Attachment 1: Product information for AusPAR Sunvepra asunaprevir Bristol-Myers Squibb Australia Pty Ltd PM- 2014-00648-1-2 Final 14 December 2015. This Product Information was approved at the time this AusPAR was published.

SUNVEPRA®

asunaprevir

PRODUCT INFORMATION

WARNING: POTENTIAL FOR HEPATOTOXICITY

For patients receiving SUNVEPRA-containing regimens, frequent monitoring of liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) and bilirubin is required until completion of therapy (see PRECAUTIONS).

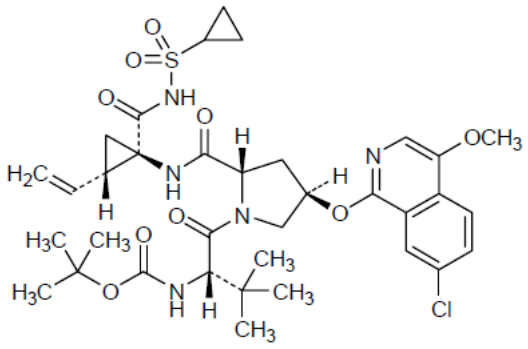
Discontinue SUNVEPRA immediately and do not resume in patients who experience:

- **on-treatment elevations in ALT levels 10 x ULN or greater, or**
- **on-treatment elevations in both ALT levels > 5 x ULN and total bilirubin > 2 x ULN.**

In clinical trials, observed liver enzyme and bilirubin elevations were reversible upon treatment discontinuation.

NAME OF THE MEDICINE

SUNVEPRA (asunaprevir), is a selective inhibitor of the HCV nonstructural protein 3/4A (NS3/4A) protease. Asunaprevir is described chemically as cyclopropanecarboxamide, *N*-[(1,1-dimethylethoxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-[(7-chloro-4-methoxy-1-isoquinolinyl)oxy]-L-prolyl-1-amino-*N*-(cyclopropylsulfonyl)-2-ethenyl-,*(1R,2S)*-. Asunaprevir has the following structural formula:



CAS number: 630420-16-5

Molecular formula: $C_{35}H_{46}ClN_5O_9S$

Molecular weight: 748.29

DESCRIPTION

Asunaprevir drug substance is a white to off-white powder. The aqueous solubility at pH 5.72 is 0.0003 mg/mL.

SUNVEPRA is available for oral administration as soft-gelatin capsules containing 100 mg of asunaprevir. Each capsule contains a solution of asunaprevir drug substance in the following inactive ingredients: medium-chain triglycerides, caprylic/capric glycerides, polysorbate 80, and butylated hydroxytoluene (BHT). The capsule shell contains gelatinpartially dehydrated liquid sorbitol, glycerol, titanium dioxide and OPACODE WB monogramming ink NSP-78-17827 BLACK (proprietary ingredient number 12427).

PHARMACOLOGY

Mechanism of Action

Asunaprevir is a direct acting antiviral agent (DAA) against the hepatitis C virus Asunaprevir is an inhibitor of the HCV NS3/4A serine protease complex. This NS3/4A enzyme complex is responsible for processing the HCV polyprotein to yield mature viral proteins required for viral replication.

In biochemical assays, asunaprevir was most active against NS3/4A protease complexes representing HCV genotypes 1a, 1b, 4a, 5a, and 6a, with IC50 [50% inhibitory concentration] values of 0.7 to 1.8 nM, 0.3 nM, 1.6 nM, 1.7 nM, and 0.9 nM, respectively. Reduced activity was seen against genotypes 2 (2a IC50 value = 15 nM; 2b IC50 value = 78 nM) and 3 (3a IC50 value = 320 nM).

Antiviral Activity

In cell-based HCV replicon assays, asunaprevir inhibited HCV genotypes 1a(H77 strain) and, 1b(Con1 strain) with effective concentration (50% reduction, EC50) values of 4 nM and 1.2 nM, , respectively. The EC50 values against a genotype 2a replicon and hybrid replicons encoding the NS3 protease domain representing HCV genotypes 2b and 3a were 230 nM, 480 nM, and 1162 nM, respectively. Against hybrid replicons encoding the NS3 protease domain representing HCV genotype 4a, observed EC50 values ranged from 1.8 nM to 7.6 nM.

Asunaprevir showed additive and/or synergistic interactions in combination with interferon alfa, daclatasvir, HCV NS5B active-site or allosteric inhibitors targeting either the NS5B thumb-1 or palm site, and ribavirin in two- or three-drug combination studies using a cell-based HCV replicon system.

Resistance

In cell culture

HCV genotype 1a and genotype 1b replicons with reduced susceptibility to asunaprevir were selected in cell culture and characterized for asunaprevir genotypic and phenotypic resistance. Resistance to asunaprevir was evaluated by introducing emergent NS3 protease variants into the respective replicon backbone. In HCV genotype 1a asunaprevir-resistant replicons, predominant substitutions were detected at amino acids R155K, D168G, and I170T. Recombinant replicons containing these substitutions confirmed their role in resistance to asunaprevir (5- to 21-fold reduced susceptibility to asunaprevir).

In the HCV genotype 1b asunaprevir-resistant replicons, predominant substitutions were detected at amino acid D168A/G/H/V/Y. Recombinant replicons containing these

substitutions confirmed their role in resistance to asunaprevir (16- to 280-fold reduced susceptibility to asunaprevir).

In clinical studies

Effect of baseline HCV polymorphisms on treatment response

Analyses were conducted to explore the association between naturally occurring baseline NS3 amino acid substitutions (polymorphisms) and treatment outcome.

SUNVEPRA and Daclatasvir (DAKLINZA®): In a pooled analysis of treatment-naive and experienced HCV genotype 1b infected subjects from phase 2/3 clinical trials (n=905), virus from 6 (0.7%) subjects had NS3-D168E detected at baseline. This polymorphism was present at baseline in 2% (3/138) of the subjects who failed treatment and had NS3 sequence.

The efficacy of SUNVEPRA in combination with DAKLINZA was reduced in HCV genotype 1b infected patients whose virus had HCV NS5A sequence polymorphisms detected at positions L31 (F, I, M or V) or Y93 (H). The pooled SVR rate in phase 2/3 trials for patients whose virus had L31F/I/M/V or Y93H was 48/119 (40%) compared with 686/742 (93%) for patients whose virus lacked L31F/I/M/V or Y93H polymorphisms (see also CLINICAL TRIALS).

SUNVEPRA, DAKLINZA, peginterferon alfa, and ribavirin: Of 379 subjects with available baseline NS3 sequence data in HALLMARK QUAD [see CLINICAL TRIALS], 4 had pre-existing signature asunaprevir-resistant substitutions at R155 (R155K/T) and/or D168 (D168E/N). Of the 4 subjects, 3 experienced virologic failure (all 3 were infected with HCV genotype 1a).

Treatment-emergent resistance in subjects not achieving SVR

*SUNVEPRA and DAKLINZA:*In a pooled analysis of HCV genotype 1b infected patients treated with SUNVEPRA and DAKLINZA, treatment-emergent NS3 amino acid substitutions were detected in the viruses from 114/118 (97%) patients who experienced virologic failure and had available resistance data (see Table 1). Most of these patients (111/118, 94%) had virus with treatment-emergent substitutions at NS3 amino acid position D168. Of 121 patients with available resistance data at failure for both NS3 and NS5A, 95 (79%) patients had virus with both D168 substitutions in NS3 and L31 plus Y93H substitutions in NS5A.

