Attachment 1: Product information for AusPAR Daclatasvir Dihydrochloride Daklinza Bristol-Myers Squibb Australia Pty Ltd PM-2014-00647-1-2 Final 14 December 2015. This Product Information was approved at the time this AusPAR was published.

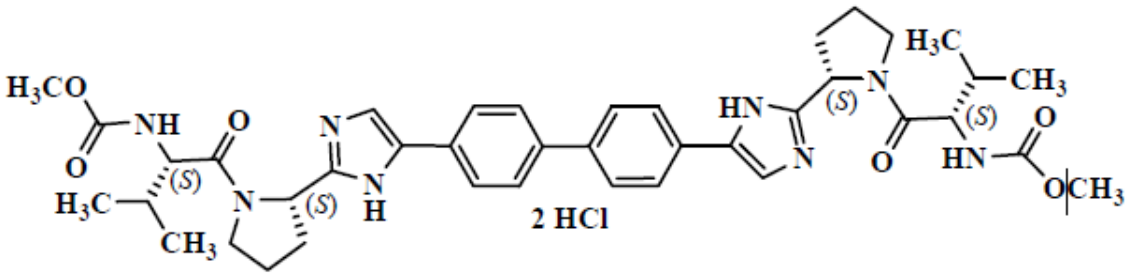
DAKLINZA®

daclatasvir

PRODUCT INFORMATION

NAME OF THE MEDICINE

DAKLINZA (daclatasvir), is a highly selective inhibitor of HCV nonstructural protein 5A (NS5A) replication complex. The chemical name for daclatasvir dihydrochloride is carbamic acid, *N,N'*-[[1,1'-biphenyl]-4,4'-diylbis[1*H*-imidazole-5,2-diyl-(2*S*)- 2,1-pyrrolidinediyl[(1*S*)-1-(1-methylethyl)-2-oxo-2,1-ethanediyl]]]bis-, *C,C'*-dimethyl ester, hydrochloride (1:2). Daclatasvir dihydrochloride has the following structural formula:



CAS number: 1009119-65-6

Molecular formula: $C_{40}H_{50}N_8O_6.2HCl$

Molecular weight: 738.88 (free base); 811.80 (dihydrochloride salt)

DESCRIPTION

Daclatasvir drug substance is white to yellow. Daclatasvir dihydrochloride is freely soluble in water.

DAKLINZA 60 mg tablets contain the inactive ingredients anhydrous lactose (116 mg), microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, and OPADRY complete film coating system 03B110007 Green (proprietary ingredient number109448).

DAKLINZA 30 mg tablets contain the inactive ingredients anhydrous lactose (58 mg), microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, and OPADRY complete film coating system 03B110005 Green (proprietary ingredient number109451).

Opadry green contains hypromellose, titanium dioxide, Macrogol 400, indigo carmine aluminum lake, and iron oxide yellow.

PHARMACOLOGY

Mechanism of Action

Daclatasvir is a direct acting antiviral agent (DAA) against the hepatitis C virus. Daclatasvir is an inhibitor of NS5A, a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir inhibits both viral RNA replication and virion assembly. *In vitro* and computer modelling data indicate that daclatasvir interacts with the N-terminus within Domain 1 of the protein, which may cause structural distortions that interfere with NS5A functions.

Antiviral Activity

Daclatasvir is a potent pan-genotypic NS5A replication complex inhibitor with effective concentration (50% reduction, EC_{50}) values from pM to low nM. EC_{50} values of daclatasvir range from 0.001 to 1.25 nM in genotype 1a, 1b, 3a, 4a, 5a, and 6a, and from 0.034 to 19 nM in genotype-2a cell-based replicon assays. In addition, daclatasvir inhibits infectious genotype 2a (JFH-1) virus with EC_{50} value of 0.020 nM. In HCV genotype 1a infected subjects, a single 60 mg dose of daclatasvir resulted in a 3.2 $\log_{10}$ IU/mL mean reduction in viral load measured after 24 hours.

Daclatasvir showed additive to synergistic interactions with interferon alfa, HCV NS3 protease inhibitors, HCV NS5B non-nucleoside inhibitors, and HCV NS5B nucleoside analogs in combination studies using the cell-based HCV replicon system. No antagonism of antiviral activity was observed.

Resistance

In cell culture

Substitutions conferring daclatasvir resistance in HCV genotypes 1-6 were selected in the cell-based replicon system and observed in the N-terminal 100 amino acid region of NS5A. L31V and Y93H were frequently observed resistance substitutions in genotype 1b, while M28T, L31V/M, Q30E/H/R, and Y93C/H/N were frequently observed resistance substitutions in genotype 1a. Single amino acid substitutions generally conferred low level resistance (EC_{50} <1 nM for L31V, Y93H) for genotype 1b, and higher levels of resistance for genotype 1a (up to 350 nM for Y93N). Resistance patterns observed in the clinic are very similar to patterns generated *in vitro* except that linked substitutions are more complex in clinical specimens.

The majority of wild-type HCV genotype 2a contain a pre-existing resistance substitution (L31M) with EC_{50} values of 9 to 19 nM. The most resistant variants with a single amino acid substitution were F28S (EC_{50} >500 nM) for genotype 2a, Y93H (EC_{50} >680 nM) for genotype 3a, L31F (EC_{50} 6.9 nM) for genotype 5a, and P32L (EC_{50} 250nM) for genotype 6a. Polymorphisms observed in wild-type HCV genotype 4a did not appear to impact the potency of daclatasvir (EC_{50} 0.007-0.013 nM), while variants at residues 30 and 93 showed resistance (EC_{50} <16 nM)

In clinical studies

Effect of Baseline HCV Polymorphisms on Treatment Response

Analyses were conducted to explore the association between naturally occurring baseline NS5A amino acid substitutions (polymorphisms) and treatment outcome. The impact of NS5A polymorphisms is regimen specific.

DAKLINZA in combination with asunaprevir (SUNVEPRA®): In a pooled analysis of treatment-naive and treatment-experienced HCV genotype 1b infected subjects from phase 2/3 clinical trials, the efficacy of DAKLINZA in combination with SUNVEPRA was reduced in subjects whose virus had NS5A sequence polymorphisms detected at 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. Among 863 HCV genotype 1b infected patients in phase 2/3 clinical trials with available NS5A sequence data, the prevalence of NS5A polymorphisms L31F/I/M/V or Y93H at baseline was 14%; 4% had virus with L31F/I/M/V without Y93H, 10% had virus with Y93H without L31F/I/M/V, and 0.5% had virus with L31F/I/M/V +Y93H. Of 127 virologic failures with baseline NS5A sequence data, 16% had L31F/I/M/V alone, 38% had Y93H alone, and 2% had L31F/I/M/V+Y93H.

DAKLINZA in combination with Sofosbuvir: Of 203 subjects with available baseline NS5A sequence data in study AI444040, 32 with pre-existing daclatasvir-resistant substitutions achieved SVR, while one subject infected with HCV genotype 3 (NS5A-A30K-S62I/V at baseline) experienced viral relapse [see CLINICAL TRIALS].

