PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrDAKLINZA™

daclatasvir tablets, 30 and 60 mg

(as daclatasvir dihydrochloride)

Antiviral Agent

Bristol-Myers Squibb Canada
Montréal, Canada

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[Pr]DAKLINZA™
(as daclatasvir dihydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Daclatasvir tablets/ 30 mg and 60 mg (as daclatasvir dihydrochloride)	Anhydrous Lactose

For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

DAKLINZA (daclatasvir) is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adult patients with hepatitis C virus (HCV) genotypes 1, 2, or 3 including patients with compensated or decompensated cirrhosis (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

The following points should be considered when initiating treatment with DAKLINZA:

- Treatment with DAKLINZA should be initiated and monitored by a physician experienced in the treatment of CHC.
- DAKLINZA must not be administered as monotherapy (see **DOSAGE AND ADMINISTRATION**).
- Treatment regimen and duration are dependent on both viral genotype and patient population (see **DOSAGE AND ADMINISTRATION**).
- The sustained virologic response (SVR) rates are reduced in HCV genotype 3 and genotype 1a infected patients with cirrhosis receiving DAKLINZA with sofosbuvir for 12 weeks (see **CLINICAL TRIALS**, **DOSAGE AND ADMINISTRATION**).

Geriatrics (≥ 65 years of age)

Similar safety and effectiveness of DAKLINZA were observed in patients <65 and ≥65 years of age.

Pediatrics (< 18 years of age)

Safety and effectiveness of DAKLINZA in pediatric patients have not been established.

Patients with Compensated and Decompensated Cirrhosis, and Post-Liver Transplantation

DAKLINZA efficacy has been established in combination with sofosbuvir in adults with chronic HCV infection including those with compensated (Child-Pugh Class A) or decompensated cirrhosis (Child-Pugh Class B and C), and those with HCV recurrence after liver transplantation.

However, limited data support the use of DAKLINZA in patients with decompensated liver disease (Child-Pugh Class B and C) (see **CLINICAL TRIALS**).

Patients Co-infected with HIV-1

DAKLINZA efficacy has been established in combination with sofosbuvir in adults with chronic HCV infection including those coinfected with human immunodeficiency virus (HIV-1).

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION and PACKAGING** section of the Product Monograph.

Since DAKLINZA is used in combination with other agents, the contraindications applicable to those agents are applicable to the combination regimen. Refer to the corresponding Product Monograph for a list of contraindications.

DAKLINZA is contraindicated in combination with drugs that strongly induce CYP3A4 and P-glycoprotein transporter (P-gp) and thus may lead to lower exposure and loss of efficacy of DAKLINZA. Contraindicated drugs include, but are not limited to carbamazepine, dexamethasone, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine and St. John's wort (*Hypericum perforatum*) (see **DRUG INTERACTIONS**; **Drug-Drug interactions** and **ACTION AND CLINICAL PHARMACOLOGY**; **Pharmacokinetics**).

WARNINGS AND PRECAUTIONS

General

The efficacy of DAKLINZA as part of a retreatment regimen in patients with prior exposure to a nonstructural protein 5A (NS5A) replication complex inhibitor has not been established.

Warnings and Precautions for other agents in the regimen also apply when coadministered with DAKLINZA.

Potential for Increased Hepatitis B Virus Replication

Cases of increased hepatitis B virus (HBV) replication, including fatal cases, have been reported during and after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. Patients with positive HBV serology should be monitored and treated according to current clinical practice guidelines to manage potential HBV replication. In case of increased HBV replication, start appropriate hepatitis B treatment.

Genotype Specific Activity

Limited data is available to support treatment of genotypes 2, 4 and 6 infection with DAKLINZA and sofosbuvir. There is no clinical data to support treatment of genotype 5.

Carcinogenesis and Mutagenesis

No evidence of carcinogenicity was observed in studies of daclatasvir in mice and rats, and no evidence of mutagenic or clastogenic activity was observed *in vitro* or *in vivo* (see **NON-CLINICAL TOXICOLOGY**).

Drug Interactions

See **CONTRAINDICATIONS** in the Product Monograph for drugs that are contraindicated for use with DAKLINZA. Contraindications for other agents in the regimen also apply when coadministered with DAKLINZA.

Serious Symptomatic Bradycardia When Coadministered with 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 DAA), including DAKLINZA. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered 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 effect is unknown.

Amiodarone should not be coadministered with DAKLINZA and sofosbuvir unless no other alternative antiarrhythmic treatments are possible (i.e. contraindicated or not tolerated). For patients with no alternative treatment option, close monitoring is recommended. Patients should be continuously monitored in an inpatient setting for the first 48 hours of coadministration, after which outpatient monitoring or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone, patients who have discontinued amiodarone just before starting DAKLINZA and sofosbuvir should also undergo cardiac monitoring as described above.

