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APPLICATION NUMBER:

208341Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530) VIROLOGY REVIEW
NDA: 208341 **SDN**: 000
DATE REVIEWED: 03/17/2015
Virology Reviewer: Lisa K. Naeger, Ph.D.

NDA#: 208341 **Serial #: 000**
Reviewer's Name(s): Lisa K. Naeger, Ph.D.

Sponsor's Name and Address:
Gilead Sciences, Inc
333 Lakeside Drive
Foster City, CA 94404

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Amendments:

SDN	Date Submitted	Date Received	Date Assigned

Related/Supporting Documents: IND115670, IND106739, NDA204671

Product Names	**Sofosbuvir (GS-7977)**	**Velpatasvir (GS-5816)**
Structures	(b) (4)	
Chemical Names	(S)- Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy) phosphorylamino) propanoate	(b) (4)
Molecular formula	$C_{22}H_{29}FN_3O_9P$	$C_{49}H_{54}N_8O_8$
Molecular weight	529.46	883.00

Drug category: Antiviral

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Indication: Fixed-dose combination of velpatasvir, a hepatitis C virus (HCV) NS5A inhibitor and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor and is indicated for the treatment of chronic hepatitis C (CHC) (b) (4) infection

Dosage Form/Route of administration: Oral

Dispensed: Rx

Abbreviations: BVDV, bovine viral diarrhea virus; BL, baseline; DAA, direct acting antiviral; EC_{50}, effective concentration at 50%; FC, fold-change; FDA, Food and Drug Administration; FDC, fixed-dose combination; GT, genotype; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IC_{50}, inhibitory concentration at 50%; IFN, recombinant human interferon; LDV, ledipasvir; NGS, next generation sequencing; NRTIs, nucleoside reverse transcriptase inhibitors; PBL, peripheral blood lymphocytes; PDVF, protocol defined virologic failure; PI, NS3/4A protease inhibitor; P/R, pegylated interferon/ribavirin; RBV, ribavirin; RSV, respiratory syncytial virus; SDM, site-directed mutants; SOF, sofosbuvir; SVR, sustained virologic response; SVR12, sustained virologic response at 12 week after end of treatment; VEL, velapatasvir; WT, wild-type

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EXECUTIVE SUMMARY

This NDA for a fixed-dose combination (FDC) of velpatasvir (VEL) and and the approved NS5B nucleotide analog inhibitor sofosbuvir (SOF), seeks an indication with and without ribavirin (RBV) for the treatment of adult patients with chronic HCV infection. From a virology perspective, this application for SOV/VEL is approvable.

SOF/VEL is indicated for the treatment of GT1, 2, 3, 4, 5, and 6 HCV infections. The recommended treatment regimen for patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A) is 12 weeks of SOF/VEL. The recommended treatment regimen for patients with decompensated cirrhosis (Child-Pugh B and C) is 12 weeks of SOF/VEL + RBV. This virology review supports adding a footnote to the Dosage and Administration Table to consider adding RBV to 12 week SOF/VEL for GT3 subjects with compensated cirrhosis, because relapse rates were higher overall in this population and the consequences of failure with resistance to all NS5A inhibitors and potentially SOF for the cirrhotic population are significant. GT3 subjects with compensated cirrhosis treated with 12 weeks SOF/VEL had a relapse rate of 9% compared to 2% for GT3 subects without cirrhosis. Importantly, relapse rates were much higher (33%) in GT3 compensated cirrhotic subjects who had baseline NS5A resistance-associated polymorphisms (RAPs). Furthermore, all the GT3 virologic failures with compensated cirrhosis had the Y93H NS5A resistance substitution at failure, which confers high-level resistance to all current NS5A inhibitors and may compromise future treatment options. Thus, it is important to optimize chances of virologic success for this advanced patient population. The data support adding RBV to 12 weeks SOF/VEL to optimize SVR12 rates in GT3 patients with compensated cirrhosis.

Sofosbuvir (SOF) is a uridine nucleotide analog inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Specifically, the SOF prodrug is hydrolyzed by cellular esterases to a uridine analog monophosphate that is subsequently converted by cellular kinases to uridine analog triphosphate. The uridine analog is incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. Velpatasvir (VEL) is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection experiments in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

SOF and VEL have antiviral activity against HCV genotypes (GT) 1, 2, 3, 4, 5, and 6. The EC_{50} values for SOF range from 15 to 264 nM against laboratory replicons and the EC_{50} values for VEL range from 0.004 to 0.130 nM. Against clinical isolates, median EC_{50} values range from 29 - 102 nM and 0.002 – 0.024 nM for SOF and VEL, respectively.

