HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DAKLINZA safely and effectively. See full prescribing information for DAKLINZA.

DAKLINZA™ (daclatasvir) tablets, for oral use

Initial U.S. Approval: 2015

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	2/2016
Dosage and Administration, Testing Prior to Initiation of Therapy (2.1)	2/2016
Dosage and Administration, Recommended Dosage (2.2)	2/2016
Contraindications (4)	2/2016
Warnings and Precautions, Risks Associated with Ribavirin Combination Treatment (5.3)	2/2016

---------- INDICATIONS AND USAGE ----------

DAKLINZA is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir, with or without ribavirin, for the treatment of chronic HCV genotype 1 or 3 infection. (1)

Limitations of Use:

- Sustained virologic response (SVR12) rates are reduced in genotype 3 patients with cirrhosis receiving DAKLINZA in combination with sofosbuvir for 12 weeks. (14)

----------DOSAGE AND ADMINISTRATION ----------

- Testing prior to initiation: HCV genotype 1a with cirrhosis, consider testing for the presence of virus with NS5A resistance-associated polymorphisms. (2.1)
- 60 mg taken orally once daily with or without food in combination with sofosbuvir with or without ribavirin. (2.2)
- Recommended treatment duration: 12 weeks. (2.2)
- Dose modification: Reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------

- Tablets: 60 mg, 30 mg, and 90 mg (3)

---------- CONTRAINDICATIONS ----------

- Strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Bradycardia When Coadministered with Sofosbuvir and Amiodarone: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent, including DAKLINZA (daclatasvir), particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended. (5.2, 6.2, 7.3)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (≥10%) observed with DAKLINZA in combination with sofosbuvir were headache and fatigue. (6.1)

Most common adverse reactions (≥10%) observed with DAKLINZA in combination with sofosbuvir and ribavirin were headache, anemia, fatigue, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------

- Drug Interactions: Coadministration of DAKLINZA can alter the concentration of other drugs and other drugs may alter the concentration of daclatasvir. Consult the full prescribing information before use for contraindicated drugs and other potential drug-drug interactions. (2.3, 4, 5.1, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DAKLINZA is indicated for use with sofosbuvir, with or without ribavirin, for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1 or genotype 3 infection [*see Dosage and Administration (2) and Clinical Studies (14)*].

Limitations of Use:

- Sustained virologic response (SVR12) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving DAKLINZA in combination with sofosbuvir for 12 weeks [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of Therapy

NS5A Resistance Testing in HCV Genotype 1a-Infected Patients with Cirrhosis: Consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93 in patients with cirrhosis who are infected with HCV genotype 1a prior to the initiation of treatment with DAKLINZA and sofosbuvir with or without ribavirin [*see Microbiology (12.4), Table 11*].

2.2 Recommended Dosage

The recommended dosage of DAKLINZA is 60 mg, taken orally, once daily, with or without food [*see Clinical Pharmacology (12.3)*].

Table 1 provides the recommended DAKLINZA-containing treatment regimens and duration based on HCV genotype and patient population. The optimal duration of DAKLINZA and sofosbuvir with or without ribavirin has not been established for HCV genotype 3 patients with cirrhosis or for HCV genotype 1 patients with Child-Pugh C cirrhosis [*see Clinical Studies (14.2, 14.4)*].

For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 1 [*see Clinical Studies (14)*]. Refer to *Drug Interactions (7)* for dosage recommendations for concomitant HIV-1 antiviral drugs.

For specific dosage recommendations for sofosbuvir, refer to the prescribing information.

For HCV genotype 1 or 3 patients with Child-Pugh B or C cirrhosis or post-transplantation patients, the starting dose of ribavirin is 600 mg once daily, increasing up to 1000 mg daily as tolerated. The starting dose and on-treatment dose of ribavirin can be decreased based on hemoglobin and creatinine clearance.

For HCV genotype 3 patients with compensated cirrhosis (Child-Pugh A), the recommended dosing of ribavirin is based on weight (1000 mg for patients weighing less than 75 kg and 1200 mg for those weighing at least 75 kg administered orally in two divided doses with food).

Table 1: Recommended Treatment Regimen and Duration for DAKLINZA in Patients with Genotype 1 or 3 HCV

	Patient Population	Treatment and Duration
Genotype 1	Without cirrhosis	DAKLINZA + sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) cirrhosis	
	Decompensated (Child-Pugh B or C) cirrhosis	DAKLINZA + sofosbuvir + ribavirin for 12 weeks
	Post-transplant	
Genotype 3	Without cirrhosis	DAKLINZA + sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis	DAKLINZA + sofosbuvir + ribavirin for 12 weeks
	Post-transplant	

2.3 Dosage Modification Due to Drug Interactions

Refer to the drug interactions and contraindications sections for other drugs before coadministration with DAKLINZA.

Table 2: Recommended DAKLINZA Dosage Modification with CYP3A Inhibitors and Inducers

Concomitant Drugs	DAKLINZA Dosage
Strong CYP3A inhibitors and certain HIV antiviral agents *[see Drug Interactions (7.3)]*	30 mg once daily
Moderate CYP3A inducers and nevirapine *[see Drug Interactions (7.3)]*	90 mg once daily
Strong CYP3A inducers *[see Contraindications (4)]*	Contraindicated

Dosage reduction of DAKLINZA for adverse reactions is not recommended.

2.4 Discontinuation of Therapy

If sofosbuvir is permanently discontinued in a patient receiving DAKLINZA with sofosbuvir, then DAKLINZA should also be discontinued.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 60 mg: 60 mg of daclatasvir (equivalent to 66 mg daclatasvir dihydrochloride), light green, biconvex, pentagonal, and debossed with “BMS” on one side and “215” on the other side.
- 30 mg: 30 mg of daclatasvir (equivalent to 33 mg daclatasvir dihydrochloride), green, biconvex, pentagonal, and debossed with “BMS” on one side and “213” on the other side.
- 90 mg: 90 mg of daclatasvir (equivalent to 99 mg daclatasvir dihydrochloride), light green, biconvex, round, and embossed with “BMS” on one side and “011” on the other side.

4 CONTRAINDICATIONS

- When DAKLINZA is used in combination with other agents, the contraindications applicable to those agents are applicable to the combination regimen. Refer to the respective prescribing information for a list of contraindications.
- DAKLINZA is contraindicated in combination with drugs that strongly induce CYP3A and, thus, may lead to lower exposure and loss of efficacy of DAKLINZA. Contraindicated drugs include, but are not limited to those listed in Table 3 [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

Table 3: Drugs that are Contraindicated with DAKLINZA

Drug Class	Drugs Within Class that are Contraindicated with DAKLINZA[a]	Clinical Comments
Anticonvulsants	phenytoin, carbamazepine	May lead to loss of virologic response to DAKLINZA
Antimycobacterial agents	rifampin	
Herbal products	St. John’s wort (*Hypericum perforatum*)	

[a] This table is not a comprehensive list of all drugs that strongly induce CYP3A.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of DAKLINZA and other drugs may result in known or potentially significant drug interactions, some of which may lead to [*see Contraindications (4) and Drug Interactions (7)*]:

- loss of therapeutic effect of DAKLINZA and possible development of resistance,
- dosage adjustments of concomitant medications or DAKLINZA,
- possible clinically significant adverse reactions from greater exposures of concomitant drugs or DAKLINZA.

See Table 3 for drugs contraindicated with DAKLINZA due to loss of efficacy and possible development of resistance [*see Contraindications (4)*]. See Table 7 for steps to prevent or manage other possible and known significant drug interactions [*see Drug Interactions (7)*]. Consider the potential for drug interactions before and during DAKLINZA therapy, review concomitant medications during DAKLINZA therapy, and monitor for the adverse reactions associated with the concomitant drugs.

5.2 Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with another HCV direct-acting antiviral, including DAKLINZA. A fatal cardiac arrest was reported in a patient receiving a sofosbuvir-containing regimen (ledipasvir/sofosbuvir). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this bradycardia effect is unknown.

Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. For patients taking amiodarone who have no alternative treatment options and who will be coadministered DAKLINZA and sofosbuvir:

- Counsel patients about the risk of serious symptomatic bradycardia.
- Cardiac monitoring in an inpatient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking sofosbuvir in combination with DAKLINZA who need to start amiodarone therapy due to no other alternative treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone’s long elimination half-life, patients discontinuing amiodarone just prior to starting sofosbuvir in combination with DAKLINZA should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion, or memory problems [*see Adverse Reactions (6.2) and Drug Interactions (7.3), Table 7*].

