MyHep All®
Sofosbuvir and Velpatasvir
400 mg/100 mg
75096417

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For the use of a Hepatologist only

℞ Sofosbuvir and Velpatasvir Tablets 400 mg/100 mg

MyHep All®

Name of the medicinal product

MyHep All®

Sofosbuvir and Velpatasvir 400 mg/100 mg

COMPOSITION

Each film-coated tablet contains:

Sofosbuvir IP .... 400 mg

Velpatasvir .... 100 mg

Colours: Lake of Indigo Carmine, Yellow oxide of Iron, Titanium dioxide IP

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 (the active metabolite of Sofosbuvir) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Velpatasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. *In vitro* resistance selection and cross-resistance studies indicate Velpatasvir targets NS5A as its mode of action.

Antiviral activity

The 50% effective concentration (EC_{50}) values of Sofosbuvir and Velpatasvir against full-length or chimeric replicons encoding NS5B and NS5A sequences from the laboratory strains are presented in Table 1. The EC_{50} values of Sofosbuvir and Velpatasvir against clinical isolates are presented in Table 2.

Table 1: Activity of Sofosbuvir and Velpatasvir against full-length or chimeric laboratory replicons

Replicon genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]
1a	40	0.014
1b	110	0.016
2a	50	0.005-0.016[c]
2b	15[b]	0.002-0.006[c]
3a	50	0.004
4a	40	0.009
4d	NA	0.004
5a	15[b]	0.021-0.054[d]
6a	14[b]	0.006-0.009
6e	NA	0.130[d]

NA = Not available

a. Mean value from multiple experiments of same laboratory replicon.

b. Stable chimeric 1b replicons carrying NS5B genes from genotype 2b, 5a or 6a were used for testing.

c. Data from various strains of full length NS5A replicons or chimeric NS5A replicons carrying full-length NS5A genes that contain L31 or M31 polymorphisms.

d. Data from a chimeric NS5A replicon carrying NS5A amino acids 9-184.

Table 2: Activity of Sofosbuvir and Velpatasvir against transient replicons containing NS5A or NS5B from clinical isolates

Replicon genotype	Replicons containing NS5B from clinical isolates		Replicons containing NS5A from clinical isolates	
	Number of clinical isolates	Median Sofosbuvir EC_{50}, nM (range)	Number of clinical isolates	Median Velpatasvir EC_{50}, nM (range)
1a	67	62 (29-128)	23	0.019 (0.011-0.078)
1b	29	102 (45-170)	34	0.012 (0.005-0.500)
2a	15	29 (14-81)	8	0.011 (0.006-0.364)
2b	NA	NA	16	0.002 (0.0003-0.007)
3a	106	81 (24-181)	38	0.005 (0.002-1.871)
4a	NA	NA	5	0.002 (0.001-0.004)
4d	NA	NA	10	0.007 (0.004-0.011)
4r	NA	NA	7	0.003 (0.002-0.006)
5a	NA	NA	42	0.005 (0.001-0.019)
6a	NA	NA	26	0.007 (0.0005-0.113)
6e	NA	NA	15	0.024 (0.005-0.433)

NA = Not available

The presence of 40% human serum had no effect on the anti-HCV activity of Sofosbuvir but reduced the anti-HCV activity of Velpatasvir by 13-fold against genotype 1a HCV replicons.

Evaluation of Sofosbuvir in combination with Velpatasvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In cell culture

HCV replicons with reduced susceptibility to Sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to Sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of genotype 1 to 6 conferred 2- to 18-fold reduced susceptibility to Sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, the ability of the active triphosphate of Sofosbuvir (GS-461203) to inhibit recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution was reduced compared to its ability to inhibit wild-type recombinant NS5B polymerase, as indicated by a 8.5- to 24-fold increase in the 50% inhibitory concentration (IC_{50}).

In vitro selection of HCV replicons with reduced susceptibility to Velpatasvir was performed in cell culture for multiple genotypes including 1a, 1b, 2a, 3a, 4a, 5a and 6a. Variants were selected at NS5A resistance associated positions 24, 28, 30, 31, 32, 58, 92 and 93. The resistance associated variants (RAVs) selected in 2 or more genotypes were F28S, L31I/V and Y93H. Site-directed mutagenesis of known NS5A RAVs showed that substitutions conferring a > 100-fold reduction in Velpatasvir susceptibility are M28G, A92K and Y93H/N/R/W in genotype 1a, A92K in genotype 1b, C92T and Y93H/N in genotype 2b, Y93H in genotype 3, and L31V and P32A/L/Q/R in genotype 6. No individual substitutions tested in genotypes 2a, 4a, or 5a conferred a > 100-fold reduction in Velpatasvir susceptibility. Combinations of these variants often showed greater reductions in susceptibility to Velpatasvir than single RAVs alone.

In clinical studies

Studies in patients without cirrhosis and patients with compensated cirrhosis

In a pooled analysis of patients without cirrhosis or with compensated cirrhosis who received Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks in three Phase 3 studies, 12 patients (2 with genotype 1 and 10 with genotype 3) qualified for resistance analysis due to virologic failure. One additional patient with genotype 3 HCV infection at baseline was reinfected with genotype 1a HCV at virologic failure and was excluded from the virological analysis. No patients with genotype 2, 4, 5, or 6 HCV infection experienced virologic failure.

Of the 2 genotype 1 virologic failure patients, one patient had virus with emergent NS5A RAV Y93N and the other patient had virus with emergent NS5A RAVs L31I/V and Y93H at virologic failure. Both patients had virus at baseline harboring NS5A RAVs. No NS5B nucleoside inhibitor (NI) RAVs were observed at failure in the 2 patients.

Of the 10 genotype 3 virologic failure patients, Y93H was observed in all 10 patients at failure (6 had Y93H emerge post-treatment and 4 patients had Y93H at baseline and post-treatment). No NS5B NI RAVs were observed at failure in the 10 patients.

Studies in patients with decompensated cirrhosis

In one Phase 3 study in patients with decompensated cirrhosis who received Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV for 12 weeks, 3 patients (1 with genotype 1 and 2 with genotype 3) qualified for resistance analysis due to virologic failure. No patients with genotype 2 or 4 HCV infection in the Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV 12 weeks group experienced virologic failure.

The 1 virologic failure patient with genotype 1 HCV had no NS5A or NS5B RAVs at failure.

Of the 2 genotype 3 virologic failure patients, one had NS5A RAV Y93H emerge at failure. Another patient had virus with Y93H at baseline and virologic failure and also developed low levels (< 5%) of NS5B NI RAVs N142T and E237G at failure. Pharmacokinetic data from this patient was consistent with non-adherence to treatment.

In this study, 2 patients treated with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 or 24 weeks without ribavirin had emergent NS5B S282T at low levels (< 5%) along with L159F.

Effect of baseline HCV resistance-associated variants on treatment outcome

Studies in patients without cirrhosis and patients with compensated cirrhosis

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients without cirrhosis or with compensated cirrhosis in three Phase 3 clinical studies (ASTRAL-1, ASTRAL-2 and ASTRAL-3). Of the 1,035 patients treated with Sofosbuvir/Velpatasvir in the three Phase 3 clinical studies, 1,023 patients were included in the analysis of NS5A RAVs; 7 patients were excluded as they neither achieved sustained virologic response (SVR12) nor had virologic failure and 5 additional patients were excluded as NS5A gene sequencing failed. In the pooled analysis of the Phase 3 studies, 380/1,023 (37%) patients' virus had baseline NS5A RAVs. Genotype 2, 4, and 6 HCV-infected patients had a higher prevalence of NS5A RAVs (70%, 63% and 52%, respectively) compared to genotype 1 (23%), genotype 3 (16%), and genotype 5 (18%) HCV-infected patients.