In an analysis of 147 patients with available baseline resistance data in ALLY-3 (Study AI444218), virus from 52% (76/147) of patients had baseline NS5A polymorphisms at resistance-associated positions (any change from reference at NS5A amino acid positions 28, 30, 31, 58, 62, 92, or 93) identified by population sequencing. Nine percent (13/147) of patients had NS5A-Y93H at baseline. For patients without baseline NS5A-Y93H, SVR12 rates were 92% (123/134) compared with 54% (7/13) for patients with this baseline polymorphism. For patients with baseline polymorphisms at NS5A residues other than Y93 (positions included M28, A30, L31, P58, S62, and E92), SVR12 rates were 91% (57/63) compared with 93% (66/71) in patients without these polymorphisms. Thirteen patients with Y93H at baseline were excluded from the non-Y93H analysis. The sofosbuvir resistance-associated substitution S282T was not detected in the baseline NS5B sequence of any patients in ALLY-3 by population-based sequencing.

DAKLINZA in combination with SUNVEPRA, Peginterferon alfa, and Ribavirin: Of 373 subjects with baseline NS5A sequence data in HALLMARK QUAD [see CLINICAL TRIALS], 42 had pre-existing daclatasvir-resistant substitutions. Of these 42 subjects, 38 achieved SVR12, 1 was a non-virologic failure, and 3 experienced virologic failure (1 genotype 1a had NS5A-L31M and 1 had NS5A-Y93F at baseline; 1 genotype 1b had NS5A-L31M at baseline).

Treatment-emergent resistance substitutions in subjects not achieving SVR

DAKLINZA in combination with SUNVEPRA: In a pooled analysis of HCV genotype 1b infected patients treated with DAKLINZA and SUNVEPRA, treatment-emergent NS5A amino acid substitutions were detected in the viruses from 116/117 (99%) patients who experienced virologic failure and had available resistance data (see Table 1). Most of these patients (105/117, 90%) had virus with treatment-emergent substitutions at NS5A amino acid positions L31 and/or Y93. Of 121 patients with available resistance data for both NS5A and NS3, 95 (79%) patients had virus with both D168 substitutions NS3 and L31 plus Y93H substitutions in NS5A.

DAKLINZA in combination with Sofosbuvir: Of 211 subjects from study AI444040 treated with DAKLINZA and sofosbuvir, there was a single genotype 3 subject with virologic relapse. NS5A resistance-associated substitutions observed at failure (A30K, S62I) were

also detected at baseline [see CLINICAL TRIALS]. NS5B resistance-associated substitutions were not detected by standard sequencing methods.

Of 152 HCV genotype 3 infected patients treated in the ALLY-3 trial, 17 experienced virologic failure. Post-baseline NS5A and NS5B sequencing data were available for virus from 17/17 and 16/17 patients, respectively. Virus from all 17 patients harboured one or more NS5A resistance-associated substitutions at A30K/S, L31I, S62A/L/P/T, and Y93H at failure. The most common substitution at failure was Y93H (15 patients), which was observed at baseline in 6 patients and emerged in 9 patients. For NS5B, 1 of 16 patients had virus with the emergent NS5B resistance-associated substitution S282T at failure.

DAKLINZA in combination with SUNVEPRA, Peginterferon alfa, and Ribavirin: Treatment-emergent NS5A amino acid substitutions were detected in the viruses of 17/17 (100%) HCV genotype 1a infected patients who experienced virologic failure with DAKLINZA, SUNVEPRA, peginterferon alfa, and ribavirin (see Table 1); 15/16 (94%) patients with available data had virus with treatment-emergent asunaprevir resistance-associated substitutions in NS3. Treatment-emergent substitutions at NS5A position Q30 were most commonly observed (88%, 15/17). A single HCV genotype 1b infected patient who experienced virologic failure had virus with treatment-emergent substitutions in NS5A and NS3.

Table 1: Treatment-Emergent NS5A Amino Acid Substitutions in Pooled Data from Phase 2 and Phase 3 Clinical Trials: Subjects who did not Achieve SVR with DAKLINZA and SUNVEPRA, with DAKLINZA and Sofosbuvir or with DAKLINZA, SUNVEPRA, Peginterferon Alfa, and Ribavirin

Treated Subjects	**DAKLINZA and SUNVEPRA**	**DAKLINZA, SUNVEPRA, Peginterferon Alfa, and Ribavirin**			**DAKLINZA and Sofosbuvir**
Category (%, n)	**Genotype 1b n = 141**	**Genotype 1a n= 23[a]**	**Genotype 1b n = 1[a]**	**Genotype 4 n= 0[a]**	**Genotype 1, 2, 3 n= 18**
Treated subjects with NS5A sequence	117	20	1	0	17
Emergent substitution at NS5A position 28, 29, 30, 31, 32, 54, 58, 62, 93	99 (116)	100 (17)	0	0	71 (12)
R30: G, H, P, Q	9 (11)	NA	0	NA	0
Q30: E, H, K, R	NA	88 (15)	NA	NA	0
L31: F, I, L, M, V	67 (78)	35 (6)	100 (1)	0	6 (1)
P58: A, G, S	10 (12)	NA	0	0	0
Y93: C, H, N	51 (60)	35 (6)	100 (1)	0	0
Y93H	50 (58)	12 (2)	100 (1)	0	53 (9)
Only Q30X [b]	NA	29 (5)	NA	NA	0

Q30 + other noted NS5A substitutions [c]	NA	59 (10)	NA	NA	0
L31X and Y93X [d]	28 (33)	0	100 (1)	0	0
GT-1b: L28M/T, P29S/Δ[e], P32F/L/Δ, Q54H, or Q62D	Less than 10%	0	0	0	0

[a] Of the 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 represents E, H, K, or R

[c] Other noted NS5A substitutions include M28T, L31M/V, E62V or Y93H/N

[d] X represents L31F, I, M or V and Y93H or N.

[e] Δ represents a deletion of the designated amino acid.

NA = not applicable

Persistence of Resistance-Associated Substitutions

Persistence of emergent NS5A resistance-associated substitutions was monitored post-treatment in subjects who failed daclatasvir containing regimens in phase 2/3 clinical trials. Among subjects treated with DAKLINZA and SUNVEPRA, emergent genotype 1b NS5A resistance-associated substitutions remained at detectable levels in all subjects monitored; 31 subjects only monitored at 24 weeks post-treatment and 9 subjects monitored for 36 weeks or more post treatment. No data on the persistence of daclatasvir resistance-associated substitutions are available from study ALLY-3. The long-term clinical impact of virus containing emergent daclatasvir resistant substitutions is unknown.

Cross-resistance

HCV replicons expressing daclatasvir-associated resistance substitutions remained fully sensitive to interferon alfa and other anti-HCV agents with different mechanisms of action, such as NS3 protease and NS5B polymerase inhibitors (nucleoside and non-nucleoside).

Pharmacokinetics

The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in subjects with chronic HCV. Following multiple oral doses of daclatasvir 60 mg once daily in combination with peginterferon alfa and ribavirin in HCV-infected subjects, the geometric mean (CV%) daclatasvir C_{max} was 1534 (58) ng/mL, AUC_{0-24h} was 14122 (70) ng•h/mL, and C_{min} was 232 (83) ng/mL.