SUNVEPRA, DAKLINZA, peginterferon alfa, and ribavirin: Treatment-emergent NS3 amino acid substitutions were detected in the viruses from 15/16 (94%) HCV genotype 1a infected patients who experienced virologic failure with SUNVEPRA, DAKLINZA, peginterferon alfa, and ribavirin (see Table 1); all virologic failure patients with available data also had treatment-emergent daclatasvir resistance-associated substitutions in NS5A. A single HCV genotype 1b infected patient who experienced virologic failure had virus with treatment-emergent substitutions in NS3 and NS5A.

Table 1: Treatment-Emergent NS3 Amino Acid Substitutions in Pooled Data from Phase 2 and 3 Clinical Trials: Subjects Who Did Not Achieve SVR with SUNVEPRA and DAKLINZA or with SUNVEPRA, DAKLINZA, Peginterferon Alfa, and Ribavirin

Treated Subjects	**SUNVEPRA and DAKLINZA**	**SUNVEPRA, DAKLINZA, Peginterferon Alfa, and Ribavirin**		
Category (%, n)	**Genotype 1b n = 141**	**Genotype 1a n = 22[a]**	**Genotype 1b n = 2 [a]**	**Genotype 4 n = 0[a]**
Treated subjects with NS3 sequence	118	16	1	0
Emergent substitution at NS3 position 36, 54, 56H/L, 77, 80, 122, 155, 168, and/or 170A/M/T	97 (114)	94 (15)	100.0 (1)	0
V36X + other noted NS3 substitutions[b]	0.8 (1)	25 (4)	0	0
R155X[c]	3 (4)	50 (8)	0	0
R155K	0	50 (8)	0	0
D168X[d]	94 (111)	44 (7)	100 (1)	0
D168V	40 (47)	0	100 (1)	0
D168E	19 (22)	38 (6)	0	0
Only D168X	77 (91)	38 (6)	100 (1)	0
D168X + other noted NS3 substitutions[e]	17 (20)	6 (1)	0	0
V36G, V36M, T54S, N77S, Q80K/L/R, or S122D/G/I/N/T,	Less than 10%	Less than 10%	0	0

[a] Of 26 patients who were considered non SVR12 by a modified intent-to-treat analysis (subjects with missing values for a given time point were considered as a failure for the specific time point only), 2 subjects (1 with HCV genotype 1a and 1 with HCV genotype 4) achieved SVR12 by an imputed analysis (for subjects missing post-treatment week 12 HCV RNA, the next subsequent HCV RNA value was used). One subject with HCV genotype 1b had undetectable HCV RNA at Week 24 (last visit).

[b] X may include G (genotype 1b) or M (genotype 1a). Other noted NS3 substitutions include R155K or D168E.

[c] X may include G, K, or Q.

[d] X may include NS3 D168 substitutions A, E, F, H, N, T, V, or Y.

[e] For genotype 1a subjects, other NS3 substitutions included V36M; for genotype 1b subjects, other NS3 substitutions included V36G, T54S, N77S, Q80R, S122D/G/I/T, or R155Q.

Persistence of resistance-associated substitutions

Persistence of emergent NS3 resistance-associated substitutions was monitored post-treatment in subjects who experienced treatment failure in phase 2/3 clinical trials of SUNVEPRA-containing regimens. Among subjects treated with SUNVEPRA and

DAKLINZA, emergent HCV genotype 1b NS3 resistance-associated substitutions remained at detectable levels in 19 of 32 subjects only monitored at 24 weeks post-treatment and in 1 of 9 subjects monitored for 36 weeks or more post-treatment.

The lack of detection of resistance-associated substitution does not necessarily indicate that drug-resistant virus is no longer present. The long-term clinical impact of virus containing emergent asunaprevir-resistant substitutions is unknown.

Cross-resistance

Cross-resistance between asunaprevir and other NS3/4A protease inhibitors is expected. In clinical trials, asunaprevir resistance-associated substitutions were most commonly observed at NS3 positions R155 and D168. HCV replicons expressing asunaprevir resistance-associated substitutions remained fully sensitive to interferon alfa and ribavirin, as well as other direct-acting antivirals with different mechanisms of action, such as HCV NS5B polymerase inhibitors.

Pharmacokinetics

The pharmacokinetic properties of asunaprevir were evaluated in healthy adult subjects and in subjects with chronic HCV. Following multiple doses of asunaprevir 100 mg twice daily in combination with daclatasvir in HCV-infected subjects, the steady-state geometric mean (CV%) asunaprevir C_{max} was 572 (75) ng/mL, AUC_{0-12h} was 1887 (77) ng•h/mL, and C_{min} was 47.6 (105) ng/mL.

Absorption

In HCV-infected subjects, asunaprevir peak plasma concentrations occurred between 1 and 4 hours. Asunaprevir C_{max}, AUC and C_{min} increased in an approximately dose proportional manner. Steady state was achieved after 7 days of twice-daily administration in healthy subjects.

In vitro studies performed with human Caco-2 cells indicated that asunaprevir is a substrate of P-gp. The absolute oral bioavailability of asunaprevir soft capsule is 9.3%.

In healthy subjects, administration of 100 mg asunaprevir soft capsule with a high-fat meal (approximately 1000 kcal, approximately 50% from fat) increased the rate of absorption relative to fasting conditions, but did not have a clinically meaningful effect on the overall bioavailability of asunaprevir, with an increase in C_{max} and AUC of 34% and 20%, respectively. T_{max} of asunaprevir when administered with food occurred about 1.5 hours postdose relative to about 2.5 hours postdose when administered under fasting conditions.

Distribution

Protein binding of asunaprevir in HCV-infected subjects was greater than 99% and was independent of dose at the dose range studied (200 to 600 mg twice daily).

In vitro studies performed with HEK-293 cells indicated that asunaprevir is a substrate of the liver uptake transporters OATP 1B1 and 2B1. In subjects who received asunaprevir 100 mg soft capsule orally followed by a 100 µg ^{14}C-asunaprevir intravenous dose, estimated volume of distribution at steady state was 194 L.

Metabolism

In vitro studies demonstrate that asunaprevir undergoes oxidative metabolism primarily mediated by CYP3A.

Excretion

Following single-dose oral administration of ^{14}C-asunaprevir in healthy subjects, 84% of total radioactivity was recovered in faeces (primarily as metabolites) and less than 1% was recovered in the urine (primarily as metabolites). Metabolism was the major route of asunaprevir elimination. Of dose recovered in faeces, unchanged asunaprevir accounted for 7.5% of the dose. Unchanged asunaprevir comprised the majority of the circulating radioactivity in the early post-dose period, and nine minor metabolites were detected in human plasma (no single metabolite reached 20% of the exposure to unchanged asunaprevir or 10% of total exposure to asunaprevir and its metabolites after repeat dosing). Both asunaprevir and its metabolites were detected in human bile. Following multiple-dose administration of asunaprevir in healthy subjects, the terminal elimination half-life ranged from 17 to 23 hours. In subjects who received asunaprevir 100 mg soft capsule orally followed by a 100 µg ^{14}C-asunaprevir intravenous dose, estimated total body clearance of asunaprevir was 49.5 L/h.