5.3 Risks Associated with Ribavirin Combination Treatment

If DAKLINZA and sofosbuvir are administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.

6 ADVERSE REACTIONS

If DAKLINZA and sofosbuvir are administered with ribavirin, refer to the prescribing information for ribavirin regarding ribavirin-associated adverse reactions.

The following serious adverse reaction is described below and elsewhere in the labeling:

- Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone [*see Warnings and Precautions (5.2)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Approximately 2400 subjects with chronic HCV infection have been treated with the recommended dose of DAKLINZA in combination with other anti-HCV drugs in clinical trials. Six hundred seventy-nine subjects have received a DAKLINZA and sofosbuvir-based regimen. Safety experience from three clinical trials of DAKLINZA and sofosbuvir with or without ribavirin is presented.

DAKLINZA and Sofosbuvir

In the ALLY-3 trial, 152 treatment-naive and treatment-experienced subjects with HCV genotype 3 infection were treated with DAKLINZA 60 mg once daily in combination with sofosbuvir for 12 weeks. The most common adverse reactions (frequency of 10% or greater) were headache and fatigue. All adverse reactions were mild to moderate in severity. No subjects discontinued therapy for adverse events.

In the ALLY-2 trial, 153 treatment-naive and treatment-experienced subjects with HCV/HIV-1 coinfection were treated with DAKLINZA 60 mg once daily (dose-adjusted for concomitant antiretroviral use) in combination with sofosbuvir for 12 weeks. The most common adverse reaction (frequency of 10% or greater) was fatigue. The majority of adverse reactions were mild to moderate in severity. No subjects discontinued therapy for adverse events. Adverse reactions considered at least possibly related to treatment and occurring at a frequency of 5% or greater in ALLY-3 or ALLY-2 are presented in Table 4.

Table 4: Adverse Reactions (All Severity) Reported at ≥5% Frequency, DAKLINZA + Sofosbuvir, Studies ALLY-3 and ALLY-2

Adverse Reaction	ALLY-3: HCV Genotype 3 n=152	ALLY-2: HCV/HIV-1 Coinfection n=153
Headache	14%	8%
Fatigue	14%	15%
Nausea	8%	9%
Diarrhea	5%	7%

DAKLINZA, Sofosbuvir, and Ribavirin

In the ALLY-1 trial, 113 subjects with chronic HCV infection, including 60 subjects with Child-Pugh A, B, or C cirrhosis and 53 subjects with recurrence of HCV after liver transplantation, were treated with DAKLINZA 60 mg once daily in combination with sofosbuvir and ribavirin for 12 weeks. The most common adverse reactions (frequency of 10% or greater) among the 113 subjects were headache, anemia, fatigue, and nausea. The majority of adverse reactions were mild to moderate in severity. Of the 15 (13%) subjects who discontinued study drug for adverse events, 13 (12%) subjects discontinued ribavirin only and 2 (2%) subjects discontinued all study drugs. During treatment, 4 subjects in the cirrhotic cohort underwent liver transplantation. Adverse reactions considered at least possibly related to treatment and occurring at a frequency of 5% or greater in either treatment cohort in ALLY-1 are presented in Table 5.

Table 5: Adverse Reactions (All Severity) Reported at ≥5% Frequency in Either Treatment Cohort, DAKLINZA + Sofosbuvir + Ribavirin, Study ALLY-1

Adverse Reaction	Child-Pugh A, B, or C Cirrhosis n=60	Recurrence after Liver Transplantation n=53
Headache	12%	30%
Anemia	20%	19%
Fatigue	15%	17%
Nausea	15%	6%
Rash	8%	2%
Diarrhea	3%	6%
Insomnia	3%	6%
Dizziness	0	6%
Somnolence	5%	0

Laboratory Abnormalities

Selected Grade 3 and 4 treatment-emergent laboratory abnormalities observed in clinical trials of DAKLINZA in combination with sofosbuvir with or without ribavirin are presented in Table 6.

Table 6: Selected Grade 3 and 4 Laboratory Abnormalities in Clinical Trials of DAKLINZA + Sofosbuvir ± Ribavirin, Studies ALLY-3, ALLY-2, and ALLY-1

Parameter	Percent with Abnormality		
	ALLY-3: HCV Genotype 3 DAKLINZA + Sofosbuvir n=152	ALLY-2: HCV/ HIV-1 Coinfection DAKLINZA + Sofosbuvir n=153	ALLY-1: Child-Pugh A, B, or C with Cirrhosis and Post-transplant DAKLINZA + Sofosbuvir + Ribavirin n=113
Hemoglobin (≤8.9 g/dL)	0	0	6%
Alanine aminotransferase (ALT) increased (≥5.1 × ULN)	0	0	2%
Aspartate aminotransferase (AST) increased (≥5.1 × ULN)	0	0	3%
Total bilirubin increased (≥2.6 × ULN)	0	5%[a]	8%
Lipase increased (≥3.1 × ULN)	2%	4%	4%

[a] In the ALLY-2 trial, Grade 3 and 4 increases in total bilirubin were observed only in subjects receiving concomitant atazanavir.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of DAKLINZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DAKLINZA™ (daclatasvir)

Cardiac Disorders: Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with sofosbuvir in combination with another HCV direct-acting antiviral, including DAKLINZA [*see Warnings and Precautions (5.2) and Drug Interactions (7.3)*].

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect DAKLINZA

Daclatasvir is a substrate of CYP3A. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of daclatasvir [*see Dosage and Administration (2.3), Contraindications (4), and Table 7*]. Strong inhibitors of CYP3A (eg, clarithromycin, itraconazole, ketoconazole, ritonavir) may increase the plasma levels of daclatasvir [*see Dosage and Administration (2.3) and Table 7*].

7.2 Potential for DAKLINZA to Affect Other Drugs

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 or adverse reactions (*see Table 7*).

7.3 Established and Potentially Significant Drug Interactions

Refer to the prescribing information for other agents in the regimen for drug interaction information. The most conservative recommendation should be followed.

Please also refer to Section 4 (Contraindications) and Section 12.3 (Pharmacokinetics) for complete information on all drug interactions.

Table 7 provides clinical recommendations for established or potentially significant drug interactions between DAKLINZA and other drugs [*see Contraindications (4)*]. Clinically relevant increase in concentration is indicated as "↑" and clinically relevant decrease as "↓" for drug interaction data [*see Clinical Pharmacology (12.3)*].

Table 7: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
HIV antiviral agents		
Protease inhibitors: Atazanavir with ritonavir[b] Indinavir Nelfinavir Saquinavir	↑ Daclatasvir	Decrease DAKLINZA dose to 30 mg once daily.
Other antiretrovirals: Cobicistat-containing antiretroviral regimens Examples: atazanavir/cobicistat, elvitegravir/cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	↑ Daclatasvir	Decrease DAKLINZA dose to 30 mg once daily except with darunavir combined with cobicistat.
Non-nucleoside reverse transcriptase inhibitors (NNRTI): Efavirenz[b] Etravirine Nevirapine	↓ Daclatasvir	Increase DAKLINZA dose to 90 mg once daily.
Strong CYP3A inhibitors (see also HIV antiviral agents)		
Examples: clarithromycin, itraconazole, ketoconazole,[b] nefazodone, posaconazole, telithromycin, voriconazole	↑ Daclatasvir	Decrease DAKLINZA dose to 30 mg once daily when coadministered with strong inhibitors of CYP3A.
Moderate CYP3A inducers (see also HIV antiviral agents)		
Examples: bosentan, dexamethasone, modafinil, nafcillin, rifapentine	↓ Daclatasvir	Increase DAKLINZA dose to 90 mg once daily when coadministered with moderate inducers of CYP3A.
Anticoagulants		
Dabigatran etexilate mesylate	↑ Dabigatran	Use of DAKLINZA with dabigatran etexilate is not recommended in specific renal impairment groups, depending on the indication. Please see the dabigatran prescribing information for specific recommendations.

