of Ribavirin is weight-based (<75 kg = 1000 mg and ≥75 kg = 1200 mg). The daily dosage of Ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤50 mL/min) require Ribavirin dosage reduction; refer to Ribavirin prescribing information.

[f] Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to Peginterferon alfa and Ribavirin therapy).

[g] Duration of administration of Sofosbuvir in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient.

Reference: 1. Sofosbuvir Summary of Product Characteristics (Europe) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf

Savera
(Sofosbuvir) 400mg Tablets

84% SVR for GT3 patients with Sofosbuvir +Ribavirin (24 weeks)[1,5]

93% SVR for GT3 patients with Sofosbuvir +Peginterferon Alfa+Ribavirin (12 weeks)[5]

Optimal quality offered by Ferozsons only Gilead licensee in Pakistan

Brief Prescribing Information

SAVERA (Sofosbuvir 400mg) is a Hepatitis C Virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of Chronic Hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. **INDICATIONS AND USAGE:** **SAVERA** (Sofosbuvir 400mg) efficacy has been established in subjects with HCV genotype 1, 2, 3, 4, 5 or 6 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection. **DOSAGE AND ADMINISTRATION:** One 400 mg tablet taken once daily with or without food. It should be used in combination with Ribavirin or in combination with Pegylated Interferon and Ribavirin for the treatment of CHC. Recommended combination therapy for Genotypes 1-6 chronic HCV & HCV/HIV co-infection: GT 1, 4, 5, 6: Sofosbuvir + Peginterferon + Ribavirin (12 weeks), GT 2: Sofosbuvir + Ribavirin (12 weeks) & GT 3: Sofosbuvir + Ribavirin (24 weeks) or Sofosbuvir+Peginterferon+Ribavirin (12 weeks). GT 1 (interferon ineligible): Sofosbuvir + Ribavirin (24 weeks) & HCC and awaiting transplant Patient: Sofosbuvir + Ribavirin (up to 48 weeks or until liver transplantation, whichever occurs first.). A dose recommendation cannot be made for patients with severe renal impairment or end stage renal disease. **CONTRAINDICATIONS:** When used in combination with Peginterferon Alfa/Ribavirin or Ribavirin alone, all contraindications to Peginterferon Alfa and/or Ribavirin also apply to **SAVERA** (Sofosbuvir 400mg) combination therapy. Because Ribavirin may cause birth defects and fetal death, **SAVERA** (Sofosbuvir 400mg) in combination with Peginterferon Alfa/Ribavirin or Ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant. **WARNINGS AND PRECAUTIONS:** Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone and **SAVERA** (Sofosbuvir 400mg) in combination with another direct acting antiviral (DAA), particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with **SAVERA** (Sofosbuvir 400mg) in combination with another DAA is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Use with other drugs containing Sofosbuvir is not recommended. Ribavirin may cause birth defects and fetal death and animal studies have shown interferons have abortifacient effects; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least 2 effective non-hormonal methods of contraception and have monthly pregnancy tests. **ADVERSE REACTIONS:** The most common adverse events (incidence greater than or equal to 20%, all grades) observed with **SAVERA** (Sofosbuvir 400mg) in combination with Ribavirin were fatigue and headache. The most common adverse events observed with **SAVERA** (Sofosbuvir 400mg) in combination with Peginterferon Alfa and Ribavirin were fatigue, headache, nausea, insomnia and anemia. **DRUG INTERACTIONS:** Coadministration of amiodarone with **SAVERA** (Sofosbuvir 400mg) in combination with another DAA may result in serious symptomatic bradycardia. Drugs that are potent intestinal P-gp inducers (e.g., Rifampin, St. John's Wort) may alter the concentrations of Sofosbuvir. Consult the full prescribing information prior to use for potential drug-drug interactions. **USE IN SPECIFIC POPULATIONS:** Safety and efficacy have been studied in Patients with HCV/HIV-1 co-infection & hepatocellular carcinoma awaiting liver transplantation. **HOW SUPPLIED/STORAGE:** Store below 30°C in a dry and dark place. **INSTRUCTIONS**: Keep out of the reach of children. To be sold on the prescription of registered medical practitioner only. Dispensed only in original container. Do not use if seal over bottle opening is broken or missing. **PRESENTATION:** **SAVERA** (Sofosbuvir 400mg) is available as a blue-colored, oblong-shaped, film-coated tablets containing 400mg Sofosbuvir debossed with "*f*" on one side and plain on other side. Each white color HDPE bottle contains 28 film-coated tablets, a silica gel desiccant with child resistance cap.

Full Prescribing Information available on request.

Reference: 1. Sofosbuvir Summary of Product Characteristics (Europe) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf **2.** Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54:1433-1444. doi:10.1002/hep.24641. **5.** Foster G R et al. Sofosbuvir + Peginterferon/Ribavirin For 12 Weeks vs Sofosbuvir + Ribavirin for 16 or 24 Weeks in Genotype 3 HCV infected patients and treatment-experienced cirrhotic patients with genotype 2 HCV: The Boson Study. J Hepatol. 2015; 62 (N2): S259–S260

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