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

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

DAKLINZA is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir for the treatment of chronic HCV genotype 3 infection. (1)

Limitations of Use:

- Sustained virologic response (SVR) rates are reduced in patients with cirrhosis. (14)

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

- 60 mg taken orally once daily with or without food in combination with sofosbuvir. (2.1)
- Recommended treatment duration: 12 weeks. (2.1)
- 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. (2.2)

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

- Tablet: 60 mg and 30 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, 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)

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. (2.2, 4, 5.1, 7, 12.3)

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

Revised: 7/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DAKLINZA is indicated for use with sofosbuvir for the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection [*see Dosage and Administration (2) and Clinical Studies (14)*].

Limitations of Use:

- Sustained virologic response (SVR) 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 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of DAKLINZA is 60 mg, taken orally, once daily in combination with sofosbuvir for 12 weeks. DAKLINZA may be taken with or without food.

The optimal duration of DAKLINZA and sofosbuvir for patients with cirrhosis has not been established [*see Clinical Studies (14)*].

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

2.2 Dosage Modification Due to Drug Interactions

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

Strong inhibitors of cytochrome P450 enzyme 3A (CYP3A): Reduce the dosage of DAKLINZA to 30 mg once daily when coadministered with strong CYP3A inhibitors using the 30 mg tablet [*see Drug Interactions (7)*].

Moderate CYP3A inducers: Increase the dosage of DAKLINZA to 90 mg once daily using an appropriate combination of tablets (three 30 mg tablets or one 60 mg and one 30 mg tablet) when coadministered with moderate CYP3A inducers [*see Drug Interactions (7)*].

Strong CYP3A inducers: DAKLINZA is contraindicated in combination with strong CYP3A inducers [*see Contraindications (4)*].

Dosage reduction of DAKLINZA for adverse reactions is not recommended.

2.3 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 daclatasvir (equivalent to 66 mg daclatasvir dihydrochloride), light green, biconvex, pentagonal, and debossed with "BMS" on one side and "215" on the other side.
- Tablets: 30 mg daclatasvir (equivalent to 33 mg daclatasvir dihydrochloride), green, biconvex, pentagonal, and debossed with "BMS" on one side and "213" on the other side.

4 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 1 [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

Table 1: Drugs that are Contraindicated with DAKLINZA

Mechanism of Interaction	Clinical Comment	Drugs that are Contraindicated with DAKLINZA[a]
Strong induction of CYP3A by coadministered drug	May lead to loss of virologic response to DAKLINZA	*Anticonvulsants* phenytoin, carbamazepine *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 1 for drugs contraindicated with DAKLINZA due to loss of efficacy and possible development of resistance [*see Contraindications (4)*]. See Table 3 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, Table 3 (7.3)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are 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 1900 subjects with chronic HCV infection have been treated with the recommended dose of DAKLINZA in combination with other anti-HCV drugs in clinical trials.

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. One subject experienced a serious adverse event that was considered unrelated to DAKLINZA, and 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 are presented in Table 2.

Table 2: Adverse Reactions Reported at ≥5% Frequency, DAKLINZA + Sofosbuvir for 12 Weeks

Adverse Reaction	n (%) n=152
Headache	21 (14%)
Fatigue	21 (14%)
Nausea	12 (8%)
Diarrhea	7 (5%)

Laboratory Abnormalities

Lipase Elevations: Transient, asymptomatic lipase elevations of greater than 3 times the upper limit of normal (ULN) were observed in 2% of subjects in ALLY-3.

6.2 Postmarketing Experience

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 (2.2), Contraindications (4), and Table 3*]. Strong inhibitors of CYP3A (eg, clarithromycin, itraconazole, ketoconazole, ritonavir) may increase the plasma levels of daclatasvir [*see Dosage and Administration (2.2) and Table 3*].

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 3*).

7.3 Established and Potentially Significant Drug Interactions

Refer to the prescribing information for sofosbuvir for drug interaction information. The most conservative recommendation should be followed.