Absorption

Daclatasvir administered as a tablet was readily absorbed following multiple oral doses with peak plasma concentrations occurring between 1 and 2 hours. Daclatasvir C_{max}, AUC, and C_{min} increased in an approximately dose-proportional manner. Steady state was achieved after 4 days of once-daily administration. At the 60 mg dose, exposure to daclatasvir was similar between healthy and HCV-infected subjects.

In vitro studies with human Caco-2 cells indicated that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.

In healthy subjects, administration of daclatasvir 60 mg tablet after a high-fat meal

(approximately 1000 kcal, approximately 50% from fat) decreased daclatasvir C_{max} and AUC by 28% and 23%, respectively, compared with administration under fasting conditions. Administration of daclatasvir 60 mg tablet after a light meal (approximately 275 kcal, approximately 15% from fat) resulted in no reduction in daclatasvir exposure [see DOSAGE AND ADMINISTRATION].

Distribution

At steady state, protein binding of daclatasvir in HCV-infected subjects was approximately 99% and independent of dose at the dose range studied (1 mg to 100 mg). In subjects who received daclatasvir 60 mg tablet orally followed by 100 μg [^{13}C,^{15}N]-daclatasvir intravenous dose, estimated volume of distribution at steady state was 47.1 L.

Metabolism

In vitro studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 the major CYP isoform responsible for the metabolism. No metabolites circulated at levels more than 5% of the parent concentration.

Excretion

Following single-dose oral administration of ^{14}C–daclatasvir in healthy subjects, 88% of total radioactivity was recovered in faeces (53% as unchanged drug) and 6.6% was excreted in the urine (primarily as unchanged drug). Following multiple-dose administration of daclatasvir in HCV-infected subjects, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 μg [^{13}C, ^{15}N]- daclatasvir intravenous dose, the total clearance was 4.24 L/h.

Special Populations

Hepatic Impairment

No dose adjustment of DAKLINZA is necessary for patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment [see PRECAUTIONS, Hepatic Impairment and Cirrhosis].

The pharmacokinetics of daclatasvir following a 30 mg single dose were studied in non-HCV infected subjects with mild, moderate, and severe hepatic impairment compared with unimpaired subjects. The C_{max} and AUC of total daclatasvir (free and protein-bound drug) were lower in subjects with hepatic impairment; however, hepatic impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir.

Renal Impairment

No dose adjustment of DAKLINZA is necessary for patients with any degree of renal impairment [see PRECAUTIONS, Renal Impairment]. Compared to non-HCV infected subjects with normal renal function [creatinine clearance (CLcr) of 90 mL/min, defined using the Cockcroft-Gault CLcr formula], the AUC of daclatasvir was estimated to be 26.4%, 59.8%, and 79.6% higher in subjects with CLcr values of 60, 30, and 15 mL/min, respectively. Daclatasvir unbound AUC was estimated to be 18.0%, 39.2%, and 51.2% higher for subjects with CLcr values of 60, 30, and 15 mL/min, respectively, relative to subjects with normal renal function. Subjects with end-stage renal disease requiring hemodialysis had a 26.9% increase in daclatasvir AUC and a 20.1% increase in unbound AUC compared to subjects with normal renal function. Population pharmacokinetic

analysis of data from clinical trials indicated that mild to moderate renal impairment had no clinically meaningful effect on the pharmacokinetics of daclatasvir. Daclatasvir is highly protein bound to plasma proteins and is unlikely to be removed by dialysis.

Elderly Patients

Population pharmacokinetic analysis of data from clinical trials indicated that age had no apparent effect on the pharmacokinetics of daclatasvir.

Paediatric and Adolescent

The pharmacokinetics of daclatasvir 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 daclatasvir.

Race

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

Pharmacodynamics

The effect of daclatasvir 60 mg and 180 mg on the QTc interval was evaluated in a randomized, partially blinded, placebo-controlled, positive-controlled thorough QT study in 56 healthy subjects. Single doses of 60 mg or 180 mg daclatasvir did not have a clinically relevant effect on QTc interval as corrected by Fridericia's method (QTcF). There was no significant relationship between increased daclatasvir plasma concentration and change in QTc. A daclatasvir dose of 180 mg is expected to bracket the highest plasma concentrations expected clinically.

CLINICAL TRIALS

The efficacy of DAKLINZA in combination with another oral agent has been evaluated in four phase 2/3 studies, in combination with SUNVEPRA (HALLMARK DUAL and HALLMARK NIPPON) and in combination with sofosbuvir, with or without ribavirin (AI444040 and ALLY-3). The efficacy and safety of DAKLINZA in combination with SUNVEPRA, peginterferon alfa, and ribavirin was 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 quantitation (LLOQ) at post-treatment Week 12.

DAKLINZA in Combination with SUNVEPRA 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 DAKLINZA 60 mg once daily in combination with SUNVEPRA 100 mg twice daily for 24 weeks or placebo for 12 weeks (placebo subjects were rolled over into another study and offered treatment with DAKLINZA in combination with SUNVEPRA for 24 weeks). Subjects in the null or

partial responder and intolerant/ineligible cohorts were treated with DAKLINZA 60 mg once daily in combination with SUNVEPRA 100 mg twice 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 DAKLINZA in combination with SUNVEPRA. 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, and 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 DAKLINZA in combination with SUNVEPRA.

SVR, the primary endpoint, and outcomes in 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.

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

Treatment outcomes	Treatment-Naive n=203	Failed Prior Therapy All (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/V[b]	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, IL28B allele, presence or absence of cirrhosis, or age in any of the treatment populations. SVR rates were consistently high across all categories of baseline viral load. Among subjects 65 and 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 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 DAKLINZA 60 mg once daily in combination with SUNVEPRA 100 mg twice 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: 24-75); 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 subjects 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.

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

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 from 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 SVR. 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, baseline HCV RNA level, IL28B allele, presence or absence of cirrhosis or age. Among subjects 65 years and older, 91% (81/89) achieved SVR and among subjects 75 years or older, 100% (4/4) achieved SVR.

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

The efficacy of DAKLINZA and SUNVEPRA combination therapy in the treatment of chronic hepatitis C genotype 1a infection has not been established. In a study of

DAKLINZA and SUNVEPRA 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.

DAKLINZA in Combination with Sofosbuvir

The efficacy and safety of DAKLINZA in combination with sofosbuvir in the treatment of patients with HCV infection were evaluated in two open-label randomized studies (AI444040 and ALLY-3).

