CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212477Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

VIROLOGY REVIEW
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
NDA 205834 SE 029, SDN 835; NDA 212477 SDN 1
Review Completed: 05/01/19

Reviewer: LALJI MISHRA, Ph.D.
Date Submitted: 02/28/19
Date Received: 02/28/19
Date Assigned: 03/5/19

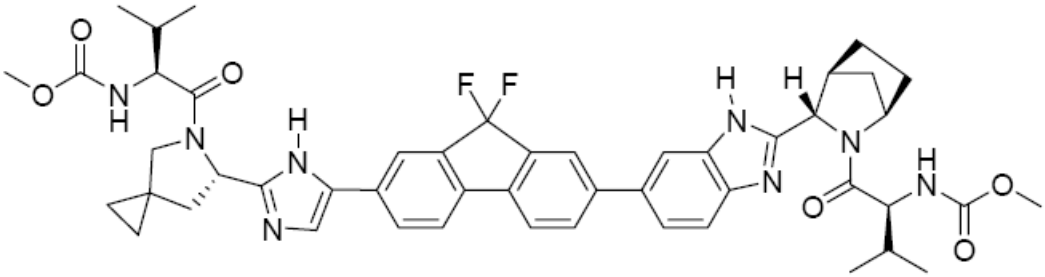
Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Product Names:

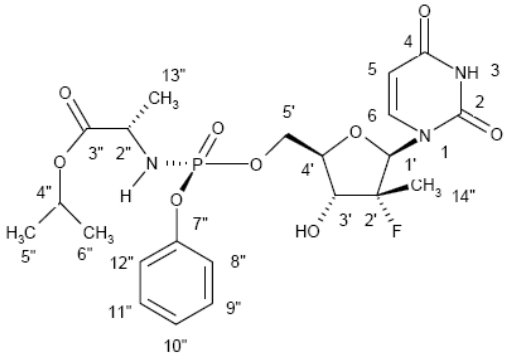
a. **Proprietary:** GS-5885, Sovaldi®
b. **Non-proprietary:** ledipasvir; sofosbuvir
c. **Chemical:**
Ledipasvir: Methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7-{2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1*H*benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Sofosbuvir: (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

Structure



LEDIPASVIR



SOFOSBUVIR

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Molecular Formula (ledipasvir; sofosbuvir**):** $C_{49}H_{54}F_2N_8O_6$; $C_{22}H_{29}FN_3O_9P$
Molecular Weight (ledipasvir; sofosbuvir**)**: 889.0; 529.46
Drug Category: Antiviral
Indication:

Adult Patients:

- HARVONI is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis.
- genotype 1 infection with decompensated cirrhosis, for use in combination with ribavirin.
- genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin.

Pediatric Patients:

HARVONI is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis.

Dosage Form/Route of Administration: Oral/Tablet (90 mg ledipasvir/400 mg sofosbuvir

Additional submissions reviewed:

Supplement #	**Date of Correspondence**	**Date of Receipt**	**Date Assigned**
N205834 SDN 840	03/18/19	03/18/19	03/18/19
N205834 SDN 869	07/10/19	07/10/19	07/10/19
N212477 SDN 001	02/28/19	02/28/19	02/28/19
N212477 SDN 002	03/18/19	03/18/19	03/18/10
N212477 SDN 009	07/10/19	07/10/19	07/10/19

Abbreviations:

BLAST, basic local alignment search tool; EC_{50}, effective concentration at 50%; FDC, fixed-dose combination; FU, follow-up visit; GT, genotype; HBV, hepatitis B virus; HBcAb, hepatitis B virus core antibody; HBsAb, antibody against hepatitis B virus surface protein; HBsAg, hepatitis B virus surface protein antigen; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; IFN, recombinant human interferon; LDV, ledipasvir; LiPA, line probe assay; RBV; ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; SVR4, 12 and 24, sustained virologic response at 4 , 12 and 24 weeks after end of treatment

BACKGROUND

VIROLOGY REVIEW
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
NDA 205834 SE 029, SDN 835; NDA 212477 SDN 1
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Gilead Sciences Inc. (GSI) has submitted an efficacy supplement to NDA 205834 in support of the approval of Harvoni 45/200 mg tablets for use in pediatric patients. In addition, GSI has submitted an original NDA 212477 in support of the marketing approval of Harvoni oral granules for use in the treatment of hepatitis C virus (HCV) infection in pediatric patients. These submissions contain results of Study GS-US-337-1116 entitled "A Phase 2, Open-Label, Multicenter, Multi cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination +/- Ribavirin in Adolescents and Children with Chronic HCV Infection"

Study GS-US-337-1116 is also submitted in fulfillment of PMRs 2780-1, 2983-1, and 2985-1 which state the following:

Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 to 17 years of age with chronic hepatitis C.