Table 3 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 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration[a]**	**Clinical Comment**
Strong CYP3A inhibitors		
Examples: atazanavir/ritonavir,[b] clarithromycin, indinavir, itraconazole, ketoconazole,[b] nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, voriconazole	↑ Daclatasvir	Decrease DAKLINZA dose to 30 mg once daily when coadministered with strong inhibitors of CYP3A.
Moderate CYP3A inhibitors		
Examples: atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil	↑ Daclatasvir	Monitor for daclatasvir adverse events.
Moderate CYP3A inducers		
Examples: bosentan, dexamethasone, efavirenz,[b] etravirine, 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.

Table 3: Established and Other Potentially Significant Drug Interactions

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 30% to 50% 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.

[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 5 and 6)*].

7.4 Drugs without Clinically Significant Interactions with DAKLINZA

Based on the results of drug interaction trials [*see Clinical Pharmacology (12.3)*], no clinically relevant changes in exposure were observed for cyclosporine, escitalopram, ethinyl estradiol/norgestimate, methadone, midazolam, tacrolimus, or tenofovir with concomitant use of daclatasvir. No clinically relevant changes in daclatasvir exposure were observed with cyclosporine, escitalopram, famotidine, omeprazole, sofosbuvir, tacrolimus, or tenofovir. No clinically relevant interaction is anticipated for daclatasvir or the following concomitant medications: peginterferon alfa, ribavirin, or antacids.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No data with DAKLINZA in pregnant women are available to inform a drug-associated risk. 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. 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 [*see Data*]. Consider the benefits and risks of DAKLINZA when prescribing DAKLINZA to a pregnant woman.

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.

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-fold 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-fold 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-fold higher than the RHD. Daclatasvir was present in rat milk with concentrations 1.7- to 2-fold maternal plasma levels.

8.2 Lactation

Risk Summary

No information regarding the presence of daclatasvir in human milk, the effects on the breastfed infant, or the effects on milk production is available. Daclatasvir is present in the milk of lactating rats [*see Use in Specific Populations (8.1)*]. The development 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 infant from DAKLINZA or from the underlying maternal condition.

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

Safety was similar across older and younger subjects and there were no safety findings unique to subjects 65 years and older. Sustained virologic response (SVR) 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)*].

8.7 Hepatic Impairment

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)*]. Safety and efficacy of DAKLINZA have not been established in patients with decompensated cirrhosis.

8.8 Liver Transplant Patients

The safety and efficacy of DAKLINZA combination therapy have not been established in liver transplant patients.

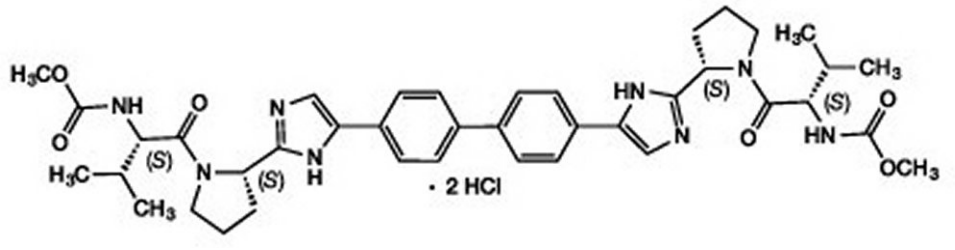
10 OVERDOSAGE

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.

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. 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 does 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 4.

Table 4: 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)
$AUC_{0\text{-}24h}$ (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 $AUC_{(0\text{-}inf)}$ 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 $AUC_{(0\text{-inf})}$ 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 $AUC_{(0\text{-inf})}$ 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 $AUC_{(0\text{-inf})}$ and a 20% increase in unbound $AUC_{(0\text{-inf})}$ 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 $AUC_{(0\text{-inf})}$ 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 $AUC_{(0\text{-inf})}$ 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)*].

Geriatric

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)*].

Pediatric and Adolescent

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

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} >40 µM) 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 organic cation transporter (OCT) 2 and did not have a clinically relevant effect on the pharmacokinetics of tenofovir, an organic anion transporter (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 5, and the effects of the coadministered drug on the C_{max}, AUC, and C_{min} of daclatasvir are summarized in Table 6. 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 5: Effect of DAKLINZA on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
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)

Table 5: Effect of DAKLINZA on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a]
Methadone	40-120 mg QD individualized dose[b]	60 mg QD	Total methadone[c]: 1.09 (0.99, 1.21) R-methadone[c]: 1.07 (0.97, 1.18)	Total methadone[c]: 1.11 (0.97, 1.26) R-methadone[c]: 1.08 (0.94, 1.24)	Total methadone[c]: 1.12 (0.96, 1.29) R-methadone[c]: 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 5, 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] Evaluated in adults on stable methadone maintenance therapy.