(Continued)

Table 7: Established and Other Potentially Significant Drug Interactions *(Continued)*

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Cardiovascular agents		
Antiarrhythmic: Amiodarone	Amiodarone: effects unknown	Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If coadministration is required, cardiac monitoring is recommended. [*See Warnings and Precautions (5.2) and Adverse Reactions (6.2)*.]
Antiarrhythmic: Digoxin[b]	↑ Digoxin	Patients already receiving daclatasvir initiating digoxin: Initiate treatment using the lowest appropriate digoxin dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. Patients already receiving digoxin prior to initiating daclatasvir: Measure serum digoxin concentrations before initiating daclatasvir. Reduce digoxin concentrations by decreasing digoxin dosage by approximately 15% to 30% or by modifying the dosing frequency and continue monitoring.
Lipid-lowering agents		
HMG-CoA reductase inhibitors: Atorvastatin Fluvastatin Pitavastatin Pravastatin Rosuvastatin[b] Simvastatin	↑ Atorvastatin ↑ Fluvastatin ↑ Pitavastatin ↑ Pravastatin ↑ Rosuvastatin ↑ Simvastatin	Monitor for HMG-CoA reductase inhibitor-associated adverse events such as myopathy.
Narcotic Analgesic/Treatment of Opioid Dependence		
buprenorphine buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine	For buprenorphine or buprenorphine/naloxone, no adjustment is needed, but clinical monitoring for buprenorphine-associated adverse events is recommended.

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

[b] These interactions have been studied [*see Clinical Pharmacology (12.3), Tables 9 and 10*].

7.4 Drugs without Clinically Significant Interactions with DAKLINZA

Please see Section 12.3 (Pharmacokinetics) for information regarding anticipated interactions that are not clinically relevant.

Based on the results of drug interaction trials [*see Clinical Pharmacology (12.3)*], no clinically relevant changes in exposure were observed for cyclosporine, darunavir (with ritonavir), dolutegravir, escitalopram, ethinyl estradiol/norgestimate, lopinavir (with ritonavir), methadone, midazolam, tacrolimus, or tenofovir with concomitant use of daclatasvir. No clinically relevant changes in daclatasvir exposure were observed with cyclosporine, darunavir (with ritonavir), dolutegravir, escitalopram, famotidine, lopinavir (with ritonavir), omeprazole, sofosbuvir, tacrolimus, or tenofovir. No dosage adjustment for daclatasvir is necessary with darunavir/cobicistat or moderate CYP3A inhibitors, including atazanavir (unboosted), fosamprenavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, or verapamil.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No adequate human data are available to determine whether or not DAKLINZA poses a risk to pregnancy outcomes. In animal reproduction studies in rats and rabbits, no evidence of fetal harm was observed with oral administration of daclatasvir during organogenesis at doses that produced exposures up to 6 and 22 times, respectively, the recommended human dose (RHD) of 60 mg of DAKLINZA. However, embryofetal toxicity was observed in rats and rabbits at maternally toxic doses that produced exposures of 33 and 98 times the human exposure, respectively, at the RHD of 60 mg of DAKLINZA [*see Data*]. In rat pre- and postnatal developmental studies, no developmental toxicity was observed at maternal systemic exposure (AUC) to daclatasvir approximately 3.6 times higher than the RHD of DAKLINZA.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

If DAKLINZA and sofosbuvir are administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy.

Data

Animal Data

Daclatasvir was administered orally to pregnant rats at doses of 0, 50, 200, or 1000 mg/kg/day on gestation days 6 to 15. Maternal toxicity (mortality, adverse clinical signs, body-weight losses, and reduced food consumption) was noted at doses of 200 and 1000 mg/kg/day. In the offspring, malformations of the fetal brain, skull, eyes, ears, nose, lip, palate, or limbs were observed at doses of 200 and 1000 mg/kg. The dose of 1000 mg/kg was associated with profound embryolethality and lower fetal body weight. No malformations were noted at 50 mg/kg/day. Systemic exposure (AUC) at 50 mg/kg/day in pregnant females was 6 times higher than exposures at the RHD.

In rabbits, daclatasvir was initially administered at doses of 0, 40, 200, or 750 mg/kg/day during the gestation days 7 to 19. Daclatasvir dosing was modified due to vehicle toxicity during the study to doses of 20, 99, and 370 mg/kg/day, respectively. Maternal toxicity was noted at doses of 200/99 and 750/370 mg/kg/day with adverse clinical signs and severe reductions in body weight and food consumption. Mortality and euthanasia occurred in multiple dams at 750/370 mg/kg/day. At 200/99 mg/kg/day, fetal effects included increased embryofetal lethality, reduced fetal body weights, and increased incidences of fetal malformations of the ribs as well as head and skull. No malformations were noted in rabbits at 40/20 mg/kg/day. Systemic exposures (AUC) at 40/20 mg/kg/day were 22 times higher than exposures at the RHD.

In a pre- and postnatal developmental study, daclatasvir was administered orally at 0, 25, 50, or 100 mg/kg/day from gestation day 6 to lactation day 20. At 100 mg/kg/day, maternal toxicity included mortality and dystocia; developmental toxicity included slight reductions in offspring viability in the perinatal and neonatal periods and reductions in birth weight that persisted into adulthood. There was neither maternal nor developmental toxicity at doses up to 50 mg/kg/day. Systemic exposures (AUC) at this dose were 3.6 times higher than the RHD.

8.2 Lactation

Risk Summary

It is not known whether DAKLINZA is present in human milk, affects human milk production, or has effects on the breastfed infant. Daclatasvir was present in the milk of lactating rats (*see Data*).

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DAKLINZA and any potential adverse effects on the breastfed child from DAKLINZA or from the underlying maternal condition.

If DAKLINZA is administered with ribavirin, the nursing mothers information for ribavirin also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

Data

Milk concentrations of daclatasvir were evaluated on lactation day 10 as part of the rat pre- and postnatal development study (*see Data in 8.1*). Daclatasvir was present in rat milk with concentrations 1.7 to 2 times maternal plasma levels.

8.3 Females and Males of Reproductive Potential

If DAKLINZA and sofosbuvir are administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 1184 subjects treated with the recommended dose of DAKLINZA in ten clinical trials, 7% of subjects were 65 years of age or older. Safety was similar across older and younger subjects and there were no safety findings unique to subjects 65 years and older. SVR12 rates were comparable among older and younger subjects. No dosage adjustment of DAKLINZA is required for elderly patients [*see Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

No dosage adjustment of DAKLINZA is required for patients with any degree of renal impairment [*see Clinical Pharmacology (12.3)*]. Refer also to the sofosbuvir and ribavirin prescribing information for information regarding use in patients with renal impairment.

8.7 Hepatic Impairment

Based on a hepatic impairment study in non–HCV-infected subjects, no dosage adjustment of DAKLINZA is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment [*see Clinical Pharmacology (12.3)*].

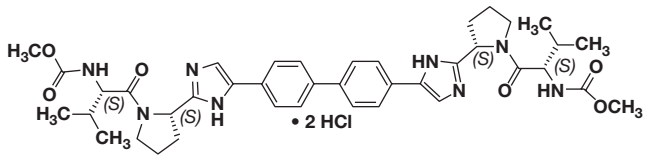
10 OVERDOSAGE

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%), dialysis is unlikely to significantly reduce plasma concentrations of the drug.

DAKLINZA™ (daclatasvir)

11 DESCRIPTION

DAKLINZA (daclatasvir) is an inhibitor of HCV nonstructural protein 5A (NS5A). The chemical name for drug substance 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). Its molecular formula is $C_{40}H_{50}N_8O_6$•2HCl, and its molecular weight is 738.88 (free base). Daclatasvir dihydrochloride has the following structural formula:



Daclatasvir dihydrochloride drug substance is white to yellow. Daclatasvir is freely soluble in water (>700 mg/mL).

DAKLINZA 60 mg tablets contain 60 mg daclatasvir (equivalent to 66 mg daclatasvir dihydrochloride) and the inactive ingredients anhydrous lactose (116 mg), microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, and Opadry green.

DAKLINZA 30 mg tablets contain 30 mg daclatasvir (equivalent to 33 mg daclatasvir dihydrochloride) and the inactive ingredients anhydrous lactose (58 mg), microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, and Opadry green.

DAKLINZA 90 mg tablets contain 90 mg daclatasvir (equivalent to 99 mg daclatasvir dihydrochloride) and the inactive ingredients anhydrous lactose (173 mg), microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, and Opadry green.