Baseline RAVs had no relevant impact on SVR12 rates in patients infected with genotype 1, 2, 4, 5 and 6 HCV, as summarised in Table 3. Genotype 3 infected patients with the NS5A RAV Y93H at baseline had a lower SVR12 rate than patients without Y93H after treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks, as summarised in Table 4. In the ASTRAL-3 study, the Y93H RAV was detected at baseline in 9% of patients treated with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.

Table 3: SVR12 in patients with or without baseline NS5A RAVs by HCV genotype (studies ASTRAL-1, ASTRAL-2 and ASTRAL-3)

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks			
	Genotype 1	Genotype 3	Genotypes 2, 4, 5 or 6	Total
With any baseline NS5A RAVs	97% (73/75)	88% (38/43)	100% (262/262)	98% (373/380)
Without baseline NS5A RAVs	100% (251/251)	97% (225/231)	100% (161/161)	99% (637/643)

Table 4: SVR12 in patients with and without baseline Y93H, 1% Cut-off (Resistance Analysis Population Set) ASTRAL 3

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 Weeks		
	All Subjects (n=274)	Cirrhotic (n=80)	Non-Cirrhotic (n=197)
Overall	95.3% (263/274)	91.3% (73/80)	97.9% (190/194)
95% CI	92.9% to 98.0%	82.8% to 96.4%	92.8% to 98.6%
SVR with Y93H	84.0% (21/25)	50.0% (2/4)	90.5% (19/21)
95% CI	63.9% to 95.5%	6.8% to 93.2%	69.6% to 98.8%
SVR without Y93H	96.4% (242/249)	93.4% (71/76)	98.8% (171/173)
95% CI	94.3% to 98.9%	85.3% to 97.8%	95.9% to 99.9%

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 studies. SVR12 was achieved in all 77 patients who had baseline NS5B NI RAVs including N142T, L159F, E/N237G, C/M289L/I, L320F/I/V, V321A/I, and S282G+V321I.

Studies in patients with decompensated cirrhosis (CPT Class B)

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients with decompensated cirrhosis in one Phase 3 study (ASTRAL-4). Of the 87 patients treated with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV, 85 patients were included in the analysis of NS5A RAVs; 2 patients were excluded as they neither achieved SVR12 nor had virologic failure. Among the patients who received treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV for 12 weeks, 29% (25/85) of patients had baseline virus with NS5A RAVs: 29% (19/66), 75% (3/4), 15% (2/13), and 50% (1/2) for patients with genotype 1, 2, 3 and 4 HCV, respectively.

SVR12 in patients with or without baseline NS5A RAVs in the Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV 12 week group for this study is shown in Table 5.

Table 5: SVR12 in patients with or without baseline NS5A RAVs by HCV genotype (study ASTRAL-4)

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV 12 weeks			
	Genotype 1	Genotype 3	Genotypes 2 or 4	Total
With any baseline NS5A RAVs	100% (19/19)	50% (1/2)	100% (4/4)	96% (24/25)
Without baseline NS5A RAVs	98% (46/47)	91% (10/11)	100% (2/2)	98% (58/60)

The single genotype 3 patient who had baseline NS5A RAVs and failed to achieve SVR12 had NS5A substitution Y93H at baseline; pharmacokinetic data from this patient was consistent with non-adherence to treatment.

Three patients in the Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV 12 week group had baseline NS5B NI RAVs (N142T and L159F) and all three patients achieved SVR12.

Cross-resistance

In vitro data suggests that the majority of NS5A RAVs that confer resistance to ledipasvir and daclatasvir remained susceptible to Velpatasvir. Velpatasvir was fully active against the Sofosbuvir resistance-associated substitution S282T in NS5B while all Velpatasvir resistance-associated substitutions in NS5A were fully susceptible to Sofosbuvir. Both Sofosbuvir and Velpatasvir were fully active against substitutions associated with resistance to other classes of direct acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. The efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir has not been assessed in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

Clinical efficacy and safety

The efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir was evaluated in three Phase 3 studies in patients with genotype 1 to 6 HCV infection with or without compensated cirrhosis and one Phase 3 study in patients with genotype 1 to 6 HCV infection with decompensated cirrhosis, as summarised in Table 6.

Table 6: Studies conducted with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection

Study	Population	Study arms (Number of patients treated)
ASTRAL-1	Genotype 1, 2, 4, 5 and 6 TN and TE, without cirrhosis or with compensated cirrhosis	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks (624) Placebo 12 weeks (116)
ASTRAL-2	Genotype 2 TN and TE, without cirrhosis or with compensated cirrhosis	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks (134) SOF+RBV 12 weeks (132)
ASTRAL-3	Genotype 3 TN and TE, without cirrhosis or with compensated cirrhosis	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks (277) SOF+RBV 24 weeks (275)
ASTRAL-4	Genotype 1, 2, 3, 4, 5 and 6 TN and TE, with CPT Class B decompensated cirrhosis	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks (90) Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV 12 weeks (87) Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 24 weeks (90)
ASTRAL-5	Genotype 1, 2, 3, 4, 5 and 6 TN and TE, without cirrhosis or with compensated cirrhosis, with HCV/HIV-1 co-infection	Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 12 weeks (106)
GS-US-342-4062	TN and TE with or without cirrhosis, with ESRD requiring dialysis	Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 12 weeks (59)

TN = treatment-naïve patients; TE = treatment-experienced patients (including those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor)

The ribavirin dose was weight-based (1,000 mg daily administered in two divided doses for patients < 75 kg and 1,200 mg for those ≥ 75 kg) and administered in two divided doses when used in combination with Sofosbuvir in the ASTRAL-2 and ASTRAL-3 studies or in combination with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in the ASTRAL-4 study.

Ribavirin dose adjustments were performed according to the ribavirin prescribing information. Serum HCV RNA values were measured during the clinical studies using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL. Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint to determine the HCV cure rate.

Clinical studies in patients without cirrhosis and patients with compensated cirrhosis

Genotype 1, 2, 4, 5 and 6 HCV-infected adults – ASTRAL-1 (study 1138)

ASTRAL-1 was a randomised, double-blind, placebo-controlled study that evaluated 12 weeks of treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir compared with 12 weeks of placebo in patients with genotype 1, 2, 4, 5, or 6 HCV infection. Patients with genotype 1, 2, 4 or 6 HCV infection were randomised in a 5:1 ratio to treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks or placebo for 12 weeks. Patients with genotype 5 HCV infection were enrolled to the Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir group. Randomisation was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) and the presence or absence of cirrhosis.

Demographics and baseline characteristics were balanced between the Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir and placebo group. Of the 740 treated patients, the median age was 56 years (range: 18 to 82); 60% of the patients were male; 79% were White, 9% were Black; 21% had a baseline body mass index of at least 30 kg/m²; the proportions of patients with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5% and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels of at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced.

Table 7 presents the SVR12 for the ASTRAL-1 study by HCV genotypes. No patients in the placebo group achieved SVR12.

Table 7: SVR12 in study ASTRAL-1 by HCV genotype

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks (n = 624)							
	Total (all GTs) (n = 624)	GT-1: GT-1a (n = 210)	GT-1: GT-1b (n = 118)	GT-1: Total (n = 328)	GT-2 (n = 104)	GT-4 (n = 116)	GT-5 (n = 35)	GT-6 (n = 41)
SVR12	99% (618/624)	98% (206/210)	99% (117/118)	98% (323/328)	100% (104/104)	100% (116/116)	97% (34/35)	100% (41/41)
Outcome for patients without SVR12								
On-treatment virologic failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapse[a]	< 1% (2/623)	< 1% (1/209)	1% (1/118)	1% (2/327)	0/104	0/116	0/35	0/41
Other[b]	1% (4/624)	1% (3/210)	0/118	1% (3/328)	0/104	0/116	3% (1/35)	0/41

GT = genotype

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

Genotype 2 HCV-infected adults – ASTRAL-2 (study 1139)

ASTRAL-2 was a randomised, open-label study that evaluated 12 weeks of treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir compared with 12 weeks of treatment with SOF+RBV in patients with genotype 2 HCV infection. Patients were randomised in a 1:1 ratio to treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks or SOF+RBV for 12 weeks. Randomisation was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve *versus* treatment-experienced).