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

NA = Not available.

Table 6: 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	60 mg QD (reference arm) 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)
Efavirenz	600 mg QD	60 mg QD (reference arm) 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)
Ketoconazole	400 mg QD	10 mg single dose	1.57 (1.31, 1.88)	3.00 (2.62, 3.44)	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 6, 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.

NA = Not available.

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 a median EC_{50} value of 0.2 nM (range, 0.006-3.2 nM, n=17) against hybrid replicons containing genotype 3a subject-derived NS5A sequences without detectable daclatasvir resistance-associated polymorphisms at NS5A amino acid positions 28, 30, 31, or 93. Daclatasvir activity was reduced against genotype 3a subject-derived replicons with resistance-associated polymorphisms at positions 28, 30, 31, or 93, with a median EC_{50} value of 13.5 nM (range, 1.3-50 nM). 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 or 31 were ≥3620 nM.

The median EC_{50} values of daclatasvir for genotypes 1a, 1b, 2, 4, and 5 subject-derived NS5A hybrid replicons were 0.008 nM (range, 0.002-2409 nM, n=40), 0.002 nM (range, 0.0007-10 nM, n=42), 16 nM (range, 0.005-60 nM, n=16), 0.025 nM (range, 0.001-158 nM, n=14), and 0.004 nM (range, 0.003-0.019 nM, n=3), respectively. The EC_{50} value against a single HCV genotype 6 derived replicon was 0.054 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 3a replicon variants with reduced susceptibility to daclatasvir were selected in cell culture, and the genotype and phenotype of daclatasvir-resistant variants were characterized. Phenotypic analysis of stable replicon cell lines showed that variant replicons containing A30K, A30T, L31F, S62L, and Y93H substitutions exhibited 56-, 1-, 603-, 1.75-, and 2737-fold reduced susceptibility to daclatasvir, respectively.

In Clinical Studies

Of 152 HCV genotype 3-infected subjects treated in the ALLY-3 trial, 17 experienced virologic failure, of whom 12 had cirrhosis. Post-baseline NS5A and NS5B population nucleotide sequencing data were available for virus from 17/17 and 16/17 subjects, respectively. Virus from all 17 subjects at the time of virologic failure harbored one or more of the NS5A resistance-associated substitutions A30K/S, L31I, S62A/L/P/T, or Y93H. The most common substitution at failure was Y93H (15/17 subjects), which was observed at baseline in 6 subjects and emerged in 9 subjects. For NS5B, 1 of 16 subjects had virus with the emergent NS5B resistance-associated substitution S282T at failure.

Persistence of Resistance-Associated Substitutions

Limited data from ALLY-3 on the persistence of daclatasvir resistance-associated substitutions in HCV genotype 3-infected subjects 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 Polymorphisms on Treatment Response

In an analysis of 148 subjects with available baseline resistance data in ALLY-3, virus from 52% (77/148) of subjects had baseline NS5A polymorphisms at resistance-associated positions (defined as any change from reference at NS5A amino acid positions 28, 30, 31, 58, 62, 92, or 93) identified by population sequencing. The Y93H polymorphism was detected in 9% (13/148) of subjects receiving DAKLINZA and sofosbuvir and was associated with reduced SVR12 rates (Table 7). Polymorphisms detected at other NS5A resistance-associated positions were not associated with reduced SVR12 rates; these polymorphisms included M28V (n=1), A30K/S/T/V (n=14), P58R/S (n=3), and S62-any (n=66). Polymorphisms at positions associated with sofosbuvir resistance or exposure (defined as any change from reference at NS5B positions L159, S282, C316, L320, or V321) were not detected in the baseline NS5B sequence of any subject (n=150) in ALLY-3 by population-based sequencing. Phylogenetic analysis of NS5A sequences indicated that all subjects with available data (n=148) were infected with HCV subtype 3a.