Special Populations

Hepatic Impairment

No dose adjustment of SUNVEPRA is required for patients with mild hepatic impairment. The pharmacokinetic properties of asunaprevir were studied in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment and compared with unimpaired subjects. Subjects received asunaprevir (nonmarketed hard capsule) 200 mg twice daily for 7 days. Mild hepatic impairment had minimal effect on asunaprevir pharmacokinetics. Asunaprevir steady state exposures (C_{max}, AUC_{TAU}, and C_{min}) were markedly higher in subjects with moderate (5.0-, 9.8-, and 32.9-fold, respectively) or severe hepatic impairment (22.9-, 32.1-, and 76.5-fold, respectively) than in subjects without hepatic impairment [see CONTRAINDICATIONS and PRECAUTIONS - Hepatic Impairment and Cirrhosis].

Renal Impairment

The pharmacokinetic properties of asunaprevir, as one of three components of an investigational fixed dose combination tablet (asunaprevir/daclatasvir/an investigational non-nucleoside NS5B inhibitor), were studied after multiple-dose administration in non-HCV infected subjects with normal renal function (CrCL ≥90 mL/min, defined using the Cockcroft-Gault CrCL formula), with mild (CrCl 60 to <90 mL/min), moderate (CrCl 30 to <60 mL/min), or severe (CrCl <30 mL/min) renal impairment not on hemodialysis, and with end-stage renal disease (ESRD) on hemodialysis. Asunaprevir unbound C_{max} was estimated to be 37%, 87% and 119% higher and asunaprevir unbound AUC was estimated to be 41%, 99% and 137% higher for subjects with mild, moderate and severe renal impairment, respectively, compared with subjects with normal renal function. Asunaprevir unbound C_{max} and AUC decreased 2% and 6%, respectively, soon after hemodialysis in subjects with ESRD requiring hemodialysis compared to subjects with normal renal function [see PRECAUTIONS - Renal Impairment].

Elderly Patients

Population pharmacokinetic analysis of data from clinical trials indicated that within the age range evaluated (20-79 years) age had no clinically meaningful effect on the pharmacokinetics of asunaprevir.

Paediatric and Adolescent

The pharmacokinetics of SUNVEPRA in paediatric patients have not been evaluated.

Gender

Population pharmacokinetic analysis of data from clinical trials indicated that gender had no clinically meaningful effect on the pharmacokinetics of asunaprevir.

Race

Population pharmacokinetic analysis of data from clinical trials of SUNVEPRA indicated that race had no clinically relevant effect on the pharmacokinetics of asunaprevir.

Pharmacodynamics

The effect of asunaprevir on the QTc interval was evaluated in a randomized, double-blind, positive-controlled, placebo-controlled, parallel-group, nested-crossover study in 120 healthy subjects. The effect of a supratherapeutic dose of asunaprevir 300 mg twice daily relative to placebo on QTc (using Fridericia's correction) was evaluated on Days 3 and 10 of active dosing. No statistically significant effects of asunaprevir on placebo-corrected change in QTc or significant relationship between plasma concentration and change in QTc were observed.

CLINICAL TRIALS

The efficacy and safety of SUNVEPRA in combination with DAKLINZA as an all-oral regimen were evaluated in two phase 3 trials (HALLMARK DUAL and HALLMARK NIPPON). The efficacy and safety of SUNVEPRA in combination with DAKLINZA, peginterferon alfa and ribavirin were evaluated in the phase 3 HALLMARK QUAD trial. HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL except in the HALLMARK NIPPON study, where the LLOQ was 15 IU per mL. SVR (virologic cure) was defined as HCV RNA below the lower limit of quantification (LLOQ) at post-treatment Week 12.

SUNVEPRA in Combination with DAKLINZA in Subjects with HCV Genotype 1b

HALLMARK DUAL (Study AI447028) was a global open-label study that included subjects with chronic HCV genotype 1b infection and compensated liver disease who were treatment-naive, null or partial responders to peginterferon alfa and ribavirin, or were intolerant of or ineligible to receive interferon-based therapy. Subjects in the treatment-naive cohort were randomized 2:1 to receive SUNVEPRA 100 mg twice daily in combination with DAKLINZA 60 mg once daily for 24 weeks or placebo for 12 weeks (placebo subjects were rolled over into another study and offered treatment with SUNVEPRA in combination with DAKLINZA for 24 weeks). Subjects in the null or partial responder and intolerant/ineligible cohorts were treated with SUNVEPRA 100 mg twice daily in combination with DAKLINZA 60 mg once daily for 24 weeks. Subjects were monitored for 24 weeks post treatment.

Of the 745 treated subjects in HALLMARK DUAL included in the efficacy analyses, 643 subjects received SUNVEPRA in combination with DAKLINZA. These 643 subjects had a median age of 57 years (range: 20 to 79); 48% of the subjects were male; 70% were white, 24% were Asian, 5% were black; 4% were Hispanic/Latino. The mean baseline HCV RNA level was 6.4 $\log_{10}$ IU/mL; 32% of the subjects had compensated cirrhosis (Child-Pugh A)

and 29% had the IL28B CC genotype. Baseline characteristics of the 102 placebo-treated subjects were similar to those of subjects treated with SUNVEPRA in combination with DAKLINZA.

SVR, the primary endpoint, and outcomes for subjects without SVR in HALLMARK DUAL are shown by patient population in Table 2. SVR rates for patients with and without baseline NS5A resistance associated polymorphisms are included in the table. See the prescribing information for DAKLINZA for information on the prevalence of these polymorphisms.

Table 2: Treatment Outcomes in HALLMARK DUAL, SUNVEPRA in Combination with DAKLINZA in Subjects with HCV Genotype 1b Infection

Treatment outcomes	**Treatment-Naive n=203**	**Failed Prior Therapy (Partial and Null Responders) n=205**	**Interferon Intolerant/ Ineligible n=235**
SVR12[a]			
All	91% (184/203)	82% (169/205)	83% (194/235)
With Y93H or L31F/I/M/Vb	59% (10/17)	28% (7/25)	37% (11/30)
Without Y93H or L31F/I/M/V	96% (162/169)	92% (151/165)	90% (172/191)
With cirrhosis	91% (29/32)	87% (55/63)	81% (90/111)
No cirrhosis	91% (155/171)	80% (114/142)	84% (104/124)
Outcomes for subjects without SVR			
On-treatment virologic failure[c]	6% (12/203)	14% (29/205)	12% (28/235)
Relapse[d]	3% (5/189)	4% (7/174)	6% (12/204)
Missing post-treatment data	1% (2/203)	0	<1% (1/235)

[a] Missing HCV RNA data at follow-up week 12 were imputed using the Next Value Carried Backwards (NVCB) approach, i.e., using the next and closest available HCV RNA measurement after the follow-up week 12 HCV RNA visit window.

[b] Analysis includes patients with available baseline NS5A sequence data.