Opadry green contains hypromellose, titanium dioxide, polyethylene glycol 400, FD&C blue #2/indigo carmine aluminum lake, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Daclatasvir is a direct-acting antiviral agent (DAA) against the hepatitis C virus [*see Microbiology (12.4)*].

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 3 times the maximum recommended dose, daclatasvir did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in subjects with chronic HCV. Administration of daclatasvir tablets in HCV-infected subjects resulted in approximately dose-proportional increases in C_{max}, AUC, and C_{min} up to 60 mg once daily. Steady state is anticipated after approximately 4 days of once-daily daclatasvir administration. Exposure of daclatasvir was similar between healthy and HCV-infected subjects. Population pharmacokinetic estimates for daclatasvir 60 mg once daily in chronic HCV-infected subjects are shown in Table 8.

Table 8: Population Pharmacokinetic Estimates for Daclatasvir in Chronic HCV-Infected Subjects Receiving Daclatasvir 60 mg Once Daily and Sofosbuvir 400 mg Once Daily

Parameters	Daclatasvir 60 mg once daily (n=152)
AUC_{0-24h} (ng•h/mL)	
Mean ± standard deviation	10973 ± 5288
Median (range)	9680 (3807-41243)
C_{24h} (ng/mL)	
Mean ± standard deviation	182 ± 137
Median (range)	148 (21-1050)

Absorption and Bioavailability

In HCV-infected subjects following multiple oral doses of daclatasvir tablet ranging from 1 mg to 100 mg once daily, peak plasma concentrations occurred within 2 hours post dose.

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%.

Effect of Food on Oral Absorption

In healthy subjects, administration of a daclatasvir 60 mg tablet after a high-fat, high-caloric meal (approximately 951 total kcal, 492 kcal from fat, 312 kcal from carbohydrates, 144 kcal from protein) decreased daclatasvir C_{max} and $AUC_{(0-inf)}$ by 28% and 23%, respectively, compared with fasted conditions. A food effect was not observed with administration of a daclatasvir 60 mg tablet after a low-fat, low-caloric meal (approximately 277 total kcal, 41 kcal from fat, 190 kcal from carbohydrates, 44 kcal from protein) compared with fasted conditions [*see Dosage and Administration (2)*].

Distribution

With multiple dosing, protein binding of daclatasvir in HCV-infected subjects was approximately 99% and independent of dose at the dose range studied (1-100 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 L.

Metabolism

Daclatasvir is a substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism. Following single-dose oral administration of 25 mg ^{14}C-daclatasvir in healthy subjects, the majority of radioactivity in plasma was predominately attributed to parent drug (97% or greater).

Elimination

Following single-dose oral administration of 25 mg ^{14}C-daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% of the dose as unchanged daclatasvir) and 6.6% of the dose was excreted in the urine (primarily as unchanged daclatasvir). Following multiple-dose administration of daclatasvir in HCV-infected subjects, with doses ranging from 1 mg to 100 mg once daily, the terminal elimination half-life of daclatasvir ranged from approximately 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 4.2 L/h.

Specific Populations

Renal Impairment

The pharmacokinetics of daclatasvir following a single 60 mg oral dose was studied in non–HCV-infected subjects with renal impairment. Using a regression analysis, the predicted $AUC_{(0-inf)}$ of daclatasvir was estimated to be 26%, 60%, and 80% higher in subjects with creatinine clearance (CLcr) values of 60, 30, and 15 mL/min, respectively, relative to subjects with normal renal function (CLcr of 90 mL/min, defined using the Cockcroft-Gault CLcr formula), and daclatasvir unbound $AUC_{(0-inf)}$ was predicted to be 18%, 39%, and 51% higher for subjects with CLcr values of 60, 30, and 15 mL/min, respectively, relative to subjects with normal renal function. Using observed data, subjects with end-stage renal disease requiring hemodialysis had a 27% increase in daclatasvir $AUC_{(0-inf)}$ and a 20% increase in unbound $AUC_{(0-inf)}$ compared to subjects with normal renal function as defined using the Cockcroft-Gault CLcr formula [*see Use in Specific Populations (8.6)*].

Daclatasvir is highly protein bound to plasma proteins and is unlikely to be removed by dialysis.

Hepatic Impairment

The pharmacokinetics of daclatasvir following a single 30 mg oral dose was studied in non–HCV-infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared to a corresponding matched control group. The C_{max} and $AUC_{(0-inf)}$ of total daclatasvir (free and protein-bound drug) were lower by 46% and 43%, respectively, in Child-Pugh A subjects; by 45% and 38%, respectively, in Child-Pugh B subjects; and by 55% and 36%, respectively, in Child-Pugh C subjects. The C_{max} and $AUC_{(0-inf)}$ of unbound daclatasvir were lower by 43% and 40%, respectively, in Child-Pugh A subjects; by 14% and 2%, respectively, in Child-Pugh B subjects; and by 33% and 5%, respectively, in Child-Pugh C subjects [*see Use in Specific Populations (8.7)*].

Pediatric Patients

The pharmacokinetics of daclatasvir in pediatric patients has not been evaluated.

Geriatric Patients

Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18-79 years) analyzed, age did not have a clinically relevant effect on the pharmacokinetics of daclatasvir [*see Use in Specific Populations (8.5)*].

Gender

Population pharmacokinetic analyses in HCV-infected subjects estimated that female subjects have a 30% higher daclatasvir AUC compared to male subjects. This difference in daclatasvir AUC is not considered clinically relevant.

Race

Population pharmacokinetic analyses in HCV-infected subjects indicated that race had no clinically relevant effect on daclatasvir exposure.

Drug Interactions

Cytochrome P450 (CYP) Enzymes

Daclatasvir is a substrate of CYP3A. *In vitro*, daclatasvir did not inhibit (IC_{50} greater than 40 microM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6. Daclatasvir did not have a clinically relevant effect on the exposure of midazolam, a sensitive CYP3A substrate.

Transporters

Daclatasvir is a substrate of P-gp. However, cyclosporine, which inhibits multiple transporters including P-gp, did not have a clinically relevant effect on the pharmacokinetics of daclatasvir. Daclatasvir, *in vitro*, did not inhibit OCT2 and did not have a clinically relevant effect on the pharmacokinetics of tenofovir, an OAT substrate. Daclatasvir demonstrated inhibitory effects on digoxin (a P-gp substrate) and rosuvastatin (an OATP 1B1, OATP 1B3, and BCRP substrate) in drug-drug interaction trials.

Drug interaction studies were conducted with daclatasvir and other drugs likely to be coadministered or drugs used as probes to evaluate potential drug-drug interactions. The effects of daclatasvir on the C_{max}, AUC, and C_{min} of the coadministered drug are summarized in Table 9, and the effects of the coadministered drug on the C_{max}, AUC, and C_{min} of daclatasvir are summarized in Table 10. For information regarding clinical recommendations, see *Contraindications (4)* and *Drug Interactions (7.3)*. Drug interaction studies were conducted in healthy adults unless otherwise noted.

Table 9: Effect of DAKLINZA on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co-Administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/ No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Buprenorphine /Naloxone	Stable maintenance 8/2 mg to 24/6 mg QD	60 mg QD	Buprenorphine[b] 1.30 (1.03, 1.64) Norbuprenorphine[b] 1.65 (1.38, 1.99)	Buprenorphine[b] 1.37 (1.24, 1.52) Norbuprenorphine[b] 1.62 (1.30, 2.02)	Buprenorphine[b] 1.17 (1.03, 1.32) Norbuprenorphine[b] 1.46 (1.12, 1.89)
Darunavir[c]	600 mg BID with ritonavir 100 mg BID	30 mg QD	0.97 (0.80, 1.17)	0.90 (0.73, 1.11)	0.98 (0.67, 1.44)
Digoxin	0.125 mg QD	60 mg QD	1.65 (1.52, 1.80)	1.27 (1.20, 1.34)	1.18 (1.09, 1.28)
Dolutegravir	50 mg QD	60 mg QD	1.29 (1.07, 1.57)	1.33 (1.11, 1.59)	1.45 (1.25, 1.68)
Lopinavir[c]	400 mg BID with ritonavir 100 mg BID	30 mg QD	1.22 (1.06, 1.41)	1.15 (0.77, 1.72)	1.54 (0.46, 5.07)
Methadone	Stable maintenance 40-120 mg QD	60 mg QD	Total methadone[d]: 1.09 (0.99, 1.21) R-methadone[d]: 1.07 (0.97, 1.18)	Total methadone[d]: 1.11 (0.97, 1.26) R-methadone[d]: 1.08 (0.94, 1.24)	Total methadone[d]: 1.12 (0.96, 1.29) R-methadone[d]: 1.08 (0.93, 1.26)
Rosuvastatin	10 mg single dose	60 mg QD	2.04 (1.83, 2.26)	1.58 (1.44, 1.74)	NA
Simeprevir	150 mg QD	60 mg QD	1.39 (1.27, 1.52)	1.44 (1.32, 1.56)	1.49 (1.33, 1.67)

Note: In Table 9, for the concomitant medication, drug-drug interaction data were not included if 90% CIs for C_{max}, AUC, and C_{min} (if applicable for C_{min}) were within 80% to 125%. These concomitant medications include cyclosporine, escitalopram, ethinyl estradiol/norgestimate, midazolam, tacrolimus, and tenofovir disoproxil fumarate.