Demographics and baseline characteristics were balanced across the two treatment groups. Of the 266 treated patients, the median age was 58 years (range: 23 to 81); 59% of the patients were male; 88% were White, 7% were Black; 33% had a baseline body mass index of at least 30 kg/m²; 62% had non-CC IL28B alleles (CT or TT); 80% had baseline HCV RNA levels of at least 800,000 IU/mL; 14% had compensated cirrhosis and 15% were treatment-experienced.

Table 8 presents the SVR12 for the ASTRAL-2 study.

Table 8: SVR12 in study ASTRAL-2 (HCV genotype 2)

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks (n = 134)	SOF+RBV 12 weeks (n = 132)
SVR12	99% (133/134)	94% (124/132)
Outcome for patients without SVR12		
On-treatment virologic failure	0/134	0/132
Relapse[a]	0/133	5% (6/132)
Other[b]	1% (1/134)	2% (2/132)

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

Treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks demonstrated the statistical superiority (p = 0.018) over treatment with SOF+RBV for 12 weeks (treatment difference +5.2%; 95% confidence interval: +0.2% to +10.3%).

Genotype 3 HCV-infected adults – ASTRAL-3 (study 1140)

ASTRAL-3 was a randomised, open-label study that evaluated 12 weeks of treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir compared with 24 weeks of treatment with SOF+RBV in patients with genotype 3 HCV infection. Patients were randomised in a 1:1 ratio to treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks or SOF+RBV for 24 weeks. Randomisation was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve *versus* treatment-experienced).

Demographics and baseline characteristics were balanced across the two treatment groups. Of the 552 treated patients, the median age was 52 years (range: 19 to 76); 62% of the patients were male; 89% were White, 9% were Asian; 1% were Black; 20% had a baseline body mass index of at least 30 kg/m²; 61% had non-CC IL28B alleles (CT or TT); 70% had baseline HCV RNA levels of at least 800,000 IU/mL, 30% had compensated cirrhosis and 26% were treatment-experienced.

Table 9 presents the SVR12 for the ASTRAL-3 study.

Table 9: SVR12 in study ASTRAL-3 (HCV genotype 3)

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks (n = 277)	SOF+RBV 24 weeks (n = 275)
SVR12	95% (264/277)	80% (221/275)
Outcome for patients without SVR12		
On-treatment virologic failure	0/277	< 1% (1/275)
Relapse[a]	4% (11/276)	14% (38/272)
Other[b]	1% (2/277)	5% (15/275)

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

Treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks demonstrated the statistical superiority (p < 0.001) compared to treatment with SOF+RBV for 24 weeks (treatment difference +14.8%; 95% confidence interval: +9.6% to +20.0%).

SVR12 for selected subgroups are presented in Table 10.

Table 10: SVR12 for selected subgroups in study ASTRAL-3 (HCV genotype 3)

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks		SOF+RBV 24 weeks[a]	
SVR12	Treatment-naïve (n = 206)	Treatment-experienced (n = 71)	Treatment-naïve (n = 201)	Treatment-experienced (n = 69)
Without cirrhosis	98% (160/163)	91% (31/34)	90% (141/156)	71% (22/31)
With cirrhosis	93% (40/43)	89% (33/37)	73% (33/45)	58% (22/38)

a. Five patients with missing cirrhosis status in the SOF+RBV 24 week group were excluded from this subgroup analysis.

Clinical studies in patients with decompensated cirrhosis– ASTRAL-4 (study 1137)

ASTRAL-4 was a randomised, open-label study in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection and CPT Class B cirrhosis. Patients were randomised in a 1:1:1 ratio to treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks, Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV for 12 weeks or Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 24 weeks. Randomisation was stratified by HCV genotype (1, 2, 3, 4, 5, 6 and indeterminate).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated patients, the median age was 59 years (range: 40 to 73); 70% of the patients were male; 90% were White, 6% were Black; 42% had a baseline body mass index of at least 30 kg/m². The proportions of patients with genotype 1, 2, 3, 4 or 6 HCV were 78%, 4%, 15%, 3%, and < 1% (1 patient), respectively. No patients with genotype 5 HCV infection were enrolled. 76% of the patients had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels of at least 800,000 IU/mL, 55% were treatment-experienced; 90% and 95% of patients had CPT Class B cirrhosis and Model for End Stage Liver Disease (MELD) score ≤ 15 at baseline, respectively.

Table 11 presents the SVR12 for the ASTRAL-4 study by HCV genotype.

Table 11: SVR12 in study ASTRAL-4 by HCV genotype

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks (n = 90)	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV 12 weeks (n = 87)	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 24 weeks (n = 90)
Overall SVR12	83% (75/90)	94% (82/87)	86% (77/90)
Genotype 1	88% (60/68)	96% (65/68)	92% (65/71)
Genotype 1a	88% (44/50)	94% (51/54)	93% (51/55)
Genotype 1b	89% (16/18)	100% (14/14)	88% (14/16)
Genotype 3	50% (7/14)	85% (11/13)	50% (6/12)
Genotype 2, 4 and 6	100% (8/8)[a]	100% (6/6)[b]	86% (6/7)[c]

a. n = 4 for genotype 2 and n = 4 for genotype 4

b. n = 4 for genotype 2 and n = 2 for genotype 4

c. n = 4 for genotype 2, n = 2 for genotype 4 and n = 1 for genotype 6.

Table 12 presents the virologic outcome for patients with genotype 1 or 3 HCV infection in the ASTRAL-4 study.

No patients with genotype 2, 4 or 6 HCV infection experienced virologic failure.

Table 12: Virologic outcome for patients with genotype 1 and 3 HCV infection in study ASTRAL-4

	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 12 weeks	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV 12 weeks	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir 24 weeks
Virologic failure (relapse and on-treatment failure)			
Genotype 1[a]	7% (5/68)	1% (1/68)	4% (3/71)
Genotype 1a	6% (3/50)	2% (1/54)	4% (2/55)
Genotype 1b	11% (2/18)	0% (0/14)	6% (1/16)
Genotype 3	43% (6/14)	15% (2[b]/13)	42% (5[c]/12)
Other[d]	5% (4/82)	2% (2/81)	5% (4/83)

a. No patients with genotype 1 HCV had on-treatment virologic failure.

b. One patient had on-treatment virologic failure; pharmacokinetic data from this patient was consistent with non-adherence to treatment.

c. One patient had on-treatment virologic failure.

d. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

Changes in the parameters found in the CPT score system in patients achieving SVR12 in ASTRAL-4 (all 3 regimens) are shown in Table 13.

Table 13: Changes in CPT score parameters from baseline to week 12 and 24 post-treatment in patients achieving SVR12, ASTRAL-4

	Albumin	Bilirubin	INR	Ascites	Encephalopathy
Post-treatment Week 12 (N=236), % (n/N)					
Decreased score (Improvement)	34.5% (79/229)	17.9% (41/229)	2.2% (5/229)	7.9% (18/229)	5.2% (12/229)
No change	60.3% (138/229)	76.4% (175/229)	96.5% (221/229)	89.1% (204/229)	91.3% (209/229)
Increased score (Worsening)	5.2% (12/229)	5.7% (13/229)	1.3% (3/229)	3.1% (7/229)	3.5% (8/229)
No assessment	7	7	7	7	7
Post-treatment Week 24 (N=236), % (n/N)					
Decreased score (Improvement)	39.4% (84/213)	16.4% (35/213)	2.3% (5/213)	15.0% (32/213)	9.4% (20/213)
No change	54.0% (115/213)	80.8% (172/213)	94.8% (202/213)	81.2% (173/213)	88.3% (188/213)
Increased score (Worsening)	6.6% (14/213)	2.8% (6/213)	2.8% (6/213)	3.8% (8/213)	2.3% (5/213)
No assessment	23	23	23	23	23

Note: Baseline frequency of ascites was: 20% none, 77% mild/moderate, 3% severe

Baseline frequency of encephalopathy was: 38% none, 62 % grade 1-2.