In Study AI444040, 211 adults with HCV genotype 1, 2 or 3 infection and without cirrhosis received daclatasvir and sofosbuvir, with or without ribavirin. Among the 167 subjects with HCV genotype 1 infection, 126 were treatment naive and 41 had failed prior therapy with a protease inhibitor (PI) regimen (boceprevir or telaprevir). All 44 subjects with HCV genotype 2 or 3 infection were treatment-naive. The dose of DAKLINZA was 60 mg once daily and the dose of sofosbuvir was 400 mg once daily. Treatment duration was 12 weeks for 82 treatment-naive HCV genotype 1 subjects, and 24 weeks for the other 129 subjects (treatment-naive HCV genotype 1, 2, or 3 and genotype 1 subjects who had failed prior PI therapy). All subjects were followed for 48 weeks post-treatment. Among the 211 subjects, median age was 54 years (range: 20 to 70); 83% were white, 12% were black, 2% were Asian; and 20% were Hispanic or Latino. The mean score on the FibroTest (a validated non-invasive diagnostic assay for liver fibrosis status) for all 211 subjects was 0.460 (range: 0.03 to 0.89). Conversion of the FibroTest score to the corresponding METAVIR score suggests that 35% of all subjects (49% of subjects with prior PI failure, 30% of subjects with genotype 2 or 3) had F3 or greater liver fibrosis. Most subjects in this study (71%, including 98% of prior PI failures) had IL-28B rs12979860 non-CC genotypes.

SVR was achieved by 99% of subjects with HCV genotype 1, 96% of those with genotype 2, and 89% of those with genotype 3. Response was rapid (more than 97% of subjects had HCV RNA <LLOQ at Week 4) and was not influenced by HCV subtype (1a/1b), IL28B genotype, or use of ribavirin. Treatment-naive subjects with HCV genotype 1 who received 12 weeks of treatment had a similar response as those treated for 24 weeks.

While the addition of ribavirin to the regimen did not result in an increase in efficacy, the frequencies of adverse reactions commonly associated with ribavirin therapy (rash, cough, anaemia, dyspnoea, insomnia, and anxiety) were higher for subjects in this study who received ribavirin than for subjects who did not.

SVR12 and outcomes in subjects without SVR in AI444040 are shown by patient population in Tables 4 and 5.

Table 4: Treatment Outcomes, DAKLINZA in Combination with Sofosbuvir with or without Ribavirin in Subjects with HCV Genotype 1 in Study AI444040

	Treatment-naive			Prior telaprevir or boceprevir failures		
	DAKLINZA + sofosbuvir n=70	DAKLINZA + sofosbuvir + ribavirin n=56	All n=126	DAKLINZA + sofosbuvir n=21	DAKLINZA + sofosbuvir + ribavirin n=20	All n=41
SVR12 (overall)[a,b]	100% (70/70)	98% (55/56)	99% (125/126)	100% (21/21)	100% (20/20)	100% (41/41)

	Treatment-naive			Prior telaprevir or boceprevir failures		
	DAKLINZA + sofosbuvir n=70	**DAKLINZA + sofosbuvir + ribavirin n=56**	**All n=126**	**DAKLINZA + sofosbuvir n=21**	**DAKLINZA + sofosbuvir + ribavirin n=20**	**All n=41**
≥ F3 liver fibrosis	--	--	100% (41/41)	--	--	100% (20/20)
Outcomes for subjects without SVR						
Virologic breakthrough[c]	0	0	0	0	0	0
Relapse[c]	0	0	0	0	0	0
Missing post-treatment data	0	2% (1/56)	1% (1/126)	0	0	0
Outcomes (SVR) for Subjects with Multiple Baseline Factors						
Metavir F3/F4 fibrosis, IL28B non-C/C, HCV RNA >800,000 IU/mL			100% (17/17)			

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

[b] In study AI444040, 31 subjects received a 7 day lead-in with sofosbuvir monotherapy. When these subjects are excluded, SVR rates for treatment naive subjects with HCV genotype 1 are 99% (110/111).

[c] Virologic breakthrough was defined as confirmed increase in viral load of at least 1 log from nadir or any confirmed HCV RNA ≥LLOQ on or after treatment Week 8. Relapse was defined as HCV RNA ≥ LLOQ during follow-up after HCV RNA < LLOQ at end of treatment.

Table 5: Treatment Outcomes, DAKLINZA in Combination with Sofosbuvir with or without Ribavirin for 24 Weeks, Treatment-Naive Patients with HCV Genotype 2 or 3 in Study AI444040

	Genotype 2			Genotype 3		
	DAKLINZA + sofosbuvir n=17	**DAKLINZA + sofosbuvir + ribavirin n=9**	**All Genotype 2 n=26**	**DAKLINZA + sofosbuvir n=13**	**DAKLINZA + sofosbuvir + ribavirin n=5**	**All Genotype 3 n=18**
SVR12[a]	100% (17/17)	89% (8/9)	96% (25/26)	85% (11/13)	100%(5/5)	89% (16/18)
≥ F3 liver fibrosis	--	--	100% (8/8)	--	--	100% (5/5)
Outcomes for subjects without SVR						
Virologic breakthrough[c]	0	0	0	8% (1/13)	0	6% (1/18)
Relapse[c]	0	0	0	9% (1/11)	0	6% (1/16)
Missing post-treatment data	0	11% (1/9)	4% (1/26)	0	0	0
Outcomes (SVR) for Subjects with Multiple Baseline Factors						

Table 5: Treatment Outcomes, DAKLINZA in Combination with Sofosbuvir with or without Ribavirin for 24 Weeks, Treatment-Naive Patients with HCV Genotype 2 or 3 in Study AI444040

	Genotype 2			Genotype 3		
	DAKLINZA + sofosbuvir n=17	DAKLINZA + sofosbuvir + ribavirin n=9	All Genotype 2 n=26	DAKLINZA + sofosbuvir n=13	DAKLINZA + sofosbuvir + ribavirin n=5	All Genotype 3 n=18
Metavir F3/F4 fibrosis, IL28B non-C/C, HCV RNA >800,000 IU/mL			100% (1/1)			0

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

[b] In study AI444040, 31 subjects received a 7 day lead-in with sofosbuvir monotherapy. When these subjects are excluded, SVR rates are 94% (16/17) in subjects with HCV genotype 2 and 100% (11/11) in subjects with HCV genotype 3.

[c] Virologic breakthrough was defined as confirmed increase in viral load of at least 1 log from nadir or any confirmed HCV RNA ≥LLOQ on or after treatment Week 8. Relapse was defined as HCV RNA ≥ LLOQ during follow-up after HCV RNA < LLOQ at end of treatment.

Outcomes in Study AI444040 are expected to be applicable to a broader patient population because patients who failed peginterferon alfa and ribavirin, with or without telaprevir or boceprevir, are treatment-naive to DAKLINZA and sofosbuvir, and would be expected to achieve similar SVR rates as treatment-naive patients treated with DAKLINZA and sofosbuvir. These patient populations include HCV genotype 1 patients who failed prior treatment with peginterferon alfa and ribavirin. Among the 167 HCV genotype 1 subjects in the study, 17 subjects fit the profile associated with difficult-to-treat patients who typically fail treatment with peginterferon alfa and ribavirin (Metavir F3/F4 fibrosis, IL28B non-CC, and HCV RNA >800,000 IU/mL); all 17 subjects achieved SVR with DAKLINZA and sofosbuvir. Among the 41 HCV genotype 1 subjects who failed prior treatment with telaprevir or boceprevir in combination with peginterferon alfa and ribavirin, all 41 achieved SVR with DAKLINZA and sofosbuvir.