[c] On-treatment virologic failure includes subjects with virologic breakthrough (confirmed >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir or any confirmed HCV RNA ≥LLOQ after <LLOQ during treatment), those with HCV RNA ≥LLOQ at treatment Week 8, and those with detectable HCV RNA at end of treatment.

[d] Relapse rates are calculated with a denominator of subjects with undetectable HCV RNA at the end of treatment.

Among subjects who had failed prior therapy, SVR rate was the same (82%) among the 84 subjects with prior partial response and the 119 subjects with prior null response. Response was rapid (95% of subjects had HCV RNA <LLOQ at Week 4). There were no

differences in antiviral response due to race, gender, age, IL28B allele, or presence or absence of cirrhosis in any of the treatment populations. SVR rates were consistently high across all categories of baseline viral load. Among subjects 65 years of age or older, 88% (117/133) achieved SVR, and among subjects 75 years or older, 100% (10/10) achieved SVR.

HALLMARK NIPPON (Study AI447026) was an open-label study that included Japanese subjects with chronic HCV genotype 1b infection and compensated liver disease who were nonresponders (null or partial responders) to interferon alfa or beta and ribavirin, or who were intolerant of or ineligible to receive interferon-based therapy. Subjects in both the nonresponder and intolerant/ineligible cohorts were treated with SUNVEPRA 100 mg twice daily in combination with DAKLINZA 60 mg once daily for 24 weeks and monitored for 24 weeks post-treatment.

The 222 treated subjects in HALLMARK NIPPON had a median age of 63 years (range: 24 to 75); 35% of the subjects were male. Mean baseline HCV RNA level was 7 $\log_{10}$ IU/mL, and 10% of subjects had compensated cirrhosis (Child-Pugh A). Among 87 subjects in the nonresponder cohort, 36 subjects were prior partial responders and 48 were prior null responders to interferon/ribavirin. Among 135 subjects in the interferon intolerant/ineligible cohort, 35 subjects were in the intolerant category and 100 in the ineligible. Most of the nonresponder cohort had a non-CC IL28B genotype, while most of the intolerant/ineligible cohort had IL28B genotype CC.

SVR and outcomes for subjects without SVR in HALLMARK NIPPON are shown by patient population in Table 3. SVR rates for patients with and without baseline NS5A resistance associated polymorphisms are included in the table. See the prescribing information for DAKLINZA for information on the prevalence of these polymorphisms.

Table 3: Treatment Outcomes in HALLMARK NIPPON, SUNVEPRA in Combination with DAKLINZA in Subjects with HCV Genotype 1b

Treatment outcomes	Failed Prior Therapy (Partial and Null) n=87	Interferon Intolerant/Ineligible n=135
SVR12[a]		
All	81% (70/87)	88% (119/135)
With Y93H or L31F/I/M/V[b]	29% (4/14)	54% (13/24)
Without Y93H or L31F/I/M/V	90% (65/72)	96% (100/104)
With cirrhosis	91% (10/11)	91% (10/11)
No cirrhosis	79% (60/76)	88% (109/124)
Outcomes for subjects without SVR		
On-treatment virologic failure[c]	13% (11/87)	4% (6/135)
Relapse[d]	8% (6/76)	8% (10/129)

[a] Missing HCV RNA data were imputed using the NVCB approach.

[b] Analysis includes patients with available baseline NS5A sequence data.

[c] On-treatment virologic failure includes subjects with virologic breakthrough (confirmed >1 $\log_{10}$ IU/mL increase in HCV RNA over nadir or any confirmed HCV RNA ≥LLOQ after <LLOQ during treatment), those with confirmed HCV RNA ≥LLOQ on or after treatment Week 8, and those with detectable HCV RNA at end of treatment.

[d] Relapse rates are calculated with a denominator of subjects with undetectable HCV RNA at the end of treatment.

In the nonresponder cohort, 78% of prior partial responders and 81% of prior null responders achieved SVR12. In the intolerant/ineligible cohort, 94% of subjects who were intolerant and 86% of those who were ineligible achieved SVR. Response was rapid (96% of subjects had HCV RNA <LLOQ at Week 4).Within the prior nonresponder and interferon intolerant/ineligible populations, there were no differences in antiviral response due to gender, age, baseline HCV RNA level, IL28B allele, or presence or absence of cirrhosis. Among subjects 65 years of age or older, 91% (81/89) achieved SVR, and among subjects 75 years or older, 100% (4/4) achieved SVR.

SUNVEPRA in Combination with DAKLINZA in Subjects with HCV Genotype 1a: The efficacy of SUNVEPRA and DAKLINZA combination therapy in the treatment of chronic hepatitis C genotype 1a infection has not been established. In a study of SUNVEPRA and DAKLINZA combination therapy for 24 weeks in subjects with chronic HCV genotype 1 infection who were prior null responders to peginterferon alfa plus ribavirin, 2 (22%) of the 9 subjects with HCV genotype 1a infection had undetectable HCV RNA at post-treatment week 24.

SUNVEPRA in Combination with DAKLINZA, Peginterferon Alfa, and Ribavirin in Subjects with HCV Genotype 1 or 4

The efficacy and safety of SUNVEPRA in combination with DAKLINZA, peginterferon alfa, and ribavirin in the treatment of chronic HCV genotype 1 or 4 infection were evaluated in the single-arm, open-label phase 3 HALLMARK QUAD study (AI447029) in adults with compensated liver disease who were partial or null responders to therapy with peginterferon alfa 2a or 2b and ribavirin. Subjects received SUNVEPRA 100 mg twice daily, DAKLINZA 60 mg once daily, peginterferon alfa-2a 180 μg subcutaneously once weekly, and ribavirin 1000 mg per day (body weight less than 75 kg) or 1200 mg per day (at least 75 kg) in two divided doses for 24 weeks followed by 24 weeks of follow-up after completion of treatment or early discontinuation.

The 398 treated subjects in HALLMARK QUAD had a median age of 53 years (range: 19 to 76); 69% of the subjects were male; 76% were white, 12% were Asian, and 9% were black; 9% were Hispanic or Latino. The mean baseline HCV RNA level was 6.46 $\log_{10}$ IU/mL; 23% of subjects had compensated cirrhosis (Child-Pugh A); 89% had HCV genotype 1 and 11% had HCV genotype 4; 91% of subjects had non-CC IL28B genotype.

SVR, the primary endpoint, and outcomes for subjects who did not achieve SVR in HALLMARK QUAD are shown by patient population in Table 4. The demonstrated effectiveness of SUNVEPRA, DAKLINZA, peginterferon alfa and ribavirin treatment in HCV genotype 1 and 4 null responders indicates that this regimen is also expected to be effective in HCV genotype 1 and 4 subjects who are treatment-naive.