Clinical studies in patients with HCV/HIV-1 Co-infection – ASTRAL-5 (study 1202)

ASTRAL-5 evaluated 12 weeks of treatment with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg in patients with genotype 1, 2, 3, or 4 HCV infection who were co-infected with HIV-1 (HCV genotype 5 and 6 allowed, but no such patients were included). Patients were on a stable HIV-1 antiretroviral therapy that included emtricitabine/tenofovir disoproxil fumarate or abacavir/lamivudine administered with a ritonavir boosted protease inhibitor (atazanavir, darunavir, or lopinavir), rilpivirine, raltegravir or emtricitabine/tenofovir disoproxil fumarate /elvitegravir/cobicistat.

Of the 106 treated patients, the median age was 57 years (range: 25 to 72); 86% of the patients were male; 51% were white; 45% were black; 22% had a baseline body mass index ≥ 30 kg/m2; 19 patients (18%) had compensated cirrhosis; and 29% were treatment experienced. The overall mean CD4+ count was 598 cells/μL (range: 183−1513 cells/μL).

Table 14 presents the SVR12 for the ASTRAL-5 study by HCV genotype.

Table 14: SVR12 in study ASTRAL-5 by HCV genotype Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 12 weeks

	Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 12 weeks (n = 106)						
	Total (all GTs) (n = 106)	GT-1: GT-1a (n = 66)	GT-1: GT-1b (n = 12)	GT-1: Total (n = 78)	GT-2 (n = 11)	GT-3 (n = 12)	GT-4 (n = 5)
SVR12	95% (101/106)	95% (63/66)	92% (11/12)	95% (74/78)	100% (11/11)	92% (11/12)	100% (5/5)
Outcome for patients without SVR							
On-treatment virologic failure	0/106	0/66	0/12	0/78	0/11	0/12	0/5
Relapsea	2% (2/103)	3% (2/65)	0/11	3% (2/76)	0/11	0/11	0/5
Otherb	3%(3/106)	2%(1/66)	8%(1/12)	3%(2/78)	0/11	8% (1/12)	0/5

GT = genotype

a The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.

b Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

SVR12 was achieved by 19/19 patients with cirrhosis. No patient had HIV-1 rebound during the study, and CD4+ counts were stable during treatment.

Clinical studies in patients with Renal Impairment – study 4062

Study 4062 was an open-label clinical trial that evaluated 12 weeks of treatment with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg in 59 HCV-infected patients with ESRD requiring dialysis. The proportions of patients with genotype 1, 2, 3, 4, 6 or indeterminate HCV infection were 42%, 12%, 27%, 7% , 3%, and 9%, respectively. At baseline, 29% of patients had cirrhosis, 22% were treatment experienced, 32% had received a kidney transplant, 92% were on haemodialysis, and 8% were on peritoneal dialysis; mean duration on dialysis was 7.3 years (range: 0 to 40 years). The overall SVR rate was 95% (56/59); of the three patients that did not achieve SVR12, one had completed Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg treatment and relapsed and two did not meet virologic failure criteria.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in one or more subsets of the paediatric population in the treatment of chronic hepatitis C.

Elderly

Clinical studies of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir included 156 patients aged 65 and over (12% of total number of patients in the Phase 3 clinical studies). The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

Pharmacokinetics

Absorption

The pharmacokinetic properties of Sofosbuvir, GS-331007 and Velpatasvir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir, Sofosbuvir was absorbed quickly and the peak median plasma concentration was observed 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed 3 hours post-dose. Velpatasvir median peak concentrations were observed at 3 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected patients, mean steady-state AUC_{0-24} for Sofosbuvir (n = 982), GS-331007 (n = 1,428) and Velpatasvir (n = 1,425) were 1,260, 13,970 and 2,970 ng•h/mL, respectively. Steady-state C_{max} for Sofosbuvir, GS-331007 and Velpatasvir were 566, 868 and 259 ng/mL, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and patients with HCV infection. Relative to healthy subjects (n = 331), Velpatasvir AUC_{0-24} and C_{max} were 37% lower and 41% lower, respectively in HCV-infected patients.

Effects of food

Relative to fasting conditions, the administration of a single dose of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with a moderate fat (~600 kcal, 30% fat) or high fat (~800 kcal, 50% fat) meal resulted in a 34% and 21% increase in Velpatasvir AUC_{0-inf}, respectively, and a 31% and 5% increase in Velpatasvir C_{max}, respectively. The moderate or high fat meal increased Sofosbuvir AUC_{0-inf} by 60% and 78%, respectively, but did not substantially affect the Sofosbuvir C_{max}. The moderate or high fat meal did not alter GS-331007 AUC_{0-inf}, but resulted in a 25% and 37% decrease in its C_{max}, respectively. The response rates in Phase 3 studies were similar in HCV-infected patients who received Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with food or without food. Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir can be administered without regard to food.

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-Sofosbuvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity was approximately 0.7.

Velpatasvir is > 99.5% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09 μg/mL to 1.8 μg/mL. After a single 100 mg dose of [^{14}C]-Velpatasvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.52 and 0.67.

Biotransformation

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro.* Sofosbuvir and GS-331007 are not substrates or inhibitors of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes. After a single 400 mg oral dose of [^{14}C]-Sofosbuvir, GS-331007 accounted for approximately > 90% of total systemic exposure.

Velpatasvir is a substrate of CYP2B6, CYP2C8, and CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-Velpatasvir, the majority (> 98%) of radioactivity in plasma was parent drug. The monohydroxylated and desmethylated Velpatasvir were the metabolites identified in human plasma. Unchanged Velpatasvir is the major species present in faeces.

Elimination

Following a single 400 mg oral dose of [^{14}C]-Sofosbuvir, mean total recovery of the [^{14}C]-radioactivity was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, faeces, and expired air, respectively. The majority of the Sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as Sofosbuvir. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of Sofosbuvir and GS-331007 following administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir were 0.5 and 25 hours, respectively.

Following a single 100 mg oral dose of [^{14}C]-Velpatasvir, mean total recovery of the [^{14}C]-radioactivity was 95%, consisting of approximately 94% and 0.4% recovered from the faeces and urine, respectively. Unchanged Velpatasvir was the major species in faeces accounting for a mean of 77% of the administered dose, followed by monohydroxylated Velpatasvir (5.9%) and desmethylated Velpatasvir (3.0%). These data indicate that biliary excretion of parent drug was a major route of elimination for Velpatasvir. The median terminal half-life of Velpatasvir following administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir was approximately 15 hours.

Linearity/non-linearity

Velpatasvir AUC increases in a nearly dose proportional manner over the dose range of 25 mg to 150 mg. Sofosbuvir and GS-331007 AUCs are near dose-proportional over the dose range of 200 mg to 1,200 mg.

In vitro potential for Sofosbuvir/Velpatasvir drug-drug interactions

Sofosbuvir and Velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Velpatasvir is also a substrate of OATP1B. *In vitro,* slow metabolic turnover of Velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

Velpatasvir is an inhibitor of drug transporter P-gp, BCRP, OATP1B1 and OATP1B3 and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant plasma concentration, Velpatasvir is not an inhibitor of hepatic transporters bile salt export pump (BSEP), sodium taurocholate cotransporter protein (NTCP), OATP2B1, OATP1A2 or organic cation transporter (OCT) 1, renal transporters OCT2, OAT1, OAT3, multidrug resistance-associated protein 2 (MRP2) or multidrug and toxin extrusion protein (MATE) 1, or CYP or uridine glucuronosyltransferase (UGT) 1A1 enzymes.