Table 7: SVR12 Rates in Subjects with HCV Genotype 3 with/without the Baseline NS5A Y93H Polymorphism, by Cirrhosis Status

Study Population	SVR12 with Y93H	SVR12 without Y93H
All subjects	54% (7/13)	92% (124/135)
No cirrhosis[a]	67% (6/9)	98% (105/107)
With cirrhosis	25% (1/4)	68% (19/28)

[a] Includes 11 subjects with missing or inconclusive cirrhosis status.

Cross Resistance

Based on resistance patterns observed in cell culture replicon studies and HCV genotype 3-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. 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.

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. 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. 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.

14 CLINICAL STUDIES

The efficacy and safety of DAKLINZA in combination with sofosbuvir were evaluated in the phase 3 ALLY-3 (AI444-218) clinical trial. 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 cyclophilin inhibitor. 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. HCV RNA values were measured during the clinical trial 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 (SVR) was the primary endpoint and was defined as HCV RNA below the LLOQ at post-treatment week 12 (SVR12).

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/mL; 21% of the subjects had compensated cirrhosis, and 40% had the IL28B rs12979860 CC genotype.

SVR and outcomes in subjects without SVR in ALLY-3 are shown by patient population in Table 8. For SVR outcomes related to the baseline NS5A Y93H polymorphism, see *Microbiology (12.4)*. SVR rates were comparable regardless of age, gender, IL28B allele status, or baseline HCV RNA level.

Table 8: Treatment Outcomes in ALLY-3: DAKLINZA in Combination with Sofosbuvir in Subjects with HCV Genotype 3 Infection

Treatment Outcomes	Treatment-Naive n=101	Treatment-Experienced n=51	Total n=152
SVR			
All	90% (91/101)	86% (44/51)	89% (135/152)
No cirrhosis[a]	98% (80/82)	92% (35/38)	96% (115/120)
With cirrhosis	58% (11/19)	69% (9/13)	63% (20/32)
Outcomes for subjects without SVR			
On-treatment virologic failure[b]	1% (1/101)	0	0.7% (1/152)
Relapse[c]	9% (9/100)	14% (7/51)	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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

16.2 Storage

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 Combination Therapy with Sofosbuvir

Inform patients that DAKLINZA should not be used alone to treat genotype 3 chronic hepatitis C infection. DAKLINZA should be used in combination with sofosbuvir for the treatment of genotype 3 HCV infection [*see Indications and Usage (1)*].

Missed Doses

Instruct patients that if they miss a dose of DAKLINZA, the dose should be taken as soon as possible if remembered within the same day. However, if the missed dose is not remembered within the same day, the dose should be skipped and the next dose taken at the appropriate time. For instructions for missed doses of other agents in the regimen, refer to the respective prescribing information.

Hepatitis C Virus Transmission

Inform patients that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus during treatment should be taken.

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

Product of Ireland

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Patient Information
DAKLINZA™ (dak lin za)
(daclatasvir)
tablets

Important information:
DAKLINZA is used in combination with the antiviral medicine sofosbuvir (SOVALDI).
You should not take DAKLINZA alone to treat chronic hepatitis C infection.
You should also read the Patient Information for sofosbuvir (SOVALDI).

What is DAKLINZA?

- DAKLINZA is a prescription medicine used with sofosbuvir to treat chronic (lasting a long time) hepatitis C genotype 3 infection in adults.
- DAKLINZA should not be taken alone.

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.
- are breastfeeding or plan to breastfeed. It is not known if DAKLINZA passes into your breast milk.

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 as your healthcare provider tells you to.
- Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking DAKLINZA without first talking with your healthcare provider.
- Take DAKLINZA 1 time each day with or without food.
- If you miss a dose of DAKLINZA, take the missed dose as soon as you remember the same day. Take the next dose at your regular time.
- If you miss a dose of DAKLINZA and remember the next day, skip the missed dose. Take the next dose at your regular time.
- Do not take 2 doses of DAKLINZA at the same time to make up for the missed dose.
- 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:

o fainting or near-fainting	o dizziness or lightheadedness	o not feeling well
o weakness	o tiredness	o shortness of breath
o chest pain	o confusion	o memory problems

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

- headache
- tiredness

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

It is not known if treatment with DAKLINZA will prevent you from infecting another person with the hepatitis C virus during treatment. Talk with your healthcare provider about ways to prevent spreading the hepatitis C virus.

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.

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