Table 4: Treatment Outcomes in HALLMARK QUAD, SUNVEPRA in Combination with DAKLINZA, Peginterferon Alfa, and Ribavirin in Subjects with HCV Genotype 1 or 4 Infection

Treatment outcomes	HCV Genotype 1 n=354	HCV Genotype 4 n=44
SVR12[a]		

Treatment outcomes	HCV Genotype 1 n=354	HCV Genotype 4 n=44
All	93% (330/354)	100% (44/44)
Prior partial responders	93% (111/120)	100% (10/10)
Prior null responders	94% (219/234)	100% (34/34)
With cirrhosis	90% (66/73)	100% (20/20)
No cirrhosis	94% (264/281)	100% (24/24)
Outcomes for subjects without SVR		
On-treatment virologic failure[b]	3% (12/354)	0/44
Relapse[c]	2% (8/337)	0/43
Missing post-treatment data	1% (4/354)	0/44

a [a] Missing HCV RNA data were imputed using the NVCB approach.

b On-treatment virologic failure includes subjects with virologic breakthrough (confirmed >1 $\log_{10}$ increase in HCV RNA over nadir or any confirmed HCV RNA ≥LLOQ after confirmed undetectable), those with confirmed HCV RNA ≥LLOQ at treatment Week 8, and those with detectable HCV RNA at end of treatment.

[b] Relapse rates are calculated with a denominator of subjects with undetectable HCV RNA at the end of treatment.

Response was rapid (98% of subjects had HCV RNA <LLOQ at Week 4). There were no differences in antiviral response due to gender, age, baseline HCV RNA level, presence or absence of baseline polymorphisms, IL28B allele status, or presence or absence of cirrhosis for patients in either genotype group.

Long-term Follow-up

Limited data are available from an ongoing follow-up study to assess durability of response up to 3 years after treatment with SUNVEPRA. Among 255 subjects who achieved SVR12 with SUNVEPRA and DAKLINZA with a median duration of post-SVR12 follow-up of approximately 8.5 months, 1 (<1%) relapse occurred. No relapses occurred among 31 subjects who achieved SVR12 with SUNVEPRA, DAKLINZA, peginterferon alfa, and ribavirin with a median duration of post-SVR12 follow-up of approximately 18 months.

INDICATIONS

SUNVEPRA (asunaprevir) is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) [see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION].

CONTRAINDICATIONS

SUNVEPRA is contraindicated in patients with previously demonstrated hypersensitivity to asunaprevir or any component of the product.

When SUNVEPRA is used in combination with DAKLINZA, peginterferon alfa, and ribavirin, the contraindications applicable to those medicinal products are applicable to the

combination regimen. Refer to the respective product information for a list of contraindications.

The combination of SUNVEPRA with DAKLINZA, peginterferon alfa, and ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant because of the risks of birth defects and foetal death associated with ribavirin.

SUNVEPRA is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score 7 or greater) and patients with decompensated liver disease [see PHARMACOLOGY - Special Populations].

SUNVEPRA is contraindicated in combination with :

- thioridazine, which is highly dependent on the cytochrome P450 enzyme 2D6 (CYP2D6) for clearance and for which elevated plasma concentrations are associated with serious ventricular arrhythmias and sudden death.
- drugs that strongly or moderately induce CYP3A and, thus, may lead to lower exposure and loss of efficacy of SUNVEPRA. This includes phenytoin, carbamazepine, oxcarbazepine, phenobarbital (anticonvulsants), rifampicin, rifabutin, (anti-infective agents), bosentan (endothelin receptor antagonist), dexamethasone (systemic glucocorticoid), St John's wort (*Hypericum perforatum*), efavirenz, etravirine, nevirapine (HIV non-nucleoside reverse transcriptase inhibitors) and modafinil (wakefulness promoting agent).
- drugs that strongly or moderately inhibit CYP3A and, thus, may lead to higher exposure and an increase in toxicity of SUNVEPRA. This includes itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole (antifungal agents), clarithromycin, erythromycin, (anti-infective agents), diltiazem, verapamil (calcium channel blockers) and atazanavir, darunavir/ritonavir, fosamprenavir, indinavir, lopinavir/ritonavir, ritonavir, saquinavir (HIV protease inhibitors) and cobicistat.
- drugs that strongly inhibit organic anion transporting polypeptide (OATP) 1B1 and, thus, may lead to lower liver concentrations and loss of efficacy of SUNVEPRA. This includes rifampicin (antimycobacterial agent), cyclosporin (immunosuppressant) and gemfibrozil (lipid lowering agent).

PRECAUTIONS

General

SUNVEPRA must not be administered as monotherapy [see INDICATIONS and DOSAGE AND ADMINISTRATION]. Warnings and precautions for DAKLINZA, peginterferon alfa, and ribavirin also apply when coadministered with SUNVEPRA.

Potential for Hepatotoxicity

For patients receiving SUNVEPRA-containing regimens, liver enzymes (ALT, AST) and bilirubin levels should be monitored at least once every 2 weeks for the initial 12 weeks of treatment, and every 4 weeks thereafter until completion of therapy.

Any upward trend in ALT or AST levels warrants more frequent monitoring. Treatment should be discontinued immediately and not be resumed in patients who experience:

- on-treatment elevations in ALT levels 10 times ULN or greater, or
- on-treatment elevations in both ALT levels greater than 5 times ULN and total bilirubin greater than 2 times ULN.

ALT and AST elevations were observed in phase 2 and 3 clinical trials of SUNVEPRA-containing regimens. In some cases, ALT/AST elevations were accompanied by hepatic dysfunction (suggested by concurrent elevations in total bilirubin), with or without pyrexia or eosinophilia. Severe drug-induced liver injury may occur with SUNVEPRA-containing regimens, as was observed in a patient with cirrhosis at week 6 of therapy in a clinical trial of asunaprevir and daclatasvir combined with an investigational non-nucleoside HCV NS5B inhibitor.

In clinical trials of SUNVEPRA combined with DAKLINZA or with DAKLINZA, peginterferon alfa, and ribavirin, the frequency of ALT and AST elevations at least 5 times upper limit of normal (ULN) was 3 to 4%, and the frequency of bilirubin elevations at least 2.6 times ULN was 1%. Frequencies of ALT/AST elevations were higher in trials of SUNVEPRA plus DAKLINZA conducted in Japan than in global trials of this regimen. In HALLMARK NIPPON, conducted in Japan, 7% of subjects had ALT greater than 5 times ULN while 2% of subjects in the global study HALLMARK DUAL had ALT greater than 5 times ULN. ALT/AST elevations in trials of SUNVEPRA and DAKLINZA had a median time to onset of 13 weeks after initiation of therapy (range: 4 to 24 weeks) and in most cases returned to normal limits despite continued therapy. These liver enzyme elevations were also reversible in subjects who discontinued therapy. Of 19 subjects treated with SUNVEPRA and DAKLINZA who discontinued study therapy due to elevated transaminases, 16 subjects achieved SVR.

Hepatic Impairment and Cirrhosis

No dose adjustment of SUNVEPRA is required for patients with mild hepatic impairment. In a pharmacokinetic study in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, asunaprevir steady state exposures were markedly higher in subjects with moderate or severe hepatic impairment [see PHARMACOLOGY - Special Populations]. SUNVEPRA is contraindicated for patients with moderate or severe hepatic impairment since an appropriate dose has not been established [see CONTRAINDICATIONS].

Of more than 1300 subjects in five clinical studies of SUNVEPRA combination therapy, 322 subjects had compensated cirrhosis (Child-Pugh A). No overall differences in safety or effectiveness were observed between subjects with compensated cirrhosis and subjects without cirrhosis. SUNVEPRA is contraindicated for patients with decompensated cirrhosis.