Sofosbuvir and GS-331007 are not inhibitors of drug transporters P--gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1. GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Pharmacokinetics in special populations

Race and gender

No clinically relevant pharmacokinetic differences due to race or gender have been identified for Sofosbuvir, GS-331007 or Velpatasvir.

Elderly

Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 82 years) analysed, age did not have a clinically relevant effect on the exposure to Sofosbuvir, GS-331007, or Velpatasvir.

Renal impairment

The pharmacokinetics of Sofosbuvir was studied in HCV negative patients with mild (eGFR ≥ 50 and < 80 mL/min/1.73 m²), moderate (eGFR ≥ 30 and < 50 mL/min/1.73 m²), severe renal impairment (eGFR < 30 mL/min/1.73 m²) and patients with ESRD requiring haemodialysis following a single 400 mg dose of Sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73 m²), the Sofosbuvir AUC_{0-inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{0-inf} was 55%, 88% and 451% higher, respectively. In patients with ESRD, Sofosbuvir AUC_{0-inf} was 28% higher when Sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when dosed 1 hour after haemodialysis, respectively. The AUC_{0-inf} of GS-331007 in patients with ESRD administered with Sofosbuvir 1 hour before or 1 hour after haemodialysis was at least 10-fold and 20-fold higher, respectively. GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%. Following a single 400 mg dose of Sofosbuvir, a 4 hour haemodialysis removed 18% of administered dose.

The pharmacokinetics of Velpatasvir was studied with a single dose of 100 mg Velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Relative to subjects with normal renal function, Velpatasvir AUC_{inf} was 50% higher in subjects with severe renal impairment.

Hepatic impairment

The pharmacokinetics of Sofosbuvir was studied following 7-day dosing of 400 mg Sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (CPT Class B and C). Relative to patients with normal hepatic function, the Sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to Sofosbuvir and GS-331007.

The pharmacokinetics of Velpatasvir was studied with a single dose of 100 mg Velpatasvir in HCV negative patients with moderate and severe hepatic impairment (CPT Class B and C). Compared to subjects with normal hepatic function Velpatasvir total plasma exposure (AUC_{inf}) was similar in patients with moderate or severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to Velpatasvir.

Body weight

Body weight did not have a clinically significant effect on Sofosbuvir or Velpatasvir exposure according to a population pharmacokinetic analysis.

Paediatric population

The pharmacokinetics of Sofosbuvir, GS-331007 and Velpatasvir in paediatric patients have not been established.

INDICATIONS

Fixed Dose Combination of Sofosbuvir 400 mg and Velpatasvir 100 mg is indicated for the treatment of adult patients with chronic hepatitis C virus, Genotype 1,2,3,4, 5 or 6 infection.

without cirrhosis or with compensated cirrhosis

with decompensated cirrhosis for use in combination with Ribavarin.

DOSAGE AND ADMINISTRATION

Fixed Dose Combination of Sofosbuvir 400 mg and Velpatasvir 100 mg treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

The recommended dose of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is one tablet, taken orally, once daily with or without food.

Patients should be instructed to swallow the tablet whole with or without food. Due to the bitter taste, it is recommended that the film-coated tablet is not chewed or crushed.

Table 15: Recommended treatment and duration for all HCV genotypes

Patient population [a]	Treatment and duration
Patients without cirrhosis and patients with compensated cirrhosis	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks Addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis
Patients with decompensated cirrhosis	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + ribavirin for 12 weeks

a. Includes patients co-infected with human immunodeficiency virus (HIV) and patients with recurrent HCV post-liver transplant.

When used in combination with ribavirin, refer also to the Summary of Product Characteristics of the medicinal product containing ribavirin.

The following dosing is recommended where ribavirin is divided in two daily doses and given with food:

Table 16: Guidance for ribavirin dosing when administered with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir to patients with decompensated cirrhosis

Patient	Ribavirin Dose
Child-Pugh-Turcotte (CPT) Class B cirrhosis pre-transplant	1,000 mg per day for patients < 75 kg and 1,200 mg for those weighing ≥ 75 kg
CPT Class C cirrhosis pre-transplant CPT Class B or C post-transplant	Starting dose of 600 mg, which can be titrated up to a maximum of 1,000/1,200 mg (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg) if well tolerated. If the starting dose is not well tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels

If ribavirin is used in genotype 3 infected patients with compensated cirrhosis (pre- or post-transplant) the recommended dose of ribavirin is 1,000/1,200 mg (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg).For ribavirin dose modifications, refer to the Summary of Product Characteristics of the medicinal product containing ribavirin.Patients should be instructed that if vomiting occurs within 3 hours of dosing an additional tablet of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir should be taken. If vomiting occurs more than 3 hours after dosing, no further dose of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is needed.

If a dose of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir at the usual time. Patients should be instructed not to take a double dose of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.

Patients who have previously failed therapy with an NS5A-containing regimen

Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + ribavirin for 24 weeks may be considered.

Elderly

No dose adjustment is warranted for elderly patients.

Renal impairment

No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is required for patients with mild or moderate renal impairment. The safety and efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir has not been assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2) or end stage renal disease (ESRD) requiring haemodialysis.

Hepatic impairment

No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is required for patients with mild, moderate, or severe hepatic impairment (CPT Class A, B, or C). Safety and efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir have been assessed in patients with CPT Class B cirrhosis, but not in patients with CPT Class C cirrhosis.

Paediatric population

The safety and efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in children and adolescents aged less than 18 years have not yet been established. No data are available.

CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients.

Use with potent P-gp and potent CYP inducers

Medicinal products that are potent P-glycoprotein (P-gp) or potent cytochrome P450 (CYP) inducers (rifampicin, rifabutin, St. John's wort [Hypericum perforatum], carbamazepine, phenobarbital and phenytoin). Co-administration will significantly decrease Sofosbuvir or Velpatasvir plasma concentrations and could result in loss of efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.

WARNINGS AND PRECAUTIONS

Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir should not be administered concurrently with other medicinal products containing Sofosbuvir.

Severe bradycardia and heart block

Cases of severe bradycardia and heart block have been observed when Sofosbuvir used in combination with another direct acting antiviral (DAA), is used with concomitant amiodarone with or without other medicinal products that lower heart rate. The mechanism is not established.

The concomitant use of amiodarone was limited through the clinical development of Sofosbuvir plus DAAs. Cases are potentially life threatening, therefore amiodarone should only be used in patients on Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

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		Material Code	75096417	Supersedes 75094957	Market MYLAN-INDIA
[ ] New Component		Description	LIT. MYHEP ALL TABS 400 mg/100 mg MYLAN-INDIA V6		
[ ] Immediately (Stock of superseded component to be destroyed, if applicable.)		Component	Printed Literature	Actual Size	Flat - 400 x 520 mm; Folded - 35 x 51 mm
[ ] After consumption of existing (superseded) stock.		Substrate	30 gsm ITC Tribeni Paper		
[ ] Other (Specify)		Design & Style	Supply Leaflet in folded size as proposed (with tape)		
		Reason for Issue	Change in Text ..		

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Should concomitant use of amiodarone be considered necessary, it is recommended that patients are closely monitored when initiating Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.

All patients receiving Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in combination with amiodarone with or without other medicinal products that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Patients who have previously failed therapy with an NS5A-containing regimen

There are no clinical data to support the efficacy of Sofosbuvir/Velpatasvir for the treatment of patients who have failed treatment with a regimen containing another NS5A inhibitor. However, on the basis of NS5A resistance associated variants (RAVs) typically seen in patients who have failed therapy with other NS5A inhibitor containing regimens, the *in vitro* pharmacology of Velpatasvir, and the outcomes of Sofosbuvir/Velpatasvir treatment in NS5A-naïve patients with baseline NS5A RAVs enrolled into the ASTRAL-studies, treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV for 24 weeks can be considered for patients who have failed therapy on an NS5A-containing regimen and who are deemed at high risk for clinical disease progression and who do not have alternative treatment options.