All patients receiving DAKLINZA and sofosbuvir in combination with amiodarone should be warned of the symptoms of bradycardia and heart block and advised to seek medical advice urgently should they experience them. Symptoms of bradycardia may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems. Refer to the amiodarone and sofosbuvir Product Monographs (See **DRUG INTERACTIONS**; **Drug-Drug Interactions**, **Table 6** and **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

Gastrointestinal

DAKLINZA contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption).

Hepatic

DAKLINZA can be administered to patients with mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**; **Pharmacokinetics**).

Of more than 3500 patients in 19 clinical trials of DAKLINZA combination therapy, more than 600 patients had cirrhosis, including 60 patients with advanced cirrhosis or decompensated liver disease. No overall differences in safety were observed between patients with cirrhosis and patients without cirrhosis (see **CLINICAL TRIALS**).

In a clinical trial of DAKLINZA and sofosbuvir for 12 weeks in patients with HCV genotype 3 infection, patients with cirrhosis had lower SVR rates than those without cirrhosis, and in a clinical trial of DAKLINZA, sofosbuvir, and ribavirin for 12 weeks in patients with Child Pugh A, B, or C cirrhosis, patients with decompensated (Child-Pugh C) liver disease had lower SVR rates than those whose disease was classified Child-Pugh A or B.

Renal

DAKLINZA can be administered to patients with any degree of renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**; **Pharmacokinetics**).

Sexual Function/Reproduction

There are no data on the effect of daclatasvir on human fertility. No effects on fertility were observed in animal studies (see **NON-CLINICAL TOXICOLOGY)**.

Special Populations

Pregnant Women

Daclatasvir has not been studied in pregnant women.

The potential risk for humans is unknown. Patients should be advised to notify their health care provider immediately in the event of pregnancy. DAKLINZA should not be used during pregnancy or in women of childbearing potential not using contraception. Use of effective contraception should be continued for 5 weeks after completion of DAKLINZA therapy.

Studies of daclatasvir in animals have shown both maternal and embryofetal developmental toxicity at AUC levels 4.7-fold (rat) and 72-fold (rabbit) above the recommended human dose (RHD) (see **NON-CLINICAL TOXICOLOGY**, **Reproductive Toxicology**).

Use with Ribavirin

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy

should not be started unless a report of a negative pregnancy test has been obtained immediately before initiation of therapy.

When DAKLINZA is used in combination with sofosbuvir and ribavirin, women of childbearing potential and their male partners must use 2 forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. Refer also to the corresponding Product Monograph for ribavirin.

Nursing Women

It is not known whether daclatasvir and its metabolites are present in human milk. Daclatasvir was excreted into the milk of lactating rats with concentrations 1.7- to 2-fold maternal plasma levels. A risk to the newborn/infant cannot be excluded, therefore mothers should be instructed not to breastfeed if they are taking DAKLINZA.

Pediatrics (<18 years of age)

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

Geriatrics (≥ 65 years of age)

Of more than 2000 patients in 12 clinical studies of DAKLINZA combination therapy, 310 were 65 years and older and 20 were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. No dose adjustment of DAKLINZA is required for elderly patients.

Liver Transplant Patients

The safety and efficacy of DAKLINZA in combination with sofosbuvir and ribavirin in the treatment of chronic HCV infection in patients who are pre-, peri- or post-liver transplant were established in a clinical trial (see **CLINICAL TRIALS**).

HCV/HIV-1 Co-infection

The safety and efficacy of DAKLINZA have been established in HCV patients co-infected with HIV-1 (Human Immunodeficiency Virus) (see **CLINICAL TRIALS**).

HCV/HBV Co-infection

The safety and efficacy of DAKLINZA have not been studied in HCV patients co-infected with HBV (hepatitis B virus) (see **WARNINGS AND PRECAUTIONS**, **Potential for Increased Hepatitis B Virus Replication)**. Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV co-infected (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Monitoring and Laboratory Tests

If DAKLINZA and sofosbuvir are administered with amiodarone, close monitoring for bradycardia is recommended. Refer to the amiodarone and sofosbuvir Product Monographs (see **WARNINGS AND PRECAUTIONS**, **Drug Interactions**).

Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV co-infected. HBV levels should be monitored during treatment with DAKLINZA and during post-treatment follow-up.

If DAKLINZA is administered with ribavirin, it is recommended that standard hematological and biochemical laboratory tests be performed in all patients prior to initiating combination therapy. Hematological and biochemical tests of renal and hepatic function should be performed at 2 weeks and 4 weeks after initiation of therapy, and periodically during therapy. More intensive laboratory monitoring and ribavirin dosage adjustment may be required in patients with decompensated cirrhosis or HCV post-transplant recurrence (see **DOSAGE AND ADMINISTRATION, Table 10)** .

Consider screening for the presence of NS5A polymorphisms at amino acid positions M28T, 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 **DOSAGE AND ADMINISTRATION** and **MICROBIOLOGY**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety assessment of DAKLINZA is based on data from more than 3531 patients with chronic HCV infection who received DAKLINZA 60 mg once daily in combination with other HCV therapy.