Velpatasvir was not antagonistic in reducing HCV RNA levels in replicon cells when combined with sofosbuvir or IFN-α, RBV, a HCV NS3/4A protease inhibitor, the HCV NS5A inhibitor, ledipasvir, or HCV NS5B non-nucleoside inhibitors, GS-9190 or GS-9669.

In cell culture, HCV replicons with reduced susceptibility to sofosbuvir were selected in cell culture for genotypes 1b, 2a, 2b, 3a, 4a, 5a, and 6a. Reduced susceptibility to

sofosbuvir was associated with the NS5B substitution S282T in all replicon genotypes examined. An M289L substitution developed along with the S282T substitution in genotype 2a, 5 and 6 replicons. Site-directed mutagenesis of the S282T substitution in replicons of genotypes 1 to 6 conferred 2- to 18-fold reduced susceptibility to sofosbuvir. HCV genotype 1a, 1b, 2a, 3a, 4a, 5a, and 6a replicon variants with reduced susceptibility to velpatasvir were also selected in cell culture. Selected viruses developed amino acid substitutions at NS5A resistance-associated positions 24, 28, 30, 31, 32, 58, 92, and 93. Phenotypic analysis of site-directed mutagenesis mutant replicons of the selected NS5A substitutions showed that single and double combinations of L31V and Y93H/N in genotype 1a, the combination of L31V +Y93H in genotype 1b, Y93H/S in genotype 3a, and L31V and P32A/L/Q/R in genotype 6 conferred greater than 100-fold reduction in velpatasvir susceptibility. In the genotype 2a replicon, the single mutants F28S and Y93H showed 91-fold and 46-fold reduced susceptibility to VEL, respectively. The single mutant Y93H conferred 3-fold reduced susceptibility to VEL in genotype 4a replicons. Combinations of these NS5A substitutions often showed greater reductions in susceptibility to velpatasvir than single substitutions alone.

Clinical Virology Assessment of ASTRAL Trials

For the FDA resistance analyses (see also the independent analysis of the next generation sequencing data by Virology Reviewer Eric Donaldson, Ph.D.), subjects who died, experienced an AE while serum HCV RNA was undetectable, or were lost to follow-up in the ASTRAL trials were removed from the analyses. Thus, 3 GT1a subjects in ASTRAL 1 and 16 GT3 subjects in ASTRAL 3 were censored for the FDA resistance analysis. The prevalence of baseline NS5A RAPs (any change at amino acid positions 24, 28, 30, 31, 58, 92 and 93) at a sensitivity threshold of 15% of the viral population was assessed in the ASTRAL trials. Analyses were performed to assess the effect of baseline NS5A RAPS and cirrhosis on relapse rates. In addition, the NS5A resistance-associated substitutions that emerged in virologic failures were examined.

ASTRAL 1 and 2

In the ASTRAL 1 and 2 studies of subjects with GT1, 2, 4, 5, and 6, the prevalence of baseline NS5A RAPs was 18% (38/211) in subjects with GT1a HCV infection and 31% (42/134) in subjects with GT1b HCV infection. The most prevalent NS5A RAPs in GT1a were at positions M28 (5%) and H58 (7%). The most prevalent NS5A RAPs in GT1b were at positions 30 (8%), 31 (7%), 58 (9%) and 93 (10%). The prevalence of baseline NS5A RAPs in subjects with GT2 HCV infection was 60% (233/387). The most prevalent GT2 NS5A RAPs were L31M (51%) and K24R/T/Q (17%). The prevalence of baseline NS5A RAPs in subjects with GT4, GT5, and GT6 infection was 63% (73/115), 9% (3/35), and 83% (35/42), respectively. The predominant polymorphisms were at positions 28, 30 and 58 in GT4 and at positions 24, 28, 30 and 58 in GT6.

There were only 2 GT1 virologic failures in ASTRAL 1 and there were no virologic failures in ASTRAL 2. Thus, for GT2, GT4, GT5 and GT6 subjects, SVR12 rates were 100% with or without the presence of baseline NS5A RAPs. Since there were only 2 GT1 virologic failures, the effect of baseline NS5A polymorphisms was not assessed for GT1 subjects in ASTRAL 1.

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