Liver Transplant Patients

The safety and efficacy of SUNVEPRA combination therapy in the treatment of patients who are pre-, peri-, or post-liver transplant have not been established.

Co-infection with Human Immunodeficiency Virus (HIV) or Hepatitis B Virus (HBV)

The safety and efficacy of SUNVEPRA in the treatment of chronic HCV infection in patients who are co-infected with HIV or HBV have not been established.

Renal Impairment

Dosage adjustment of SUNVEPRA to 100 mg once-daily is recommended for patients with severe renal impairment [creatinine clearance (CrCl) less than 30 mL/min] who are not receiving hemodialysis. No dosage adjustment of SUNVEPRA is required for the majority of renally impaired patients including those receiving hemodialysis or those with mild or moderate renal impairment (CrCl 30 mL/min or greater) [see DOSAGE AND ADMINISTRATION and PHARMACOLOGY - Special Populations].

Retreatment with SUNVEPRA

SUNVEPRA has not been studied in patients who have previously failed therapy with a treatment regimen that includes SUNVEPRA or other HCV NS3/4A protease inhibitors.

Oral Contraceptives

For patients using oral contraception, a high-dose oral contraceptive (containing at least 30 µg of ethinyl estradiol combined with norethindrone acetate/norethindrone) is recommended [see INTERACTIONS WITH OTHER MEDICINES].

Effects on Fertility

SUNVEPRA alone had no effects on fertility in male or female rats at any dose tested. The highest AUC values in unaffected males and females were 386- and 373-fold, respectively, the RHD AUC.

Use with DAKLINZA: DAKLINZA alone had no effects on fertility in male or female rats; reduced prostate/seminal vesicles weights, and minimally dysmorphic sperm were observed in males, but fertility was unaffected. Please refer to DAKLINZA Product Information.

Use with ribavirin and Peginterferon alfa: Ribavirin caused reversible testicular toxicity in animals; while peginterferon alfa may impair fertility in females. Please refer to Product Information for ribavirin and peginterferon alfa for additional information.

Use in Pregnancy

Use of SUNVEPRA with Peginterferon Alfa and Ribavirin (Pregnancy Category X):

Ribavirin may cause birth defects and/or death of the exposed fetus, and animal studies have shown that interferons have abortifacient effects. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant [see CONTRAINDICATIONS and PRECAUTIONS, and ribavirin prescribing information]. Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans. Refer also to the product information for peginterferon alfa and ribavirin.

Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately before initiation of therapy.

When SUNVEPRA is used in combination with DAKLINZA, peginterferon alfa, and ribavirin, women of childbearing potential and their male partners must use two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. If oral contraception is one of the forms of contraception, a high-dose oral contraceptive (containing at least 30 µg of ethinyloestradiol with norethisterone) is recommended.

SUNVEPRA and DAKLINZA (Pregnancy Category B3):

Studies of daclatasvir in animals have shown both maternal and embryofetal developmental toxicity at AUC levels above the recommended human dose (RHD). SUNVEPRA in combination with DAKLINZA should not be used during pregnancy or in women of childbearing potential not using contraception (refer to the prescribing information for DAKLINZA). For patients using oral contraception, a high-dose oral contraceptive (containing at least 30 μg of ethinyl estradiol combined with norethindrone acetate/norethindrone) is recommended [see INTERACTIONS WITH OTHER MEDICINES].

SUNVEPRA (Pregnancy Category B1):

Animal studies of asunaprevir alone do not indicate harmful effects with respect to reproductive toxicity; however, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Asunaprevir alone was not a selective developmental toxicant when administered to pregnant mice or rabbits during organogenesis at maternal doses associated with AUC values 472-fold (mouse) and 1.2-fold (rabbit) the AUC at the recommended human dose (RHD). Maternal toxicity was observed in one mouse at the highest dose. No maternal toxicities were evident in rabbits at any dose tested.

In a study of prenatal and postnatal development with asunaprevir alone in rats, developmental toxicity was not observed at doses up to 125 mg/kg/day, with AUC values 76-fold the RHD AUC. At the highest dose evaluated (400 mg/kg/day), both maternal and developmental toxicity were observed. Manifestations of developmental toxicity included reduced survival food consumption. The AUC value associated with this dose is 193-fold the RHD AUC.

Use in lactation

It is not known whether asunaprevir is excreted in human milk. Pharmacokinetic data in animals have shown excretion of asunaprevir/metabolites in milk. Mothers should be instructed not to breastfeed if they are taking SUNVEPRA. See also the product information for DAKLINZA, ribavirin and peginterferon alfa.

Paediatric use

Safety and effectiveness of SUNVEPRA in paediatric patients younger than 18 years of age have not been established.

Use in elderly

Of the 1300 subjects in five clinical studies of SUNVEPRA combination therapy, 275 were 65 years and over and 20 were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger patients. No dose adjustment of SUNVEPRA is required for elderly patients.

Genotoxicity

No evidence of asunaprevir mutagenic or clastogenic activity was observed in *in vitro* mutagenesis (Ames) tests, mammalian mutation assays in Chinese hamster ovary cells, or in an *in vivo* oral micronucleus study in rats.

See also the product information for ribavirin, peginterferon alfa, and daclatasvir.

Carcinogenicity

Asunaprevir was not carcinogenic in mice or rats given oral doses corresponding to approximately 350- and 54-times the human exposure (plasma AUC) at the MRHD of 200 mg/day, respectively.

See also the product information for ribavirin, peginterferon alfa, and daclatasvir.

INTERACTIONS WITH OTHER MEDICINES

Potential for Other Drugs to Affect SUNVEPRA

CYP3A is involved in the elimination of asunaprevir. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels of asunaprevir, and moderate or strong inhibitors of CYP3A may increase the plasma levels of asunaprevir.

Asunaprevir is also a substrate of P-gp, but coadministration of agents that modify P-gp activities alone (without concurrent effect on CYP3A) is unlikely to have a clinically meaningful effect on asunaprevir exposure.

OATP 1B1 and, to a lesser extent, 2B1 are involved in the liver distribution of asunaprevir. Therefore, strong inhibitors of OATP-mediated transport may increase the plasma concentrations of asunaprevir and decrease its therapeutic effect by reducing distribution to the liver.

See CONTRAINDICATIONS.

Potential for SUNVEPRA to Affect Other Drugs

Asunaprevir is a moderate inhibitor of CYP2D6 [see CONTRAINDICATIONS], an inhibitor of OATP 1B1/1B3- and P-gp-mediated transport, and a weak inducer of CYP3A. Caution should be used when SUNVEPRA is administered with substrates of these enzymes or transporters, with close clinical monitoring for both desired therapeutic outcomes and adverse reactions.

Established and Potentially Significant Drug Interactions

Refer to the respective product information of other medicinal products in the regimen for drug interaction information. The most conservative recommendation should be followed.

Table 5 provides clinical recommendations for established or potentially significant drug interactions between SUNVEPRA and other drugs. Clinically relevant increase in concentration is indicated as "↑" and clinically relevant decrease as "↓".