Renal Impairment

No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is required for patients with mild or moderate renal impairment. The safety of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) or ESRD requiring haemodialysis. When Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is used in combination with ribavirin refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance < 50 mL/min.

Use with moderate P-gp inducers or moderate CYP inducers

Medicinal products that are moderate P-gp or moderate CYP inducers (e.g. oxcarbazepine, modafinil or efavirenz) may decrease Sofosbuvir or Velpatasvir plasma concentrations leading to reduced therapeutic effect of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. Co-administration of such medicinal products with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is not recommended.

Use with certain HIV antiretroviral regimens

Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate in the setting of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or tenofovir disoproxil fumarate given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction.

Patients receiving Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Refer to tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate, or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate Summary of Product Characteristics for recommendations on renal monitoring.

HCV/HBV (hepatitis B virus) co-infection

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

CPT Class C cirrhosis

Safety and efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir has not been assessed in patients with CPT Class C cirrhosis.

Liver transplant patients

The safety and efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in the treatment of HCV infection in patients who are post-liver transplant have not been assessed. Treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in accordance with the recommended posology should be guided by an assessment of the potential benefits and risks for the individual patient.

DRUG INTERACTIONS

As Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir contains Sofosbuvir and Velpatasvir, any interactions that have been identified with these active substances individually may occur with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.

Potential for Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir to affect other medicinal products

Velpatasvir is an inhibitor of drug transporter P-gp, breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3. Co-administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with medicinal products that are substrates of these transporters may increase the exposure of such medicinal products. See Table 16 for examples of interactions with sensitive substrates of P-gp (digoxin), BCRP (rosuvastatin), and OATP (pravastatin).

Potential for other medicinal products to affect Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir

Sofosbuvir and Velpatasvir are substrates of drug transporters P-gp and BCRP. Velpatasvir is also a substrate of drug transporter OATP1B. *In vitro*, slow metabolic turnover of Velpatasvir by CYP2B6, CYP2C8 and CYP3A4 was observed. Medicinal products that are potent inducers of P-gp or potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin) may decrease plasma concentrations of Sofosbuvir or Velpatasvir leading to reduced therapeutic effect of Sofosbuvir/Velpatasvir. The use of such medicinal products with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is contraindicated. Medicinal products that are moderate P-gp inducers or moderate CYP inducers (e.g. oxcarbazepine, modafinil or efavirenz) may decrease Sofosbuvir or Velpatasvir plasma concentration leading to reduced therapeutic effect of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. Co-administration with such medicinal products is not recommended with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. Co-administration with medicinal products that inhibit P-gp or BCRP may increase Sofosbuvir or Velpatasvir plasma concentrations. Medicinal products that inhibit OATP, CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of Velpatasvir. Clinically significant medicinal product interactions with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir may be co-administered with P-gp, BCRP, OATP and CYP inhibitors.

Patients treated with vitamin K antagonists

As liver function may change during treatment with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg, a close monitoring of International Normalised Ratio (INR) values is recommended.

Impact of DAA therapy on drugs metabolized by the liver

The pharmacokinetics of drugs that are metabolized by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV.

Interactions between Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir and other medicinal products

Table 17 provides a listing of established or potentially clinically significant medicinal product interactions (where 90% confidence interval [CI] of the geometric least-squares mean [GLSM] ratio were within "↔", extended above "↑", or extended below "↓" the predetermined interaction boundaries). The medicinal product interactions described are based on studies conducted with either Sofosbuvir/Velpatasvir or Velpatasvir and Sofosbuvir as individual agents, or are predicted medicinal product interactions that may occur with Sofosbuvir/Velpatasvir. The table is not all-inclusive.

Table 17: Interactions between Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir and other medicinal products