[a] C_{min} was defined as either the C_{tau} or the C_{trough} concentration value.

[b] The buprenorphine and norbuprenorphine pharmacokinetic parameters were dose normalized to 8 mg.

[c] Samples up to 6 hours collected; C_{0h} substituted for C_{12h} concentration value.

[d] The methadone pharmacokinetic parameters were dose normalized to 40 mg.

NA = Not available.

Table 10: Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Atazanavir/ ritonavir	300 mg/100 mg QD	20 mg QD (test arm)	0.45 (0.41, 0.49)[b]	0.70 (0.65, 0.75)[b]	1.22 (1.08, 1.37)[b]
Cyclosporine	400 mg single dose	60 mg QD	1.04 (0.94, 1.15)	1.40 (1.29, 1.53)	1.56 (1.41, 1.71)
Darunavir/ ritonavir	800 mg/100 mg QD	30 mg QD (test arm)	0.38 (0.35, 0.42)[b]	0.70 (0.66, 0.75)[b]	NA
Dolutegravir	50 mg QD	60 mg QD	1.03 (0.84, 1.25)	0.98 (0.83, 1.15)	1.06 (0.88, 1.29)
Efavirenz	600 mg QD	120 mg QD (test arm)	1.67 (1.51, 1.84)[b]	1.37 (1.21, 1.55)[b]	0.83 (0.69, 1.00)[b]
Escitalopram	10 mg QD	60 mg QD	1.14 (0.98, 1.32)	1.12 (1.01, 1.26)	1.23 (1.09, 1.38)
Famotidine	40 mg single dose	60 mg single dose (2 hours after famotidine administration)	0.56 (0.46, 0.67)	0.82 (0.70, 0.96)	0.89 (0.75, 1.06)

(Continued)

DAKLINZA™ (daclatasvir)

Table 10: Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics *(Continued)*

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Ketoconazole	400 mg QD	10 mg single dose	1.57 (1.31, 1.88)	3.00 (2.62, 3.44)	NA
Lopinavir/ ritonavir	400 mg/100 mg BID	30 mg QD (test arm)	0.34 (0.31, 0.37)[b]	0.58 (0.54, 0.62)[b]	NA
Omeprazole	40 mg single dose	60 mg single dose	0.64 (0.54, 0.77)	0.84 (0.73, 0.96)	0.92 (0.80, 1.05)
Rifampin	600 mg QD	60 mg single dose	0.44 (0.40, 0.48)	0.21 (0.19, 0.23)	NA
Simeprevir	150 mg QD	60 mg QD	1.50 (1.39, 1.62)	1.96 (1.84, 2.10)	2.68 (2.42, 2.98)
Tenofovir disoproxil fumarate	300 mg QD	60 mg QD	1.06 (0.98, 1.15)	1.10 (1.01, 1.21)	1.15 (1.02, 1.30)

Note: In Table 10, drug-drug interaction data for daclatasvir were not included for a study with tacrolimus because the 90% CIs for C_{max}, AUC, and C_{min} were within 80% to 125%.

[a] C_{min} was defined as either the C_{tau} or the C_{trough} daclatasvir concentration value.

[b] Observed, non-dose normalized data. For the reference arm, a 60 mg QD dose of daclatasvir was administered without the HIV comedications (boosted protease inhibitors, efavirenz) in order to compare the effect on daclatasvir exposures.

NA = Not available.

No clinically relevant interaction is anticipated for daclatasvir or the following concomitant medications: peginterferon alfa, ribavirin, or antacids. No clinically relevant interaction is anticipated for daclatasvir with concomitant use of rilpivirine.

12.4 Microbiology

Mechanism of Action

Daclatasvir is an inhibitor of NS5A, a nonstructural protein encoded by HCV. Daclatasvir binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly. Characterization of daclatasvir-resistant viruses, biochemical studies, and computer modeling 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 had median EC_{50} values of 0.008 nM (range, 0.002-0.03 nM; n=35), 0.002 nM (range, 0.0007-0.006 nM; n=30), and 0.2 nM (range, 0.006-3.2 nM; n=17) against hybrid replicons containing genotypes 1a, 1b, and 3a subject-derived NS5A sequences, respectively, without detectable daclatasvir resistance-associated polymorphisms at NS5A amino acid positions 28, 30, 31, or 93. Daclatasvir activity was reduced against genotypes 1a, 1b, and 3a subject-derived replicons with resistance-associated polymorphisms at positions 28, 30, 31, or 93, with median EC_{50} values of 76 nM (range, 4.6-2409 nM; n=5), 0.05 nM (range, 0.002-10 nM; n=12), and 13.5 nM (range, 1.3-50 nM; n=4), respectively. Similarly, the EC_{50} values of daclatasvir against 3 genotype 3b and 1 genotype 3i subject-derived NS5A sequences with polymorphisms (relative to a genotype 3a reference) at positions 30+31 (genotype 3b) or 30+62 (genotype 3i) were ≥3620 nM.

Daclatasvir was not antagonistic with interferon alfa, HCV NS3/4A protease inhibitors, HCV NS5B nucleoside analog inhibitors, and HCV NS5B non-nucleoside inhibitors in cell culture combination antiviral activity studies using the cell-based HCV replicon system.

Resistance

In Cell Culture

HCV genotype 1a, 1b, and 3a replicon variants with reduced susceptibility to daclatasvir were selected in cell culture, and the genotype and phenotype of daclatasvir-resistant NS5A amino acid variants were characterized. Phenotypic analysis of genotype 1a replicons expressing single NS5A M28T, Q30E, Q30H, Q30R, L31V, Y93C, Y93H, and Y93N substitutions exhibited 500-, 18500-, 1083-, 900-, 2500-, 1367-, 8500-, and 34833-fold reduced susceptibility to daclatasvir, respectively. For genotype 1b, L31V and Y93H single substitutions and L31M/Y93H and L31V/Y93H combinations exhibited 33-, 30-, 16000-, and 33667-fold reduced susceptibility to daclatasvir, respectively. A P32-deletion (P32X) in genotype 1b reduced daclatasvir susceptibility by >1,000,000-fold. For genotype 3a, single A30K, L31F, L31I, and Y93H substitutions exhibited 117-, 320-, 240-, and 3733-fold reduced susceptibility to daclatasvir, respectively.

In Clinical Studies

Among subjects with HCV genotype 1 or genotype 3 infection and treated in the ALLY-1, -2, and -3 trials with DAKLINZA and sofosbuvir with or without ribavirin for 12 weeks, 31 subjects (11 with genotype 1a, 1 with genotype 1b, and 19 with genotype 3) qualified for resistance analysis due to virologic failure. Post-baseline NS5A and NS5B population-based nucleotide sequence analysis results were available for 31 and 28 subjects, respectively.