Outcomes in Study AI444040 with a regimen given for 24 weeks are also expected to be applicable to a duration of 12 weeks for most patients. Of 82 treatment-naive subjects with HCV genotype 1 who received 12 weeks of treatment, 99% achieved SVR with DAKLINZA and sofosbuvir. It is expected that similar outcomes would be applicable in patients with HCV genotype 1 infection who failed prior treatment with peginterferon alfa and ribavirin with or without telaprevir or boceprevir, since they are treatment naive to DAKLINZA and sofosbuvir.

Study ALLY-3 was a confirmatory phase 3 study in which the combination of daclatasvir and sofosbuvir administered for 12 weeks was evaluated in 152 adults infected with HCV genotype 3; 101 patients were treatment-naïve and 51 patients had failed prior antiviral therapy, including 7 patients who had received sofosbuvir and ribavirin. Median age was 55 years (range: 24 to 73); 90% of patients were white; 4% were black/African-American; 5% were Asian; 16% were Hispanic or Latino. Most patients (71%) had a high baseline viral load (HCV RNA level ≥800,000 IU/mL). Twenty-one percent of patients had compensated cirrhosis. Most patients (61%) had IL-28B rs12979860 non-CC genotypes.

SVR12 was achieved by 90% of treatment-naïve patients and 86% of treatment-experienced patients. Response was rapid (viral load at Week 4 showed that more than 95% of patients responded to therapy) and was not influenced by IL28B genotype. SVR12 rates were lower among patients with cirrhosis (see Table 6).

Table 6: Treatment outcomes, daclatasvir in combination with sofosbuvir for 12 weeks, patients with HCV genotype 3[a] in Study ALLY-3

	Treatment-naïve N=101	Treatment-experienced[b] N=51	Total N=152
End of treatment HCV RNA undetectable	100 (99%)	51 (100%)	151 (99%)
SVR12[c]	91 (90%)	44 (86%)	135 (89%)
No cirrhosis[d]	73/75 (97%)	32/34 (94%)	105/109 (96%)
With cirrhosis[d]	11/19 (58%)	9/13 (69%)	20/32 (63%)
Virologic failure[e]			
Virologic breakthrough	0	0	0
Relapse	9/100 (9%)	7/51 (14%)	16/151 (11%)

a All patients had HCV genotype 3a infection.

b Most of the treatment-experienced patients had received interferon-based therapy, but 7 patients received sofosbuvir + ribavirin and 2 patients received a cyclophilin inhibitor.

c Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ.

d Cirrhosis was determined by liver biopsy (METAVIR F4) for 14 patients, FibroScan >14.6 kPa for 11 patients or FibroTest score ≥0.75 and aspartate aminotransferase (AST): platelet ratio index (APRI) >2 for 7 patients. For 11 patients, cirrhosis status was missing or inconclusive (FibroTest score >0.48 to <0.75 or APRI >1 to ≤2). See PHARMACOLOGY, Resistance in Clinical Studies, for SVR rates by presence or absence of baseline polymorphisms.

e One treatment-naive patient with cirrhosis had detectable HCV RNA at end of treatment. Relapse was defined as confirmed HCV RNA ≥LLOQ during follow-up after HCV RNA undetectable at end of treatment.

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

The efficacy and safety of DAKLINZA in combination with SUNVEPRA, 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 DAKLINZA 60 mg once daily, SUNVEPRA 100 mg twice 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: 19-76); 69% of the subjects were male; 76% were white, 12% were Asian, 9% were black; 9% were Hispanic/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 in subjects without SVR in HALLMARK QUAD are shown by patient population in Table7. The demonstrated effectiveness of DAKLINZA/SUNVEPRA/peginterferon alfa/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 7: Treatment Outcomes in HALLMARK QUAD, DAKLINZA in Combination with SUNVEPRA, Peginterferon alfa, and Ribavirin in Subjects with HCV Genotype 1 or 4

Treatment outcomes	HCV Genotype 1 n=354	HCV Genotype 4 n=44
SVR12[a]		
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] 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 on or after treatment Week 8, and those with detectable HCV RNA at end of treatment.

[c] 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 in any of the treatment populations.

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 DAKLINZA. Among 255 subjects who achieved SVR12 with DAKLINZA and SUNVEPRA with a median duration of post-SVR12 follow-up of approximately 8.5 months, 1 (<1%) relapse occurred. No relapses occurred among 28 subjects who achieved SVR12 with DAKLINZA and sofosbuvir (± ribavirin) with a median duration of post-SVR12 follow-up of approximately 14.5 months or among 31 subjects who achieved SVR12 with DAKLINZA, SUNVEPRA, peginterferon alfa, and ribavirin with a median duration of post-SVR12 follow-up of approximately 18 months.

INDICATIONS

DAKLINZA 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

- DAKLINZA is contraindicated in patients with previously demonstrated hypersensitivity to daclatasvir or any component of the product.
- Since DAKLINZA is used in combination with other medicinal products, 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 DAKLINZA with 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 [see PRECAUTIONS].
- DAKLINZA is contraindicated in combination with drugs that strongly induce CYP3A4 and thus may lead to lower exposure and loss of efficacy of DAKLINZA. Contraindicated drugs include, but are not limited to, phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, dexamethasone and St John's wort *(Hypericum perforatum)* [see INTERACTIONS WITH OTHER MEDICINES].

PRECAUTIONS

General

DAKLINZA must not be administered as monotherapy. DAKLINZA must be administered in combination with other medicinal products for the treatment of chronic HCV infection [see INDICATIONS, CLINICAL TRIALS and DOSAGE AND ADMINISTRATION]. Warnings and precautions for other medicinal products in the regimen also apply when coadministered with DAKLINZA.

Potential for hepatotoxicity with SUNVEPRA-containing regimens

Drug-induced liver injury, in some cases severe, has been observed with SUNVEPRA-containing regimens. **See prescribing information for SUNVEPRA for hepatic monitoring recommendations.**

In DAKLINZA regimens that did not contain SUNVEPRA, the frequencies of clinically significant ALT or AST elevations were similar to frequencies among patients who received placebo.

Potential for drug interaction with amiodarone

Severe bradycardia has been observed in patients receiving amiodarone with DAKLINZA and sofosbuvir. Close monitoring is recommended if this medicinal product is administered with DAKLINZA and sofosbuvir. Refer to the amiodarone product information. (See ADVERSE EFFECTS - Postmarketing experience.)

Genotype-specific activity

The clinical data to support the use of DAKLINZA and sofosbuvir in patients infected with HCV genotype-2 are limited.

Hepatic Impairment and Cirrhosis

No dose adjustment of DAKLINZA is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment [see PHARMACOLOGY - Special Populations].

Of more than 2000 subjects in 12 clinical trials of DAKLINZA combination therapy, 375 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 [see CLINICAL TRIALS]. DAKLINZA combination therapy has not been studied in patients with decompensated cirrhosis.

Liver Transplant Patients

The safety and efficacy of DAKLINZA combination therapy in the treatment of patients who are pre-, peri-, or post-liver transplanthave not been established. There is limited experience from individual post- transplant case reports.