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b] Active	C_{max}	AUC	C_{min}	Recommendation concerning co-administration with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir
ACID REDUCING AGENTS					
					Velpatasvir solubility decreases as pH increases. Medicinal products that increase gastric pH are expected to decrease the concentration of Velpatasvir.
Antacids					
e.g. Aluminium or magnesium hydroxide; calcium carbonate (Increase in gastric pH)	Interaction not studied. *Expected.* ↔ Sofosbuvir ↓ Velpatasvir				It is recommended to separate antacid and Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir administration by 4 hours.
H_2-receptor antagonists					
Famotidine (40 mg single dose)/ Sofosbuvir/ Velpatasvir (400/ 100 mg single dose)[c]	Sofosbuvir	↔	↔		H_2-receptor antagonists may be administered simultaneously with or staggered from Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Famotidine dosed simultaneously with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir[d] Cimetidine[e] Nizatidine[e] Ranitidine[e] (Increase in gastric pH)	Velpatasvir	↓ 0.80 (0.70, 0.91)	↓ 0.81 (0.71, 0.91)		
Famotidine (40 mg single dose)/ Sofosbuvir/ Velpatasvir (400/ 100 mg single dose)[c]	Sofosbuvir	↓ 0.77 (0.68, 0.87)	↓ 0.80 (0.73, 0.88)		
Famotidine dosed 12 hours prior to Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir[d] (Increase in gastric pH)	Velpatasvir	↔	↔		
Proton pump inhibitors					
Omeprazole (20 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg single dose fasted)[c]	Sofosbuvir	↓ 0.66 (0.55, 0.78)	↓ 0.71 (0.60, 0.83)		Co-administration with proton pump inhibitors is not recommended. If it is considered necessary to co-administer, then Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir should be administered with food and taken 4 hours before proton pump inhibitor at max doses comparable to omeprazole 20 mg.
Omeprazole dosed simultaneously with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir[d] Lansoprazole[e] Rabeprazole[e] Pantoprazole[e] Esomeprazole[e] (Increase in gastric pH)	Velpatasvir	↓ 0.63 (0.50, 0.78)	↓ 0.64 (0.52, 0.79)		
Omeprazole (20 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg single dose fed)[c]	Sofosbuvir	↓ 0.79 (0.68, 0.92)	↔		
Omeprazole dosed 4 hours after Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir[d] (Increase in gastric pH)	Velpatasvir	↓ 0.67 (0.58, 0.78)	↓ 0.74 (0.63, 0.86)		
ANTIARRHYTHMICS					
Amiodarone	Interaction not studied. Effect on amiodarone, Velpatasvir, and Sofosbuvir concentrations unknown.				Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.
Digoxin	Interaction only studied with Velpatasvir. *Expected:* ↔ Sofosbuvir				Co-administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.
Digoxin (0.25 mg single dose)[f]/ Velpatasvir (100 mg single dose) (Inhibition of P-gp)	Effect on Velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
	Observed: Digoxin	↑ 1.9 (1.7, 2.1)	↑ 1.3 (1.1, 1.6)		
ANTICOAGULANTS					
Dabigatran etexilate (Inhibition of P-gp)	Interaction not studied. *Expected:* ↑ Dabigatran ↔ Sofosbuvir ↔ Velpatasvir				Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.
Vitamin K antagonists	Interaction not studied				Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg.
ANTICONVULSANTS					
Carbamazepine Phenytoin Phenobarbital (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is contraindicated with carbamazepine, phenobarbital and phenytoin, potent P-gp and CYP inducers.
	Observed: Sofosbuvir	↓0.52 (0.43, 0.62)	↓ 0.52 (0.46, 0.59)		
Oxcarbazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Co-administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with oxcarbazepine is expected to decrease the concentration of Sofosbuvir and Velpatasvir, leading to reduced therapeutic effect of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. Co-administration is not recommended.
ANTIFUNGALS					
Ketoconazole	Interaction only studied with Velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or ketoconazole is required.
Ketoconazole (200 mg twice daily)/ Velpatasvir (100 mg single dose)[d] (Inhibition of P-gp and CYPs) Itraconazole Voriconazole Posaconazole Isavuconazole	Effect on ketoconazole exposure not studied. *Expected:* ↔ Ketoconazole				
	Observed: Velpatasvir	↑ 1.3 (1.0, 1.6)	↑ 1.7 (1.4, 2.2)		
ANTIMYCOBACTERIALS					
Rifampicin (600 mg once daily)/ Sofosbuvir (400 mg single dose)[d] (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. *Expected:* ↔ Rifampicin				Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is contraindicated with rifampicin, a potent P-gp and CYP inducer.
	Observed: Sofosbuvir	↓ 0.23 (0.19, 0.29)	↓ 0.28 (0.24, 0.32)		
Rifampicin (600 mg once daily)/ Velpatasvir (100 mg single dose) (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. *Expected:* ↔ Rifampicin				
	Observed: Velpatasvir	↓ 0.29 (0.23, 0.37)	↓ 0.18 (0.15, 0.22)		
Rifabutin Rifapentine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is contraindicated with rifabutin, a potent P-gp and CYP inducer.
	Observed: Sofosbuvir	↓ 0.64 (0.53, 0.77)	↓ 0.76 (0.63, 0.91)		Co-administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with rifapentine is expected to decrease the concentration of Sofosbuvir and Velpatasvir, leading to reduced therapeutic effect of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. Co-administration is not recommended.
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS					
Tenofovir disoproxil fumarate	Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir has been shown to increase tenofovir exposure (P-gp-inhibition). The increase in tenofovir exposure (AUC and C_{max}) was around 40-80% during co-treatment with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir and tenofovir disoproxil fumarate/emtricitabine as part of various HIV regimens. Patients receiving tenofovir disoproxil fumarate and Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir concomitantly should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.				
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600/ 200/ 300 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)[c, d]	Efavirenz	↔	↔	↔	Co-administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is expected to decrease the concentration of Velpatasvir. Co-administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with efavirenz-containing regimens is not recommended.
	Sofosbuvir	↑ 1.4 (1.1, 1.7)	↔		
	Velpatasvir	↓ 0.53 (0.43, 0.64)	↓ 0.47 (0.39, 0.57)	↓ 0.43 (0.36, 0.52)	
Emtricitabine/**rilpivirine**/ tenofovir disoproxil fumarate (200/ 25/ 300 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)[c, d]	Rilpivirine	↔	↔	↔	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS					
Atazanavir boosted with ritonavir (300/ 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200 / 300 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)[c, d]	Atazanavir	↔	↔	↑ 1.4 (1.2, 1.6)	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir, atazanavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔		↑ 1.3 (1.5, 1.4)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↑ 1.6 (1.4, 1.7)	↑ 2.4 (2.2, 2.6)	↑ 4.0 (3.6, 4.5)	
Darunavir boosted with ritonavir (800 / 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)[c, d]	Darunavir	↔	↔	↔	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir, darunavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.62 (0.54, 0.71)	↓ 0.72 (0.66, 0.80)		
	Velpatasvir	↓ 0.76 (0.65, 0.89)	↔	↔	
Lopinavir boosted with ritonavir (4x200 mg/ 50 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)[c, d]	Lopinavir	↔	↔	↔	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir, lopinavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.59 (0.49 0.71)	↓ 0.7 (0.6, 0.8)		
	Velpatasvir	↓ 0.70 (0.59, 0.83)	↔	↑ 1.6 (1.4, 1.9)	
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS					
Raltegravir (400 mg twice daily)[g] + emtricitabine/ tenofovir disoproxil fumarate (200 / 300 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)[c, d]	Raltegravir	↔	↔	↓ 0.79 (0.42, 1.5)	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir, raltegravir or emtricitabine/ tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate (150/ 150/ 200/ 10 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)[c, d]	Elvitegravir	↔	↔	↔	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate is required.
	Cobicistat	↔	↔	↑ 2.0 (1.7, 2.5)	
	Tenofovir alafenamide	↔	↔		
	Sofosbuvir	↔	↑ 1.4 (1.2, 1.5)		
	Velpatasvir	↑ 1.3 (1.2, 1.5)	↑ 1.5 (1.4, 1.7)	↑ 1.6 (1.4, 1.8)	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (150/ 150/ 200/ 300 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)[c, d]	Elvitegravir	↔	↔	↔	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or elvitegravir/ cobicistat/emtricitabine/ tenofovir disoproxil fumarate is required.
	Cobicistat	↔	↑ 1.2 (1.2, 1.3)	↑ 1.7 (1.5, 1.9)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↑ 1.4 (1.2, 1.5)	
Dolutegravir (50 mg once daily)/ Sofosbuvir/ Velpatasvir (400/ 100 mg once daily)	Dolutegravir	↔	↔	↔	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or dolutegravir is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HERBAL SUPPLEMENTS					
St. John's wort (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir is contraindicated with St. John's wort a potent P-gp and CYP inducer.
HMG-CoA REDUCTASE INHIBITORS					
Atorvastatin (40 mg single dose) + sofosbuvir / velpatasvir (400/ 100 mg once daily)d	Observed: Atorvastatin	↑ 1.7 (1.5, 1.9)	↑ 1.5 (1.5, 1.6)		No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or atorvastatin is required.
Rosuvastatin	Interaction only studied with Velpatasvir *Expected:* ↔ Sofosbuvir				Co-administration of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir with rosuvastatin increases the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin, at a dose that does not exceed 10 mg, may be administered with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.
Rosuvastatin (10 mg single dose)/ Velpatasvir (100 mg once daily)[d] (Inhibition of OATP1B and BCRP)	*Observed:* Rosuvastatin	↑ 2.6 (2.3, 2.9)	↑ 2.7 (2.5, 2.9)		
	Effect on Velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
Pravastatin	Interaction only studied with Velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or pravastatin is required.
Pravastatin (40 mg single dose)/ Velpatasvir (100 mg once daily)[d] (Inhibition of OATP1B)	*Observed:* Pravastatin	↑ 1.3 (1.1, 1.5)	↑ 1.4 (1.2, 1.5)		
	Effect on Velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
Other statins	*Expected:* ↑ Statins				Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir, careful monitoring for statin adverse reactions should be undertaken and a reduced dose of statins should be considered if required.
NARCOTIC ANALGESICS					
Methadone (Methadone maintenance therapy [30 to 130 mg daily])/ Sofosbuvir (400 mg once daily)[d]	R-methadone	↔	↔	↔	No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or methadone is required.
	S-methadone	↔	↔	↔	
	Sofosbuvir	↔	↑ 1.3 (1.0, 1.7)		
Methadone	Interaction only studied with Sofosbuvir *Expected:* ↔ Velpatasvir				
IMMUNOSUPPRESSANTS					
Ciclosporin (600 mg single dose)/ Sofosbuvir (400 mg single dose)[f]	Ciclosporin	↔	↔		No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or ciclosporin is required.
	Sofosbuvir	↑ 2.5 (1.9, 3.5)	↑ 4.5 (3.3, 6.3)		
Ciclosporin (600 mg single dose)[f]/ Velpatasvir (100 mg single dose)[d]	Ciclosporin	↔	↓ 0.88 (0.78, 1.0)		
	Velpatasvir	↑ 1.6 (1.2, 2.0)	↑ 2.0 (1.5, 2.7)		
Tacrolimus (5 mg single dose)[f]/ Sofosbuvir (400 mg single dose)[d]	Tacrolimus	↓ 0.73 (0.59, 0.90)	↑ 1.1 (0.84, 1.4)		No dose adjustment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir or tacrolimus is required.
	Sofosbuvir	↓ 0.97 (0.65, 1.4)	↑ 1.1 (0.81, 1.6)		
Tacrolimus	Effect on Velpatasvir exposure not studied. *Expected:* ↔ Velpatasvir				
ORAL CONTRACEPTIVES					
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ Sofosbuvir (400 mg once daily)[d]	Norelgestromin	↔	↔	↔	No dose adjustment of oral contraceptives is required.
	Norgestrel	↔	↑ 1.2 (0.98, 1.5)	↑ 1.2 (1.0, 1.5)	
	Ethinyl estradiol	↔	↔	↔	
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ Velpatasvir (100 mg once daily)[d]	Norelgestromin	↔	↔	↔	
	Norgestrel	↔	↔	↔	
	Ethinyl estradiol	↑ 1.4 (1.2, 1.7)	↔	↓ 0.83 (0.65, 1.1)	