Virus from all 31 subjects at the time of virologic failure harbored one or more of the following NS5A resistance-associated substitutions (including pre-existing amino acid polymorphisms or treatment-emergent substitutions): M28T, Q30H/K/R, L31M/V, H54R, H58D/P, or Y93C/N for genotype 1a subjects, P32-deletion (P32X) for the genotype 1b subject, and A30K/S, L31I, S62A/L/P/R/T, or Y93H for genotype 3 subjects. Among HCV genotype 1a virologic failure subjects, the most common NS5A amino acid substitutions occurred at position Q30 (Q30H/K/R; 73% [8/11], all treatment-emergent). Among HCV genotype 3 virologic failure subjects, the most common NS5A amino acid polymorphism or treatment-emergent substitution was Y93H (89% [17/19], treatment-emergent in 11 of 17 subjects).

For NS5B, 6 of 28 subjects at the time of virologic failure had virus with NS5B substitutions possibly associated with sofosbuvir resistance or exposure: A112T, L159F, E237G, or Q355H (genotype 1a subjects), or S282T+Q355H (genotype 3 subject).

Persistence of Resistance-Associated Substitutions

Limited data for DAKLINZA and sofosbuvir regimens on the persistence of daclatasvir resistance-associated substitutions are available. In a separate long-term follow-up study of predominately HCV genotype 1-infected subjects treated with daclatasvir-containing regimens in phase 2/3 clinical trials, viral populations with treatment-emergent NS5A resistance-associated substitutions persisted at detectable levels for more than 1 year in most subjects.

Effect of Baseline HCV Amino Acid Polymorphisms on Treatment Response

Genotype 1a NS5A polymorphisms: In HCV genotype 1a-infected subjects with cirrhosis, the presence of an NS5A amino acid polymorphism at position M28, Q30, L31, or Y93 (defined as any change from reference identified by population-based nucleotide sequencing) was associated with reduced efficacy of DAKLINZA and sofosbuvir with or without ribavirin for 12 weeks in the ALLY-1 and ALLY-2 trials (see Table 11). Due to the limited sample size, insufficient data are available to determine the impact of specific NS5A polymorphisms at these positions on SVR12 rates in subjects with cirrhosis. Six of 54 subjects (11%) with cirrhosis had one of the following specific NS5A polymorphisms at baseline: M28V/T (n=2), Q30R (n=1), L31M (n=2), or Y93N (n=1); 2 subjects with M28V or Q30R achieved SVR12 while 4 subjects with M28T, L31M, or Y93N did not achieve SVR. Eleven of 112 subjects (10%) without cirrhosis had one or more of the following specific NS5A polymorphisms at baseline: M28T/V (n=3), Q30H/L/R (n=5), L31M (n=1), and Y93C/H/S (n=4); all noncirrhotic subjects with these baseline NS5A polymorphisms achieved SVR12. Based on an analysis of 1026 HCV genotype 1a NS5A amino acid sequences from pooled clinical trials, the prevalence of polymorphisms at these positions was 11% overall, and 11% in the U.S.

Genotype 1b NS5A polymorphisms: In a pooled analysis of 43 subjects infected with HCV genotype 1b with available baseline nucleotide sequence data in ALLY-1 and -2, virus from 21% (n=9) of subjects receiving DAKLINZA and sofosbuvir with or without ribavirin had one of the following baseline NS5A amino acid polymorphisms: R30K/M/Q (n=4), L31M (n=2), or Y93H (n=3). All 9 subjects with NS5A polymorphisms achieved SVR12, including 5 who were noncirrhotic and 4 who were in the post-transplant period.

Genotype 3 NS5A polymorphisms: In the ALLY-3 trial in which HCV genotype 3-infected subjects received DAKLINZA and sofosbuvir for 12 weeks, the presence of an NS5A Y93H polymorphism was associated with a reduced SVR12 rate (see Table 11). In a pooled analysis of 175 subjects infected with HCV genotype 3 with available baseline nucleotide sequence data in the ALLY-1, -2, and -3 trials, virus from 7% (13/175) of subjects had the NS5A Y93H polymorphism, and all 13 of these subjects were in the ALLY-3 trial. Phylogenetic analysis of NS5A sequences indicated that all genotype 3 subjects with available data in the ALLY-1, -2, and -3 trials (n=175) were infected with HCV subtype 3a.

Table 11: Impact of NS5A Amino Acid Polymorphisms on SVR12 Rates in Subjects with HCV Genotype 1a or Genotype 3 Infection in Phase 3 Trials of DAKLINZA + Sofosbuvir ± Ribavirin

NS5A Polymorphisms	SVR12 Rates after 12 Weeks of Treatment with DAKLINZA + Sofosbuvir ± Ribavirin[a]	
	With NS5A Polymorphism(s) % (n/N)	Without NS5A Polymorphism(s) % (n/N)[b]
HCV genotype 1a-infected subjects: M28,[c] Q30,[c] L31,[c] or Y93[c]	76% (13/17)	95% (142/149)
Without cirrhosis[d]	100% (11/11)	99% (100/101)
With cirrhosis (Child-Pugh A, B, or C)	33% (2/6)	88% (42/48)
HCV genotype 3-infected subjects: Y93H	54% (7/13)	92% (149/162)
Without cirrhosis[d]	67% (6/9)	98% (125/128)
With cirrhosis (Child-Pugh A, B, or C)	25% (1/4)	71% (24/34)

[a] HCV genotype 1a-infected subjects received DAKLINZA + sofosbuvir ± ribavirin for 12 weeks in the ALLY-1 and ALLY-2 trials. HCV genotype 3-infected subjects received DAKLINZA + sofosbuvir for 12 weeks in the ALLY-3 trial; no data on the impact of Y93H are available for HCV genotype 3-infected subjects treated with DAKLINZA + sofosbuvir ± ribavirin in ALLY-1 and ALLY-2 trials.
[b] None of the 11 subjects with Child-Pugh C cirrhosis had an indicated NS5A polymorphism; 5 achieved SVR (genotype 1a: 4/9; genotype 3a: 1/2).
[c] Any change from genotype 1a reference.
[d] Includes subjects who were post-transplant with undefined cirrhosis status.

DAKLINZA™ (daclatasvir)

Cross-Resistance

Based on resistance patterns observed in cell culture replicon studies and HCV-infected subjects, cross-resistance between daclatasvir and other NS5A inhibitors is expected. Cross-resistance between daclatasvir and other classes of direct-acting antivirals is not expected. The impact of prior daclatasvir treatment experience on the efficacy of other NS5A inhibitors has not been studied. Conversely, the efficacy of DAKLINZA in combination with sofosbuvir has not been studied in subjects who have previously failed treatment with regimens that include an NS5A inhibitor.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

A 2-year carcinogenicity study in Sprague Dawley rats and a 6-month study in transgenic (Tg rasH2) mice were conducted with daclatasvir. In the 2-year study in rats, no drug-related increase in tumor incidence was observed at doses up to 50 mg/kg/day (both sexes). Daclatasvir exposures at these doses were approximately 6-fold (males and females) the human systemic exposure at the therapeutic daily dose of DAKLINZA. In transgenic mice no drug-related increase in tumor incidence was observed at doses of 300 mg/kg/day (both sexes).

Daclatasvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity (Ames) assays, mammalian mutation assays in Chinese hamster ovary cells, or in an *in vivo* oral micronucleus study in rats.

If DAKLINZA and sofosbuvir are administered in a regimen containing ribavirin, the information for ribavirin on carcinogenesis and mutagenesis also applies to this combination regimen (see prescribing information for ribavirin).

Impairment of Fertility

Daclatasvir had no effects on fertility in female rats at any dose tested. Daclatasvir exposures at these doses in females were approximately 24-fold the human systemic exposure at the therapeutic daily dose of DAKLINZA. In male rats, effects on reproductive endpoints at 200 mg/kg/day included reduced prostate/seminal vesicle weights, minimally increased dysmorphic sperm, as well as increased mean pre-implantation loss in litters sired by treated males. Daclatasvir exposures at the 200 mg/kg/day dose in males were approximately 26-fold the human systemic exposure at the therapeutic daily dose of DAKLINZA. Exposures at 50 mg/kg/day in males produced no notable effects and was 4.7-fold the exposure in humans at the recommended daily dose of DAKLINZA.

If DAKLINZA and sofosbuvir are administered with ribavirin, the information for ribavirin on impairment of fertility also applies to this combination regimen (see prescribing information for ribavirin).

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy of DAKLINZA in combination with sofosbuvir and with or without ribavirin was evaluated in three phase 3 clinical trials, as summarized in Table 12 [*see Clinical Studies (14.2, 14.3, 14.4)*]. HCV RNA levels were measured during these 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. Sustained virologic response was the primary endpoint and was defined as HCV RNA below the LLOQ at post-treatment week 12 (SVR12).