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

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

Renal Impairment

No dose adjustment of DAKLINZA is required for patients with any degree of renal impairment [see PHARMACOLOGY - Special Populations].

Retreatment with DAKLINZA

The efficacy of DAKLINZA as part of a retreatment regimen in patients with prior exposure to a NS5A inhibitor has not been established.

Effects on Fertility

Daclatasvir alone had no effects on fertility in male or female rats. The highest AUC value in unaffected females was 18-fold the exposure at the recommended human dose. In male rats, effects on reproductive endpoints were limited to reduced prostate/seminal vesicle

weights, and minimally increased dysmorphic sperm at 200 mg/kg/day (19-fold the exposure at the recommended human daily clinical dose); however, neither finding adversely affected fertility or the number of viable conceptuses sired.

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 DAKLINZA 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 prior to initiation of therapy.

When DAKLINZA is used in combination with 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.

DAKLINZA (Pregnancy Category B3)

There are no adequate and well-controlled studies in pregnant women. Studies of daclatasvir in animals have shown both maternal and embryofetal developmental toxicity at AUC levels above the recommended human dose (RHD). DAKLINZA should not be used during pregnancy or in women of childbearing potential not using contraception. Use of effective contraception should be continued for 5 weeks after completion of treatment.

Daclatasvir crosses the placenta in rats. Embryofetal development studies in rats and rabbits showed embryolethality, reduced fetal bodyweights, and fetal malformations at doses which were maternotoxic (mortality, adverse clinical signs, decreases in body weight and food consumption). Fetal malformations in rats included small and misshapen cerebrum, dilated cerebral ventricles, shortened lower jaws, incomplete ossification of parietals and frontals, enlarged fontanels, misshapen and/or fused sternebrae, and supernumerary hindlimb phalanges, at 25 times the RHD AUC. Additional malformations at the high-dose were absent or small or malpositioned eyes, dilated olfactory bulbs, imperforate or absent nasal openings, exencephaly, cleft lip and palate, polydactyly of fore- and hindlimbs, shortened upper jaw, misshapen tympanic annuli, fused nasals and premaxillae, and alterations to the pectoral girdle, sternebrae, vertebrae and ribs, at 52 times the RHD AUC. Fetal malformations in rabbits involved the ribs, and variations were increased in the head and skull, at 72 times the RHD AUC. At the respective NOAELs for both fetal and maternal toxicity, the daclatasvir AUC was 4 times (rats) and 16 times (rabbits) the RHD AUC. In a study of pre- and postnatal development in rats, there was neither maternal nor developmental toxicity at doses up to 50 mg/kg/day, associated with AUC values 2.6-fold the RHD AUC. At the highest dose tested (100 mg/kg/day), maternal toxicity included mortality and dystocia; developmental toxicity included slight reductions

in offspring viability in the peri- and neonatal periods; and reductions in birth weight that persisted into adulthood. The AUC value associated with this dose is 4.7-fold the RHD AUC.

Use in lactation

Treatment of rats with daclatasvir during pregnancy and lactation caused decreased pup body weight gain (see Use in Pregnancy).

It is not known whether daclatasvir is excreted in human milk. Daclatasvir was excreted into the milk of lactating rats with concentrations 1.7- to 2-fold maternal plasma levels. Mothers should be instructed not to breastfeed if they are taking DAKLINZA. See also the product information for ribavirin and peginterferon alfa.

Paediatric use

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

Use in elderly

Of more than 2000 subjects in clinical studies of DAKLINZA combination therapy, 310 were 65 years and older and 20 were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No dose adjustment of DAKLINZA is required for elderly patients.

Genotoxicity

Daclatasvir was not mutagenic or clastogenic in an in vitro mutagenesis (Ames bacterial mutagenicity) assay, a chromosome aberration assay in Chinese hamster ovary cells, or in an in vivo oral micronucleus study in rats.

See also the product information for ribavirin and peginterferon alfa.

Carcinogenicity

Daclatasvir was not carcinogenic in mice or rats at AUC values 8.7- and 4.7-fold the human exposure at the recommended daily human clinical dose of 60 mg/day, respectively.

See also the product information for ribavirin and peginterferon alfa.

INTERACTIONS WITH OTHER MEDICINES

Potential for Other Medicines to Affect DAKLINZA

Daclatasvir is a substrate of CYP3A4. Therefore, moderate or strong inducers of CYP3A4 may decrease the plasma levels and therapeutic effect of daclatasvir. See CONTRAINDICATIONS for drugs that are contraindicated for use with DAKLINZA due to potential loss of virologic activity.

Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir [see DOSAGE AND ADMINISTRATION and Table8]. Daclatasvir is also a substrate of P-glycoprotein transporter (P-gp), but coadministration of agents that modify P-gp activity alone (without concurrent effect on CYP3A4) is unlikely to have a clinically meaningful effect on daclatasvir exposure.

Potential for DAKLINZA to Affect Other Medicines

Daclatasvir is an inhibitor of P-glycoprotein transporter (P-gp), organic anion transporting polypeptide (OATP) 1B1 and 1B3, and breast cancer resistance protein (BCRP). Administration of DAKLINZA may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B1 or 1B3, or BCRP, which could increase or prolong their therapeutic effect and adverse reactions. Caution should be used if the medicinal product has a narrow therapeutic range.

Established and Potentially Significant Drug Interactions

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

Table 8 provides clinical recommendations for established or potentially significant drug interactions between DAKLINZA and other drugs. Clinically relevant increase in concentration is indicated as "↑" and clinically relevant decrease as "↓".

Table 8: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration [a]	Clinical Comment
Antibacterials		
Clarithromycin	Interaction not studied. *Expected due to CYP3A4 inhibition by the antibacterial* ↑ Daclatasvir	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with clarithromycin or other strong inhibitors of CYP3A4.
Erythromycin	Interaction not studied. *Expected due to CYP3A4 inhibition by erythromycin* ↑ Daclatasvir	Administration of DAKLINZA with erythromycin may result in increased concentrations of daclatasvir. Caution is advised.
Anticoagulants		
Dabigatran etexilate	Interaction not studied. *Expected due to inhibition of P-gp by daclatasvir* ↑ Dabigatran etexilate	Close clinical monitoring is recommended when initiating therapy with DAKLINZA in patients receiving dabigatran etexilate or other intestinal P-gp substrates that have a narrow therapeutic range.
HCV antiviral agents		
Boceprevir	Interaction not studied. *Expected due to CYP3A4 inhibition by boceprevir* ↑ Daclatasvir	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with boceprevir or other strong inhibitors of CYP3A4.
Telaprevir	↑ Daclatasvir*	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with telaprevir or other strong inhibitors of CYP3A4.