Table 5: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Anticoagulant		
Dabigatran etexilate	↑ Dabigatran etexilate	Close clinical monitoring is recommended when initiating therapy with SUNVEPRA in patients receiving dabigatran etexilate or other intestinal P-gp substrates that have a narrow therapeutic range.
Antidepressants, tricyclics		
Amitriptyline	↑ Amitriptyline	Close clinical monitoring is recommended when

Table 5: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Imipramine Nortriptyline	↑ Imipramine ↑ Nortriptyline	sensitive substrates of CYP2D6 with a narrow therapeutic range, including certain tricyclic antidepressants (TCA), are administered with SUNVEPRA. Plasma concentrations of the TCA may need to be monitored and the dose of the TCA reduced [see CONTRAINDICATIONS].
Antitussives		
Dextromethorphan	↑ Dextromethorphan[a]	Coadministration of SUNVEPRA, an inhibitor of CYP2D6, with dextromethorphan resulted in a 4-fold increase in the AUC of dextromethorphan. Close clinical monitoring is recommended when dextromethorphan or other sensitive substrates of CYP2D6 are administered with SUNVEPRA. Dose reduction of sensitive CYP2D6 substrates should be considered [see CONTRAINDICATIONS].
Cardiovascular agents		
Antiarrhythmic: Digoxin	↑ Digoxin[a]	Digoxin and other P-gp substrates with a narrow therapeutic range should be used with caution when administered with SUNVEPRA. The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Flecainide	↑ Flecainide	Close clinical monitoring is recommended when sensitive substrates of CYP2D6 with a narrow therapeutic range, such as flecainide or propafenone, are administered with SUNVEPRA. Dose reduction of sensitive CYP2D6 substrates should be considered [see CONTRAINDICATIONS].
Hormonal contraceptives		
Ethinyloestradiol + levonorgestrel Ethinyloestradiol + norethisterone	↓ Ethinyloestradiol [a] ↓ levonorgestrel [a]	For patients using oral contraception, a high-dose oral contraceptive (containing at least 30 µg of ethinyloestradiol with norethisterone) is recommended during treatment with SUNVEPRA.
Lipid lowering agents		
HMG-CoA reductase inhibitor: Rosuvastatin Atorvastatin Fluvastatin Simvastatin Pitavastatin Pravastatin	↑ Rosuvastatin[a] ↑ Atorvastatin ↑ Fluvastatin ↑ Simvastatin ↑ Pitavastatin ↑ Pravastatin	Treatment with rosuvastatin and other OATP1B1/1B3 substrates can be initiated at the recommended dose when coadministered with SUNVEPRA. Close clinical monitoring for both desired therapeutic outcomes and side effects of the OATP1B1/1B3 substrate is recommended.

Table 5: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Sedatives		
Benzodiazepine: Midazolam	↓ Midazolam[a]	Coadministration of SUNVEPRA with midazolam and other medicinal products that are highly dependent on CYP3A for elimination and for which reduced plasma concentrations may be associated with reduced therapeutic effect should be approached with caution.

[a] These interactions have been studied.
The direction of the arrow (↑ = *increase*, ↓ = *decrease*) indicates the direction of the change in pharmacokinetic parameters.

Other Drugs

Based on the results of drug interaction studies, no dose adjustment is recommended when SUNVEPRA is given with DAKLINZA, escitalopram, buprenorphine/naloxone, methadone, peginterferon alfa, ribavirin, sertraline, or caffeine and other CYP1A2 substrates, losartan and other CYP2C9 substrates, or omeprazole and other CYP2C19 substrates.

No clinically relevant interaction is anticipated for asunaprevir or the following concomitant medications: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs, eg, tenofovir, lamivudine), rilpivirine, raltegravir, dolutegravir, enfuvirtide, maraviroc, azithromycin, warfarin, phosphodiesterase type 5 (PDE-5) inhibitors (eg, sildenafil), angiotensin-converting enzyme (ACE) inhibitors (eg, enalapril), amiodarone, disopyramide, quinidine, famotidine, or antacids.

ADVERSE EFFECTS

Refer to the full product information for DAKLINZA, peginterferon alfa, and ribavirin for their associated adverse reactions.

Clinical Experience

The safety assessment of SUNVEPRA is based on data from 1316 subjects with chronic HCV infection who received SUNVEPRA 100 mg twice daily in combination with DAKLINZA or in combination with DAKLINZA, peginterferon alfa, and ribavirin in five clinical trials. The safety experience is presented by regimen.

SUNVEPRA in Combination with DAKLINZA

The safety of SUNVEPRA 100 mg twice daily in combination with DAKLINZA was assessed in 918 subjects with chronic HCV infection in four open-label clinical trials [HALLMARK DUAL (AI447028), HALLMARK NIPPON (AI447026), AI447017, AI447011]. Median duration of study therapy was up to 24 weeks.

The most common adverse events (frequency of 10% or greater) were headache (23%), fatigue (17%), diarrhoea (15%), nasopharyngitis (14%), and nausea (10%). Most adverse events were mild to moderate in severity.

Six percent of subjects experienced a serious adverse event (SAE). Three percent of subjects discontinued for adverse events; the most common adverse events leading to discontinuation were increased ALT and increased AST.

In the HALLMARK DUAL study during the first 12 weeks of treatment, rates of adverse reactions were similar between subjects treated with placebo and subjects treated with SUNVEPRA in combination with DAKLINZA.

SUNVEPRA in Combination with DAKLINZA, Peginterferon Alfa, and Ribavirin

The safety of SUNVEPRA 100 mg twice daily in combination with DAKLINZA, peginterferon alfa, and ribavirin was assessed in 398 subjects with chronic HCV genotype 1 or 4 infection in an open-label clinical trial [HALLMARK QUAD (AI447029)]. Median duration of study therapy was 24 weeks.

The most common adverse events (frequency of 15% or greater) were fatigue (42%), headache (31%), pruritus (26%), asthenia (24%), influenza-like illness and insomnia (each in 22%), rash (21%), anaemia (19%), cough (18%), dry skin (18%), diarrhoea (18%), nausea (17%), alopecia, irritability, and pyrexia (each in 16%), and myalgia (15%). Most adverse events experienced were mild to moderate in severity.

Six percent of subjects in HALLMARK QUAD experienced an SAE. Five percent of subjects discontinued for adverse events. The most common adverse events leading to discontinuation were rash, malaise, vertigo, and neutropenia.Adverse events occurring at frequency of 5% or greater in integrated data from 4 studies of SUNVEPRA in combination with DAKLINZA or in the HALLMARK QUAD study of SUNVEPRA in combination with DAKLINZA, peginterferon alfa, and ribavirin are presented in Table 6.