Table 12: Genotype 1 and 3 Patient Populations from DAKLINZA Trials

Trial	Population	Study Arms and Duration (Number of Subjects Treated)
ALLY-3 (AI444218)	Genotype 3, treatment-naive and treatment-experienced, with or without cirrhosis	DAKLINZA and sofosbuvir for 12 weeks (N=152)
ALLY-2 (AI444216)	Genotype 1 and 3, treatment-naive and treatment-experienced, with or without cirrhosis, HCV/HIV-1 coinfection	DAKLINZA and sofosbuvir for 12 weeks (N=137)
ALLY-1 (AI444215)	Genotype 1 and 3, treatment-naive or treatment-experienced, with or without cirrhosis, including decompensated cirrhosis and post-transplant	DAKLINZA and sofosbuvir and ribavirin for 12 weeks (N=103)

14.2 Clinical Trials in HCV Genotype 3 (ALLY-3)

ALLY-3 was an open-label trial that included 152 subjects with chronic HCV genotype 3 infection and compensated liver disease who were treatment naive (n=101) or treatment experienced (n=51). Most treatment-experienced subjects had failed prior treatment with peginterferon/ribavirin, but 7 subjects had been treated previously with a sofosbuvir regimen and 2 subjects with a regimen containing an investigational agent. Previous exposure to NS5A inhibitors was prohibited. Subjects received DAKLINZA 60 mg plus sofosbuvir 400 mg once daily for 12 weeks and were monitored for 24 weeks post treatment.

The 152 treated subjects in ALLY-3 had a median age of 55 years (range, 24-73); 59% of the subjects were male; 90% were white, 5% were Asian, and 4% were black. Most subjects (76%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 21% of the subjects had compensated cirrhosis, and 40% had the IL28B rs12979860 CC genotype.

SVR12 and outcomes in subjects without SVR12 in ALLY-3 are shown by patient population in Table 13. SVR12 rates were comparable regardless of HCV treatment history, age, gender, IL28B allele status, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see *Microbiology (12.4)*.

Table 13: ALLY-3: SVR12 in Treatment-Naive and Treatment-Experienced Subjects with or without Cirrhosis with Genotype 3 HCV Treated with DAKLINZA in Combination with Sofosbuvir for 12 Weeks

Treatment Outcomes	Total n=152
SVR12	
All	89% (135/152)
No cirrhosis[a]	96% (115/120)
With cirrhosis	63% (20/32)
Outcomes for subjects without SVR12	
On-treatment virologic failure[b]	0.7% (1/152)
Relapse[c]	11% (16/151)

[a] Includes 11 subjects with missing or inconclusive cirrhosis status.
[b] One subject had quantifiable HCV RNA at end of treatment.
[c] Relapse rates are calculated with a denominator of subjects with HCV RNA not detected at the end of treatment.

14.3 Clinical Trials in HCV/HIV Coinfected Subjects (ALLY-2)

ALLY-2 was an open-label trial that included 153 subjects with chronic hepatitis C and HIV coinfection who received DAKLINZA and sofosbuvir for 12 weeks. Subjects with HCV genotype 1, 2, 3, 4, 5, or 6 infection were eligible to enroll. Subjects were HCV treatment-naive (n=101) or HCV treatment-experienced (n=52). Prior exposure to NS5A inhibitors was prohibited. The dose of DAKLINZA was 60 mg once daily (dose-adjusted for concomitant antiretroviral use) and the dose of sofosbuvir was 400 mg once daily [*see Drug Interactions (7.3)*].

The 153 treated subjects had a median age of 53 years (range, 24-71); 88% of subjects were male; 63% were white, 33% were black, and 1% were Asian. Sixty-eight percent of subjects had HCV genotype 1a, 15% had HCV genotype 1b, 8% had genotype 2, 7% had genotype 3, and 2% had genotype 4. Most subjects (80%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 16% of the subjects had compensated cirrhosis, and 73% had IL28B rs12979860 non-CC genotype. Concomitant HIV therapy included PI-based regimens (darunavir + ritonavir, atazanavir + ritonavir, or lopinavir/ritonavir) for 46% of subjects, NNRTI-based regimens (efavirenz, nevirapine, or rilpivirine) for 26%, integrase-based regimens (raltegravir or dolutegravir) for 26%, and nucleoside-only regimens (abacavir + emtricitabine + zidovudine) for 1%. Two patients were not receiving treatment for HIV.

SVR and outcomes in subjects with HCV genotype 1 without SVR12 in ALLY-2 are shown by patient population in Table 14. Available data on subjects with HCV genotype 2, 4, 5, or 6 infection are insufficient to provide recommendations for these genotypes; therefore, these results are not presented in Table 14. SVR12 rates were comparable regardless of antiretroviral therapy, HCV treatment history, age, race, gender, IL28B allele status, HCV genotype 1 subtype, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see *Microbiology (12.4)*.

No subjects switched their antiretroviral therapy regimen due to loss of plasma HIV-1 RNA suppression. There was no change in absolute CD4+ T-cell counts at the end of 12 weeks of treatment.

Table 14: ALLY-2: SVR12 in Subjects with Genotype 1 and 3 HCV/HIV Coinfection Treated with DAKLINZA in Combination with Sofosbuvir for 12 Weeks

Treatment Outcomes	Total n=137
SVR12	
Genotype 1	97% (123/127)
No cirrhosis[a]	98% (103/105)
With cirrhosis	91% (20/22)
Genotype 3[b]	100% (10/10)

(Continued)

Table 14: ALLY-2: SVR12 in Subjects with Genotype 1 and 3 HCV/HIV Coinfection Treated with DAKLINZA in Combination with Sofosbuvir for 12 Weeks *(Continued)*

Treatment Outcomes	Total n=137
Outcomes for genotype 1 subjects without SVR12	
On-treatment virologic failure[c]	0.8% (1/127)
Relapse[d]	1.6% (2/126)
Missing post-treatment data	0.8% (1/126)

[a] Includes 5 subjects with inconclusive cirrhosis status.
[b] One subject with cirrhosis.
[c] One subject had detectable HCV RNA at end of treatment.
[d] Relapse rates are calculated with a denominator of subjects with HCV RNA not detected at the end of treatment.

14.4 Clinical Trials in Subjects with Child-Pugh A, B, or C Cirrhosis or with HCV Recurrence after Liver Transplantation (ALLY-1)

ALLY-1 was an open-label trial of DAKLINZA, sofosbuvir, and ribavirin that included 113 subjects with chronic HCV infection and Child-Pugh A, B, or C cirrhosis (n=60) or HCV recurrence after liver transplantation (n=53). Subjects with HCV genotype 1, 2, 3, 4, 5, or 6 infection were eligible to enroll. Subjects could be HCV treatment-naive or treatment-experienced, although prior exposure to NS5A inhibitors was prohibited. Subjects received DAKLINZA 60 mg once daily, sofosbuvir 400 mg once daily, and ribavirin for 12 weeks and were monitored for 24 weeks post treatment. Subjects received an initial ribavirin dose of 600 mg or less daily with food; the initial and on-treatment dosing of ribavirin was modified based on hemoglobin and creatinine clearance measurements. If tolerated, the ribavirin dose was titrated up to 1000 mg per day. A high proportion of reductions in ribavirin dosing occurred in the trial. By week 6, approximately half of the subjects received 400 mg per day or less of ribavirin. In total, 16 subjects (15%) completed less than 12 weeks and 11 subjects (10%) completed less than 6 weeks of ribavirin therapy, respectively. For the cohort of patients with cirrhosis (Child-Pugh A, B, or C), the median time to discontinuation of ribavirin was 43 days (range, 8-82, n=9). For the post-transplant cohort, the median time to discontinuation of ribavirin was 20 days (range, 3-57, n=7).