HIV or HBV antiviral agents		
Protease inhibitor: Atazanavir	↑ Daclatasvir*	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with atazanavir/ritonavir or other strong inhibitors of CYP3A4.
Non-nucleoside reverse transcriptase inhibitor (NNRTI): Efavirenz	↓ Daclatasvir*	The dose of DAKLINZA should be increased to 90 mg once daily when coadministered with efavirenz, etravirine, nevirapine or other moderate inducers of CYP3A4.
Etravirine Nevirapine	Interaction not studied. *Expected due to CYP3A4 induction by etravirine or nevirapine*	
Antifungals		
Ketoconazole	↑ Daclatasvir*	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with other strong inhibitors of CYP3A4.
Itraconazole Posaconazole Voriconazole	Interaction not studied. *Expected due to CYP3A4 inhibition by the antifungal:* ↑ Daclatasvir	
Fluconazole	Interaction not studied. *Expected due to CYP3A4 inhibition by the antifungal* ↑ Daclatasvir	Modest increases in concentrations of daclatasvir are expected, but no dose adjustment of DAKLINZA or fluconazole is required.
Cardiovascular agents		
Antiarrhythmic: Digoxin	↑ Digoxin*	Digoxin and other P-gp substrates with a narrow therapeutic range should be used with caution when coadministered with DAKLINZA . 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.
Amiodarone	Interaction not studied.	Close monitoring is recommended if amiodarone is administered with DAKLINZA + sofosbuvir. Refer to the amiodarone product information. (See ADVERSE EFFECTS - Postmarketing experience.)
Calcium channel blocker: Diltiazem Verapamil	Interaction not studied. *Expected due to CYP3A4 inhibition by the calcium channel blocker* ↑ Daclatasvir	Administration of DAKLINZA with diltiazem or verapamil may result in increased concentrations of daclatasvir. Caution is advised.
Lipid lowering agents		
HMG-CoA reductase inhibitor: Rosuvastatin	↑ Rosuvastatin*	Caution should be used DAKLINZA is coadministered with rosuvastatin or other substrates of OATP1B1, OATP1B3, or BCRP.
Atorvastatin Fluvastatin Simvastatin Pitavastatin Pravastatin	Interaction not studied. *Expected due to inhibition of OATP 1B1 and/or BCRP by daclatasvir:* ↑ concentration of statin	

* These interactions have been studied.

[a] 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 of DAKLINZA is recommended when DAKLINZA is given with SUNVEPRA, cyclosporin, escitalopram, ethinyloestradiol + levonorgestrel, ethinyloestradiol + norethisterone, famotidine, buprenorphine/naloxone, methadone, midazolam, omeprazole, peginterferon alfa, ribavirin, simeprevir, sofosbuvir, tacrolimus, tenofovir.

No clinically relevant effects on the pharmacokinetics of either medicinal product are expected when DAKLINZA is coadministered with any of the following: PDE-5 inhibitors, medicinal products in the ACE inhibitor class (eg, enalapril), medicinal products in the angiotensin II receptor antagonist class (eg, losartan, irbesartan, olmesartan, candesartan, valsartan), abacavir, alprazolam, azithromycin, ciprofloxacin, didanosine, disopyramide, dolutegravir, emtricitabine, enfuvirtide, flecainide, lamivudine, maraviroc, mexiletine, mycophenolate mofetil, propafenone, quinidine, raltegravir, rilpirivine, sirolimus, stavudine, triazolam, warfarin, zidovudine or antacids.

ADVERSE EFFECTS

DAKLINZA must be administered with other drugs for the treatment of HCV infection. Refer to their respective product information for their associated adverse reactions.

Clinical Experience

The overall safety profile of DAKLINZA is based on data from 1679 patients with chronic HCV infection who received DAKLINZA 60 mg once daily in combination with SUNVEPRA (n=918), sofosbuvir with or without ribavirin (n=363, pooled data), or SUNVEPRA, peginterferon alfa, and ribavirin (n=398) in 6 clinical trials. Safety experience is presented by regimen.

All-Oral Regimens

DAKLINZA in combination with SUNVEPRA: The safety of DAKLINZA 60 mg once daily in combination with SUNVEPRA 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 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 DAKLINZA in combination with SUNVEPRA.

DAKLINZA in combination with sofosbuvir: The safety of DAKLINZA 60 mg once daily in combination with sofosbuvir (with or without ribavirin) was assessed in two open-

label randomized clinical trials (AI444040 and ALLY-3) in 363 subjects with chronic HCV genotype 1, 2, or 3 infection. Subjects were treated for 12 or 24 weeks.

The most common adverse events (frequency of 10% or greater) were fatigue (30%), headache (25%), and nausea (16%). Most adverse events experienced were mild to moderate in severity. Four percent of subjects experienced a serious adverse event. Two subjects discontinued for adverse events.

The frequencies of adverse reactions commonly associated with ribavirin therapy (rash, cough, anaemia, dyspnoea, insomnia, and anxiety) were higher for subjects who received ribavirin than for subjects who did not.

DAKLINZA in Combination with SUNVEPRA, Peginterferon Alfa, and Ribavirin

The safety of DAKLINZA 60 mg once daily in combination with SUNVEPRA, 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 DAKLINZA in combination with SUNVEPRA, in Study AI444040 of DAKLINZA in combination with sofosbuvir, or in the HALLMARK QUAD study of DAKLINZA in combination with SUNVEPRA, peginterferon alfa, and ribavirin are presented in Table9.

Table 9: Adverse Events Reported in ≥5% of Subjects in integrated data from 4 Clinical Trials of DAKLINZA in Combination with SUNVEPRA, from 2 Clinical Trials of DAKLINZA in Combination with Sofosbuvir, and in the HALLMARK QUAD study of DAKLINZA in Combination with SUNVEPRA, Peginterferon alfa and Ribavarin

Adverse Event	DAKLINZA in Combination with SUNVEPRA Percent with Adverse Event [a] n= 918	DAKLINZA and Sofosbuvir		DAKLINZA, SUNVEPRA, Peginterferon Alfa, and Ribavirin Percent with Adverse Event[c] n= 398
		With or Without Ribavirin Percent with Adverse Event[b] n= 363	Without Ribavirin Percent with Adverse Event[b] n=273	
General Disorders and Administration Site Conditions				
Fatigue	16.9	29.5	27.1	41.5

Adverse Event	DAKLINZA in Combination with SUNVEPRA Percent with Adverse Event [a] n= 918	DAKLINZA and Sofosbuvir		DAKLINZA, SUNVEPRA, Peginterferon Alfa, and Ribavirin Percent with Adverse Event[c] n= 398
		With or Without Ribavirin Percent with Adverse Event[b] n= 363	Without Ribavirin Percent with Adverse Event[b] n=273	
Asthenia	4.9	0.6	0.7	24.1
Influenza-like Illness	2.9	1.9	1.8	22.4
Pyrexia	6.2	1.4	1.1	16.1
Pain	0.7	1.7	1.5	5.3
Gastrointestinal Disorders				
Diarrhoea	14.5	9.4	8.4	17.6
Nausea	10.1	16.3	14.7	16.6
Constipation	6.8	4.7	2.2	3.5
Abdominal Pain Upper	5.6	3.9	2.2	5.3
Flatulence	2.7	4.7	4.8	0.8
Gastrooesophageal Reflux Disease	2.1	3.6	2.2	1.5
Nervous System Disorders				
Headache	23.2	24.8	23.1	31.2
Dizziness	5.9	5.8	4.4	8.0
Psychiatric Disorders				
Insomnia	6.5	7.7	6.2	22.4
Depression	2.3	3.6	2.6	8.5
Anxiety	2.0	4.1	2.9	3.3
Irritability	1.9	2.5	1.8	16.1