Table 6: Adverse Events Reported in ≥5% of Subjects in integrated data from 4 Clinical Trials of SUNVEPRA in Combination with DAKLINZA or in the HALLMARK QUAD study of SUNVEPRA in Combination with DAKLINZA, Peginterferon alfa and Ribavarin

Adverse Event	SUNVEPRA in Combination with DAKLINZA Percent with Adverse Event [a] n= 918	SUNVEPRA in Combination with DAKLINZA, Peginterferon Alfa, and Ribavirin Percent with Adverse Event[b] n= 398
General Disorders and Administration Site Conditions		
Fatigue	16.9	41.5
Asthenia	4.9	24.1
Influenza-like Illness	2.9	22.4
Pyrexia	6.2	16.1
Irritability	1.9	16.1
Pain	0.7	5.3
Gastrointestinal Disorders		
Diarrhoea	14.5	17.6
Nausea	10.1	16.6
Constipation	6.8	3.5
Abdominal Pain Upper	5.6	5.3

Adverse Event	SUNVEPRA in Combination with DAKLINZA Percent with Adverse Event [a] n= 918	SUNVEPRA in Combination with DAKLINZA, Peginterferon Alfa, and Ribavirin Percent with Adverse Event[b] n= 398
Nervous System Disorders		
Headache	23.2	31.2
Dizziness	5.9	8.0
Psychiatric Disorders		
Insomnia	6.5	22.4
Depression	2.3	8.5
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	6.3	10.1
Myalgia	5.1	15.3
Back Pain	4.7	7.3
Skin and Subcutaneous Tissue Disorders		
Pruritis	6.0	26.1
Rash	3.8	20.6
Dry Skin	2.6	17.8
Alopecia	3.8	16.1
Respiratory, Thoracic and Mediastinal Disorders		
Cough	6.3	18.3
Dyspnoea	2.1	12.3
Dyspnoea Exertional	0.5	5.3
Infections and Infestations		
Nasopharyngitis	13.7	1.5
Upper Respiratory Tract Infection	5.2	3.0
Blood and Lymphatic System Disorders		
Anaemia	1.1	19.3
Neutropenia	0.2	14.8
Thrombocytopenia	1.1	6.0
Investigations		
Increase in ALT	6.9	1.3
Weight Decreased	0.7	6.5
Metabolic and Nutrition Disorders		
Decreased Appetite	3.4	11.8
Eye Disorders		
Dry Eye	0.4	5.3

[a] Integrated data from studies HALLMARK DUAL, HALLMARK NIPPON, AI447017, and AI447011.

[b] Study HALLMARK QUAD

Less Common Adverse Reactions: Additional adverse reactions observed in clinical trials of SUNVEPRA in combination DAKLINZA occurring in less than 5% of subjects

are eosinophilia and increase in AST. These events have been included because of their seriousness or assessment of potential causal relationship to the regimen.

Potential for Hepatotoxicity

ALT and AST elevations were observed in phase 2 and 3 clinical trials of SUNVEPRA-containing regimens (see Table 7). In some cases, ALT/AST elevations were accompanied by hepatic dysfunction (suggested by concurrent increases in total bilirubin), with or without pyrexia or eosinophilia. Severe drug-induced liver injury may occur with SUNVEPRA-containing regimens, as was observed in a patient with cirrhosis at week 6 of therapy in a clinical trial of asunaprevir and daclatasvir combined with an investigational non-nucleoside HCV NS5B inhibitor in whom Grade 4 increase in ALT and increase in bilirubin was associated with hepatic encephalopathy [see PRECAUTIONS].

Laboratory Findings

Selected grade 3-4 laboratory abnormalities observed in HCV-infected subjects treated with SUNVEPRA combination therapy are presented in Table 7 [see PRECAUTIONS].

Table 7: Selected Grade 3-4 Laboratory Abnormalities in Clinical Trials of SUNVEPRA in Combination with DAKLINZA, with and without Peginterferon Alfa and Ribavirin

	Percent with Abnormality	
Parameter[a]	**SUNVEPRA in Combination with DAKLINZA n = 918[b]**	**SUNVEPRA in Combination with DAKLINZA, Peginterferon Alfa, and Ribavirin n = 398[c]**
ALT, increased ≥5.1x ULN	4%	3%
AST, increased ≥5.1x ULN	3%	3%
Total bilirubin, increased ≥2.6 x ULN	1%	1%

[a] Laboratory results were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0.
[b] Integrated data from studies HALLMARK DUAL, HALLMARK NIPPON, AI447017, and AI447011.
[c] Data from HALLMARK QUAD.

DOSAGE AND ADMINISTRATION

SUNVEPRA is for oral administration and may be taken with or without food.

The recommended dose of SUNVEPRA is 100 mg twice daily. SUNVEPRA must be administered in combination with DAKLINZA or with DAKLINZA, peginterferon alfa, and ribavirin. Recommended regimens and treatment duration are shown in Table 8. For specific dosage instructions for DAKLINZA, peginterferon alfa, and ribavirin, refer to the respective product information.

Table 8: Recommended Regimens for SUNVEPRA 100 mg Twice Daily Combination Therapy

HCV Genotype	Prior Treatment	Treatment	Duration
Genotype 1b	None, or failed peginterferon alfa/ribavirin	SUNVEPRA and DAKLINZA	24 weeks

HCV Genotype	Prior Treatment	Treatment	Duration
Genotype 1 or 4	None, or failed peginterferon alfa/ribavirin	SUNVEPRA, DAKLINZA, peginterferon alfa, and ribavirin	24 weeks

Dose Modification, Interruption and Discontinuation

Dose modification of SUNVEPRA or DAKLINZA is not recommended. Refer to the respective prescribing information for dose modification of peginterferon alfa and ribavirin. Treatment interruption should be avoided; however, if treatment interruption is necessary because of adverse reactions, neither SUNVEPRA nor DAKLINZA should be given as monotherapy. If resumption of therapy is considered, the risks and benefits should be carefully assessed [see PRECAUTIONS]. For the SUNVEPRA/DAKLINZA regimen, both drugs must be restarted at the same time.

Discontinuation of therapy is recommended for patients experiencing confirmed virologic breakthrough (greater than 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir).

Renal Impairment

For patients with severe renal impairment [creatinine clearance (CrCl) less than 30 mL/min] who are not receiving hemodialysis, the recommended dose of SUNVEPRA is 100 mg once daily. No dose adjustment of SUNVEPRA is required for the majority of renally impaired patients including those receiving hemodialysis or those with mild or moderate renal impairment (CrCl 30 mL/min or greater) [see PHARMACOLOGY].

OVERDOSAGE

There is limited clinical experience of overdose with SUNVEPRA. In phase 1 clinical trials, healthy subjects who received up to 300 mg twice daily (gelatin capsule) for up to 10 days had no unexpected adverse events. In clinical trials, asunaprevir doses higher than the recommended dose were associated with elevated liver enzymes.

There is no known antidote for overdose of SUNVEPRA. Treatment of overdose with SUNVEPRA should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Because asunaprevir is highly protein bound (>99%) and has a molecular weight greater than 700, dialysis is unlikely to significantly reduce plasma concentrations of the drug.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

SUNVEPRA is supplied as oval, opaque white to pale-yellow, soft gelatin capsules containing 100 mg of asunaprevir.

Capsules are imprinted with "BMS" in black on one line and "711" in black on a second line below "BMS" and filled with a clear solution. Capsules are packaged in PVC/PCTFE (Aclar)/Al blisters containing 14 and 56 capsules each.

Store SUNVEPRA capsules below 25°C. Protect from light. Keep in original container.

Attachment 1: Product information for AusPAR Sunvepra asunaprevir Bristol-Myers Squibb Australia Pty Ltd PM- 2014-00648-1-2 Final 14 December 2015. This Product Information was approved at the time this AusPAR was published.

NAME AND ADDRESS OF SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
Level 2, 4 Nexus Court
MULGRAVE VIC 3170

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF INCLUSION IN THE ARTG

25 May 2015

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