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics of study medicinal products alone or in combination. No effect = 1.00.
b. All interaction studies conducted in healthy volunteers.
c. Administered as Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir.
d. Lack of pharmacokinetics interaction bounds 70-143%.
e. These are medicinal products within class where similar interactions could be predicted.
f. Bioequivalence/Equivalence boundary 80-125%.
g. Lack of pharmacokinetics interaction bounds 50-200%

PREGNANCY

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of Sofosbuvir, Velpatasvir or Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in pregnant women.

Sofosbuvir

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. It has not been possible to fully estimate exposure margins achieved for Sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose.

Velpatasvir

Animal studies have shown a possible link to reproductive toxicity.

As a precautionary measure, Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir use is not recommended during pregnancy.

LACTATION

It is unknown whether Sofosbuvir, metabolites of Sofosbuvir or Velpatasvir are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of Velpatasvir and metabolites of Sofosbuvir in milk. A risk to the newborns/infants cannot be excluded. Therefore, Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir should not be used during breast-feeding.

Fertility

No human data on the effect of Epclusa on fertility are available. Animal studies do not indicate harmful effects of sofosbuvir or velpatasvir on fertility.

If ribavirin is co-administered with Epclusa, refer to the Summary of Product Characterisitics for ribavirin for detailed recommendations regarding pregnancy, contraception, and breast-feeding.

PAEDIATRIC USE

The safety and efficacy of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in children and adolescents aged less than 18 years have not yet been established. No data are available.

GERIATRIC USE

Clinical studies of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir included 156 patients aged 65 and over (12% of total number of patients in the Phase 3 clinical studies). The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

Effects on ability to drive and use machines

Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Summary of the safety profile

The safety assessment of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir was based on pooled Phase 3 clinical study data from patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection (with or without compensated cirrhosis) including 1,035 patients who received Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks.

The proportion of patients who permanently discontinued treatment due to adverse events was 0.2% and the proportion of patients who experienced any severe adverse events was 3.2% for patients receiving Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks. In clinical studies, headache, fatigue and nausea were the most common (incidence ≥ 10%) treatment emergent adverse events reported in patients treated with 12 weeks of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. These and other adverse events were reported at a similar frequency in placebo treated patients compared with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir treated patients.

Tabulated summary of adverse reactions

Assessment of adverse reactions for Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is based on safety data from clinical studies and postmarketing experience. All adverse reactions are presented in Table 4. The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000) or very rare (< 1/10,000).

Table 18: Adverse drug reactions identified with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg

Frequency	Adverse drug reaction
Gastrointestinal disorders:	
Very Common	Vomiting[a]
Skin and subcutaneous tissue disorders:	
Common	rash[b]
Uncommon	angioedema[b]

a. Adverse reaction was observed in patients aged 3 to < 6 years
b. Adverse reaction identified through post-marketing surveillance for sofosbuvir/Velpatasvir Containing products

Patients with decompensated cirrhosis

The safety profile of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir has been evaluated in one open-label study in which patients with CPT Class B cirrhosis received Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 12 weeks (n = 90), Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV for 12 weeks (n = 87) or Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir for 24 weeks (n = 90). The adverse events observed were consistent with expected clinical sequelae of decompensated liver disease, or the known toxicity profile of ribavirin for patients receiving Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir in combination with ribavirin.

Among the 87 patients who were treated with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV for 12 weeks, decreases in haemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were experienced by 23% and 7% patients, respectively. Ribavirin was discontinued in 15% of patients treated with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir + RBV for 12 weeks due to adverse events.

Patients with renal impairment

The safety of Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir has been evaluated in a 12-week non-controlled study including 59 subjects with ESRD requiring dialysis (Study 4062). In this setting, exposure of sofosbuvir metabolite GS-331007 was 20-fold increased, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not clearly elevated from what is expected in ESRD patients.

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when Sofosbuvir used in combination with another direct acting antiviral, is used with concomitant amiodarone and/or other medicinal products that lower heart rate.

Paediatric Population

The adverse reactions observed were consistent with those observed in clinical studies of sofosbuvir and velpatasvir in adults. Vomiting was observed as a very common adverse drug reaction to Epclusa in paediatric patients aged 3 to < 6 years. The safety assessment of Sofosbuvir and Velpatasvir in paediatric patients aged 3 years and older is based on data from a Phase 2, open-label clinical study (study 1143) that enrolled 216 patients who were treated with sofosbuvir/velpatasvir for 12 weeks.

Skin disorders

Frequency not known: Stevens-Johnson syndrome

OVERDOSE

The highest documented doses of Sofosbuvir and Velpatasvir were a single dose of 1,200 mg and a single dose of 500 mg, respectively. In these healthy volunteer studies, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

No specific antidote is available for overdose with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Fixed Dose Combination of 400 mg Sofosbuvir and 100 mg Velpatasvir consists of general supportive measures including monitoring of vital signs, as well as observation of the clinical status of the patient. Hemodialysis can efficiently remove the predominant circulating metabolite of Sofosbuvir, GS-331007, with an extraction ratio of 53%. Hemodialysis is unlikely to result in significant removal of Velpatasvir, since Velpatasvir is highly bound to plasma protein.

INCOMPATIBILITIES

Not applicable.

STORAGE AND HANDLING INSTRUCTIONS

Storage: Do not store above 30°C.
Store in the original container.
Protect from moisture.

Ref:http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-_Product_Information/human/004210/WC500211151.pdf

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June 2017

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Mylan Laboratories Limited Packaging Development	Artwork Implementation Schedule Check (✓) whichever is applicable (Approval is not valid without following details)	Date of Issue		Issued By	
		Date of Return			
		Material Code	75096417	Supersedes 75094957	Market MYLAN-INDIA

[ ] New Component
[ ] Immediately (Stock of superseded component to be destroyed, if applicable.)
[ ] After consumption of existing (superseded) stock.
[ ] Other (Specify) ....

Description	LIT. MYHEP ALL TABS 400 mg/100 mg MYLAN-INDIA V6
Component	Printed Literature — Actual Size: Flat - 400 x 520 mm; Folded - 35 x 51 mm
Substrate	30 gsm ITC Tribeni Paper
Design & Style	Supply Leaflet in folded size as proposed (with tape)
Reason for Issue	Change in Text ..

Printing Pantone Nos							
1	BLACK	2	NA	3	NA	4	NA
5	NA	6	NA	7	NA	8	NA
Non Printing	Die Line		NA		NA		NA

Sunil Gupta
Digitally signed by Sunil Gupta
Date: 2023.06.02

Sign. dd/mm/yy Job Function | Sign. dd/mm/yy Job Function

Proof No.	1	2	3	4	5
Date	02.06.2023	dd-mm-yy	dd-mm-yy	dd-mm-yy	dd-mm-yy
Remarks	Revised a/w.	x	x	x	x

Prepared By	Checked By			Approved By
Packaging Development	Packaging Development	Production	Regulatory Affairs	Quality Assurance

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