Musculoskeletal and Connective Tissue Disorders				
Arthralgia	6.3	8.0	8.1	10.1
Myalgia	5.1	4.1	4.0	15.3
Back Pain	4.7	6.3	5.9	7.3
Skin and Subcutaneous Tissue Disorders				
Pruritus	6.0	4.4	2.6	26.1
Rash	3.8	3.0	1.8	20.6
Dry Skin	2.6	1.9	0	17.8
Alopecia	3.8	2.5	2.2	16.1
Respiratory, Thoracic and Mediastinal Disorders				
Cough	6.3	6.3	2.6	18.3
Dyspnoea	2.1	3.6	1.5	12.3
Dyspnoea Exertional	0.5	1.1	0	5.3
Infections and Infestations				
Nasopharyngitis	13.7	5.0	5.9	1.5
Upper Respiratory Tract Infection	5.2	5.5	4.4	3.0
Urinary Tract Infection	2.1	3.0	3.7	2.0
Blood and Lymphatic System Disorders				
Anaemia	1.1	3.6	0	19.3
Neutropenia	0.2	0	0	14.8
Thrombocytopenia	1.1	0	0	6.0
Investigations				
Increase in ALT	6.9	0	0	1.3
Weight Decreased	0.7	0.8	0.4	6.5
Metabolic and Nutrition Disorders				
Decreased Appetite	3.4	1.9	1.1	11.8
Eye Disorders				
Dry Eye	0.4	0.8	0.4	5.3

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

[b] Integrated data from Study AI444040 and ALLY-3.

[c] Study HALLMARK QUAD.

Less Common Adverse Reactions: Additional adverse reactions observed in clinical trials of DAKLINZA combination therapy with SUNVEPRA or sofosbuvir occurring in less than 5% of subjects are eosinophilia and increased AST. These events have been included because of their seriousness or assessment of potential causal relationship to the regimen.

Postmarketing Experience

Cardiac arrhythmias

Cardiac arrhythmias including severe bradycardia have been observed in patients receiving amiodarone with DAKLINZA and sofosbuvir. Close monitoring is recommended if amiodarone is administered with DAKLINZA and sofosbuvir. Refer to the amiodarone product information. (See INTERACTIONS WITH OTHER MEDICINES.)

Laboratory Findings

Selected treatment-emergent grade 3-4 laboratory abnormalities observed in HCV-infected subjects treated with DAKLINZA combination therapy are presented in Table 10.

Table 10: Selected Treatment-Emergent Grade 3-4 Laboratory Abnormalities in Clinical Trials of DAKLINZA in Combination with SUNVEPRA or with Sofosbuvir

Parameter[a]	Percent with Abnormality		
	DAKLINZA in Combination with SUNVEPRA [b] n= 918	**DAKLINZA and Sofosbuvir (with or without Ribavirin) n= 363[c]**	**DAKLINZA, SUNVEPRA, Peginterferon Alfa, and Ribavirin n=398**
ALT, increased (≥5.1× ULN)	4%	0	3%
AST, increased (≥5.1×ULN)	3%	0	3%
Total bilirubin, increased (≥2.6× ULN)	1%	0	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] Studies AI444040 and ALLY-3.

DOSAGE AND ADMINISTRATION

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

The recommended dose of DAKLINZA is 60 mg once daily. DAKLINZA must be administered in combination with other agents [see Table 11]. For specific dose recommendations for other agents in the regimen, refer to the respective prescribing information.

Table 11: Recommended Regimens with DAKLINZA 60 mg Once Daily Combination Therapy

HCV Genotype	Prior Treatment	Treatment	Duration
Genotype 1	None, or failed peginterferon alfa/ribavirin	DAKLINZA and sofosbuvir [a]	12 weeks
Genotype 1	Failed protease inhibitor and peginterferon /ribavirin	DAKLINZA and sofosbuvir	24 weeks
Genotype 1b	None, or failed peginterferon alfa/ribavirin	DAKLINZA and SUNVEPRA	24 weeks
Genotype 3	None, or failed sofosbuvir/ribavirin or peginterferon alfa/ribavirin	DAKLINZA and sofosbuvir	12 weeks [b]
Genotype 1 or 4	None, or failed peginterferon alfa/ribavirin	DAKLINZA , SUNVEPRA, peginterferon alfa, and ribavirin	24 weeks

[a] Consider adding ribavirin to the DAKLINZA/sofosbuvir 12-week regimen or prolonging treatment duration to 24 weeks for patients with cirrhosis.

[b] Consider prolonging treatment duration to 24 weeks for patients with cirrhosis.

Dose Modification, Interruption, and Discontinuation

Once therapy is started, dose modification of DAKLINZA is not recommended. Treatment interruption should be avoided; however, if treatment interruption of any agent in the regimen is necessary because of adverse reactions, DAKLINZA should not be given as monotherapy.

Discontinuation of therapy is recommended for patients experiencing confirmed virologic breakthrough (greater than 1 log10 IU/mL increase in HCV RNA from nadir).

Concomitant therapy

***Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)*:** The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with strong inhibitors of CYP3A4 (using the 30 mg tablet; DAKLINZA tablets should not be broken). See INTERACTIONS WITH OTHER MEDICINES. Coadministration with strong or moderate CYP3A4 inhibitors is contraindicated with regimens that include SUNVEPRA.

***Moderate inducers of CYP3A4*:** The dose of DAKLINZA should be increased to 90 mg once daily (three 30 mg tablets or one 60 mg and one 30 mg tablet) when coadministered with moderate inducers of CYP3A4 [see INTERACTIONS WITH OTHER MEDICINES]. Coadministration with moderate CYP3A4 inducers is contraindicated with regimens that include SUNVEPRA.

OVERDOSAGE

There is limited clinical experience with overdose of DAKLINZA. In phase 1 clinical trials, healthy subjects who received up to 100 mg for up to 14 days or single doses up to 200 mg had no unexpected adverse events.

There is no known antidote for overdose of DAKLINZA. Treatment of overdose with DAKLINZA should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Because daclatasvir is highly protein

bound (>99%) and has a molecular weight greater than 500, 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

DAKLINZA is supplied as tablets containing 60 mg daclatasvir (equivalent to 66 mg daclatasvir dihydrochloride) or 30 mg daclatasvir (equivalent to 33 mg daclatasvir dihydrochloride).

DAKLINZA tablets are supplied in PVC/PCTFE (Aclar)/Al blister packs and are available in two strengths:

- 60 mg daclatasvir tablets are light green biconvex pentagonal debossed with "BMS" on one side and "215" on the other side. Available in packs of 7 and 28 tablets.
- 30 mg daclatasvir tablets are green biconvex pentagonal debossed with "BMS" on one side and "213" on the other side. Available in packs of 7 and 28 tablets.

Store DAKLINZA tablets below 30° C.

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 June 2015

DAKLINZA® and SUNVEPRA® are registered trademarks of Bristol-Myers Squibb