The 113 treated subjects in ALLY-1 had a median age of 59 years (range, 19-82); 67% of the subjects were male; 96% were white, 4% were black, and 1% Asian. Most subjects (59%) were treatment-experienced, and most (71%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL. Fifty-eight percent of subjects had HCV genotype 1a, 19% had HCV genotype 1b, 4% had genotype 2, 15% had genotype 3, 4% had genotype 4, and 1% had genotype 6, 77% had IL28B rs12979860 non-CC genotype. Among the 60 subjects in the cirrhosis cohort, 20% were Child-Pugh A, 53% were Child-Pugh B, and 27% were Child-Pugh C, and 35% had a Baseline Model for End-Stage Liver Disease (MELD) score of 15 or greater. Most (55%) of the 53 subjects in the post-transplant cohort had F3 or F4 fibrosis (based on FibroSURE® results).

SVR12 and outcomes in subjects without SVR12 in ALLY-1 are shown for subjects with HCV genotype 1 by patient population in Table 15. Available data on subjects with HCV genotype 2, 4, 5, or 6 infection are insufficient to provide recommendations; therefore, these results are not presented in Table 15.

SVR12 rates were comparable regardless of age, gender, IL28B allele status, or baseline HCV RNA level. For SVR12 outcomes related to baseline NS5A amino acid polymorphisms, see *Microbiology (12.4)*. No HCV genotype 1 or genotype 3 subjects with Child-Pugh C cirrhosis had baseline resistance-associated NS5A amino acid polymorphisms. SVR12 rates were comparable between genotype 3 (5/6 with Child-Pugh B or C cirrhosis and 10/11 post-liver transplant) and genotype 1 subjects with or without decompensated cirrhosis.

Table 15: ALLY-1: SVR12 in Genotype 1 Subjects with Child-Pugh A, B, or C Cirrhosis or with HCV Genotype 1 Recurrence after Liver Transplantation Treated with DAKLINZA in Combination with Sofosbuvir and Ribavirin for 12 Weeks

Treatment Outcomes	Child-Pugh A, B, or C Cirrhosis n=45	Post-Liver Transplant n=41
SVR12		
Genotype 1	82% (37/45)	95% (39/41)
Child-Pugh A	91% (10/11)	-
Child-Pugh B	92% (22/24)	-
Child-Pugh C	50% (5/10)	-
Genotype 1a	76% (26/34)	97% (30/31)
Genotype 1b	100% (11/11)	90% (9/10)
Outcomes for subjects without SVR12		
On-treatment virologic failure	2% (1/45)[a]	0
Relapse[b]	16% (7/44)	5% (2/41)

[a] One subject had detectable HCV RNA at end of treatment.
[b] Relapse rates are calculated with a denominator of subjects with HCV RNA not detected at end of treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

DAKLINZA is packaged in bottles as described in the table.

Tablet Strength	Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
60 mg	Light green, biconvex, pentagonal	Debossed with "BMS" on one side and "215" on the other side	Bottles of 28	0003-0215-01
30 mg	Green, biconvex, pentagonal	Debossed with "BMS" on one side and "213" on the other side	Bottles of 28	0003-0213-01
90 mg	Light green, biconvex, round	Embossed with "BMS" on one side and "011" on the other side	Bottles of 28	0003-0011-01

Store DAKLINZA tablets at 25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions

Inform patients of the potential for drug interactions with DAKLINZA, and that some drugs should not be taken with DAKLINZA [*see Contraindications (4), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

Symptomatic Bradycardia When Used in Combination with Sofosbuvir and Amiodarone

Advise patients to seek medical evaluation immediately for symptoms of bradycardia, such as near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion or memory problems [*see Warnings and Precautions (5.2), Adverse Reactions (6.2), and Drug Interactions (7.3)*].

DAKLINZA™ (daclatasvir)

DAKLINZA Combination Therapy with Sofosbuvir

Inform patients that DAKLINZA should not be used alone. DAKLINZA should be used in combination with sofosbuvir with or without ribavirin for the treatment of HCV genotype 1 or HCV genotype 3 infection [*see Indications and Usage (1)*].

Missed Doses

Advise patients to take DAKLINZA every day at the regularly scheduled time with or without food. Inform patients that it is important not to miss or skip doses and to take DAKLINZA for the duration that is recommended by the physician. For instructions for missed doses of other agents in the regimen, refer to the respective prescribing information.

Pregnancy

Advise patients to avoid pregnancy during combination treatment with DAKLINZA and sofosbuvir with ribavirin for 6 months after completion of treatment. Inform patients to notify their healthcare provider immediately in the event of a pregnancy [*see Use in Specific Populations (8.1)*].

Manufactured for:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Product of Ireland

1344554A2

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Patient Information

DAKLINZA™ (dak lin za)
(daclatasvir)
tablets

Important: DAKLINZA is used in combination with other antiviral medicines. When taking DAKLINZA in combination with sofosbuvir, you should read the Patient Information leaflet for sofosbuvir. **When taking DAKLINZA in combination with sofosbuvir and ribavirin, you should also read the Medication Guide for ribavirin.**

What is DAKLINZA?

- DAKLINZA is a prescription medicine used to treat chronic (lasting a long time) hepatitis C genotype 1 or genotype 3 infection in adults.
- Take DAKLINZA with sofosbuvir or with sofosbuvir and ribavirin. **You should not take DAKLINZA by itself.**

It is not known if DAKLINZA is safe and effective in children under 18 years of age.

Before taking DAKLINZA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems other than hepatitis C infection
- have had a liver transplant
- have heart problems
- are pregnant or plan to become pregnant. It is not known if DAKLINZA will harm your unborn baby.
  - **When taking DAKLINZA in combination with sofosbuvir and ribavirin, tell your healthcare provider right away if you or your female sexual partner becomes pregnant.**
  - **Males and females who take DAKLINZA with sofosbuvir and ribavirin should also read the ribavirin Medication Guide for important pregnancy, contraception, and infertility information.**
- are breastfeeding or plan to breastfeed. It is not known if DAKLINZA passes into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby during treatment with DAKLINZA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

DAKLINZA and other medicines may affect each other. This can cause you to have too much or not enough DAKLINZA or other medicines in your body. This may affect the way DAKLINZA or your other medicines work or may cause side effects. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with DAKLINZA.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take DAKLINZA with other medicines.

How should I take DAKLINZA?

- Take DAKLINZA exactly how you are told to by your healthcare provider.
- Do not change your dose unless you are told to by your healthcare provider.
- Do not stop taking DAKLINZA without first talking with your healthcare provider.
- Take DAKLINZA one time each day with or without food.
- If you miss a dose, call your healthcare provider or pharmacist. It is important that you do not miss or skip doses of DAKLINZA during treatment.
- If you take too much DAKLINZA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of DAKLINZA when used with sofosbuvir?

DAKLINZA in combination with sofosbuvir and amiodarone may cause serious side effects, including:

- **Slow heart rate (bradycardia).** DAKLINZA combination treatment with sofosbuvir may result in slowing of the heart rate (pulse) along with other symptoms when taken with amiodarone, a medicine used to treat certain heart problems. Get medical help right away if you take amiodarone with sofosbuvir and DAKLINZA and get any of the following symptoms:
  - fainting or near-fainting
  - weakness
  - chest pain
  - dizziness or lightheadedness
  - tiredness
  - confusion
  - not feeling well
  - shortness of breath
  - memory problems

The most common side effects of DAKLINZA when used in combination with sofosbuvir include:

- headache
- tiredness

The most common side effects of DAKLINZA when used in combination with sofosbuvir and ribavirin include:

- headache
- tiredness
- low red blood cell count (anemia)
- nausea

These are not all the possible side effects of DAKLINZA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DAKLINZA?

- Store DAKLINZA at room temperature between 68°F and 77°F (20°C and 25°C).

Keep DAKLINZA and all medicines out of the reach of children.

General information about the safe and effective use of DAKLINZA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use DAKLINZA for a condition for which it was not prescribed. Do not give DAKLINZA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about DAKLINZA that is written for health professionals.

What are the ingredients in DAKLINZA?

Active ingredient: daclatasvir

Inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, and Opadry green. Opadry green contains hypromellose, titanium dioxide, polyethylene glycol 400, FD&C blue #2/indigo carmine aluminum lake, and yellow iron oxide.

Manufactured for: Bristol-Myers Squibb Company, Princeton, NJ 08543, USA

Product of Ireland

DAKLINZA is a trademark of Bristol-Myers Squibb Company. For more information, go to www.patientsupportconnect.com or call 1-844-442-6663.

This Patient Information has been approved by the U.S. Food and Drug Administration.

1344554A2 Revised February 2016

1392US1601820-01-01

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