The original NDA for Harvoni (LDV/SOF) tablets was approved by the FDA for the treatment of chronic hepatitis C virus genotype 1 infection on 10 October 2014. Harvoni is currently indicated for the treatment of genotypes 1, 4, 5, or 6 hepatitis C virus (HCV) infection in adults and pediatric patients 12 years of age and older or weighing at least 35 kg. The clinical data for adolescents was submitted as an efficacy supplement and approved on 07 April 2017 for the treatment of chronic HCV with genotypes 1, 4, 5, or 6 in patients 12 years of age and older (see Virology Review of NDA 205834 SDN 460 dated 03/02/17 by Lisa Naeger Ph.D.

Clinical data for subjects 6 to <12 years of age and 3 to <6 years of age are provided in this submission which support proposed dosing recommendations for expansion of the current indication to include treatment of chronic HCV with genotypes 1, 4, 5, or 6 in pediatric patients who are 3 to <12 years of age.

I. Epidemiology and Prevalence of HCV genotypes in HCV infected subjects

Hepatitis C virus (HCV) is responsible for a large proportion of chronic liver disease worldwide. HCV infection is known to be associated with cirrhosis and hepatocellular carcinoma and is the most common cause for liver transplantation in the United States.

It is estimated that worldwide 177.5 million adults are infected with hepatitis C virus. In the United States alone, an estimated 3 million to 4 million persons are chronically infected with HCV (Squires and Balistreri 2017) and it is estimated that worldwide approximately 2.1 million individuals 15 years of age or younger are chronically infected with HCV (Nwaohiri et al., 2018},

HCV is classified into at least six different genotypes and multiple subtypes based on phylogeny. GT-3 is endemic in south-east Asia and is variably distributed in different countries. For example

GT-3 is the predominant genotype in India, Pakistan and Brazil and accounts for >30% cases in Greece, Poland, Netherlands and China (Hernandez et al., 2013). In the United States genotype 1 accounts for 77% of infections, genotype 2 for 11.3%, and genotype 3 for 9.6% (Nainan et al., 2006). Genotype 4 has been identified in North Africa and the Middle East; genotype 5 in South Africa; and genotype 6 in Asia (Squires and Balistreri 2017).

II. Biology of HCV

HCV is an enveloped virus which belongs to the Flaviviridae family. Its genome is a 9.6 kb, positive-sense, single-stranded RNA that encodes a polyprotein precursor of ~3000 amino acids. This polyprotein precursor is proteolytically processed by both cellular and viral proteases to 10 individual proteins: the structural proteins C, E1, E2, and p7, and the nonstructural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B (Simmonds et al., 2005). The nonstructural protein, NS3, comprises an N-terminal protease domain of 181 amino acids and a C-terminal helicase domain. The serine protease activity of NS3 in complex with the NS4A cofactor is responsible for the proteolytic cleavage at four junctions of the HCV polyprotein precursor: NS3-NS4A (self-cleavage), NS4A-NS4B, NS4B-NS5A, and NS5A-NS5B.

Nonstructural protein 3 (NS3), NS4A, NS4B, NS5A, and NS5B are sufficient for replication of HCV RNA as a replicon in cell culture. NS3-4A is the primary viral protease, and NS5B is an RNA-dependent RNA polymerase. NS4B, a hydrophobic protein with multiple *trans*-membrane domains, induces an endoplasmic reticulum-derived membranous web that harbors the HCV replication complex.

III. Mechanism of action and antiviral activity of ledipasvir and sofosbuvir

The mechanism of action and antiviral activity of ledipasvir and sofosbuvir are well documented. Please refer to Virology Review of NDA 205834 SDN 000 dated 07/10/14 by Lisa Naeger, Ph.D. The antiviral activities of ledipasvir and sofosbuvir are reproduced here from the Virology Review of NDA 205834 by Lisa Naeger, Ph.D.

Ledipasvir (LDV) inhibits HCV replication by interfering with the viral NS5A protein which is essential for both RNA replication and the assembly of HCV virions. Although the precise mechanism of inhibition has not been elucidated, several lines of evidence support NS5A as the target of LDV. Cell culture resistance selection studies, as well as LDV monotherapy clinical studies, identified LDV resistance substitutions in the NS5A gene. Additionally, HCV replicons encoding resistance substitutions to daclatasvir, another NS5A inhibitor, were shown to be cross-resistant to LDV. In biochemical studies, LDV does not inhibit NS3 protease, NS3 helicase, NS5B polymerase, the HCV IRES, or a broad panel of kinases.

The EC_{50} values of ledipasvir against HCV genotypes 1a and 1b were 0.031 nM and 0.004 nM, respectively. In addition, LDV had EC_{50} values ranging from 0.15 to 530 nM against genotypes 2 to 6 replicons. LDV had an EC_{50} value of 21 nM against the GT2a JFH-1 replicon with L31 in

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