The safety of DAKLINZA 60 mg once daily in combination with sofosbuvir (with or without ribavirin) was assessed in four open-label randomized clinical trials: Study AI444040, ALLY-3 (AI444218), ALLY-2 (AI444216) and ALLY-1 (AI444215) in 679 patients with chronic HCV genotype 1, 2, 3, 4 or 6 infection, including patients with HIV-1 coinfection, patients with compensated or decompensated cirrhosis, and patients with HCV recurrence after liver transplant. Patients were treated for 8, 12 or 24 weeks.

When DAKLINZA and sofosbuvir is administered with ribavirin, refer to the prescribing information of ribavirin regarding ribavirin associated adverse reactions.

Serious symptomatic bradycardia is reported with DAKLINZA and sofosbuvir combination coadministered with amiodarone (see **WARNINGS AND PRECAUTIONS**).

The most common adverse reactions (any severity, frequency of 10% or greater) were fatigue (19%), headache (15%), and nausea (11%). Most adverse reactions experienced were mild to moderate in severity. Five percent of patients experienced an SAE. Four patients discontinued DAKLINZA for adverse events, only one of which was considered related to study therapy.

Clinical Trial Adverse Drug Reactions

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. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety experience for DAKLINZA in combination with sofosbuvir (DCV+SOF), with or without ribavirin, is presented below.

DAKLINZA in Combination with Sofosbuvir +/- Ribavirin (AI444040)

In the AI444040 trial the most common adverse reactions (any severity, frequency of 10% or greater) were fatigue (29%), headache (19%) and nausea (14%). All adverse reactions experienced were mild to moderate in severity. Seven percent of patients experienced an SAE. One percent of patients discontinued for adverse events.

DAKLINZA in Combination with Sofosbuvir (ALLY-2 and ALLY-3)

In the ALLY-2 trial the most common adverse reaction (frequency of 10% or greater) was fatigue (14%). Most adverse reactions were mild to moderate in severity. Two percent of patients experienced an SAE; all SAEs were considered unrelated to treatment. There were no discontinuations for adverse events in this trial.

In the ALLY-3 trial the most common adverse reactions (frequency of 10% or greater) were headache and fatigue. All adverse reactions were mild to moderate in severity. One patient experienced a serious adverse event (SAE) that was considered unrelated to study therapy, and no patients 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 1**.

Table 1: Adverse Reactions Reported at ≥5% Frequency, DAKLINZA + Sofosbuvir, Studies ALLY-3 and ALLY-2

Body Systems/Preferred Terms Adverse Reaction	DCV+SOF (ALLY-3) N=152 n (%)	DCV+SOF (Co-infected with HIV, ALLY-2) N=203 n (%)
Nervous System Disorder		
Headache	21 (14%)	15 (7%)
General Disorder and Administration Site Conditions		
Fatigue	21 (14%)	28 (14%)
Gastrointestinal Disorder		
Nausea	12 (8%)	18 (9%)
Diarrhea	7 (5%)	10 (5%)

DAKLINZA in Combination with Sofosbuvir and Ribavirin (ALLY-1)

In the ALLY-1 trial the most common adverse reactions (frequency of 10% or greater) among the 113 patients were headache, anemia, fatigue, and nausea. Most adverse reactions were mild to

moderate in severity and were similar in patients with and without cirrhosis. Fifteen (13%) patients experienced an SAE; all SAEs were considered unrelated to treatment. Of the 15 (13%) patients who discontinued study drug for adverse events, 13 (12%) patients discontinued ribavirin only and 2 (2%) patients discontinued all study drugs.

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 2**.

Table 2: Adverse Reactions Reported at ≥5% Frequency in Either Treatment Cohort, DAKLINZA + Sofosbuvir + Ribavirin, Study ALLY-1

Body Systems/Preferred Terms **Adverse Reaction**	**Child-Pugh A, B, and C Cirrhosis** **N=60** **n (%)**	**Post-Liver Transplant** **N=53** **n (%)**
Nervous System Disorder		
Headache	7 (12%)	16 (30%)
Dizziness	0	3 (6%)
General Disorder and Administration Site Conditions		
Fatigue	9 (15%)	9 (17%)
Insomnia	2 (3%)	3 (6%)
Somnolence	3 (5%)	0
Gastrointestinal Disorder		
Nausea	9 (15%)	3 (6%)
Diarrhea	2 (3%)	3 (6%)
Blood and Lymphatic System Disorders		
Anemia	12 (20%)	10 (19%)
Skin and Subcutaneous Tissue Disorders:		
Rash	5 (8%)	1 (2%)

DAKLINZA in Combination with Sofosbuvir With or Without Ribavirin (AI444040, ALLY-1, 2 and 3)

Adverse reactions of at least moderate severity (Grades 2-4) and considered at least possibly related to treatment and occurring at a frequency of 3% or greater in a clinical trial of DAKLINZA in combination with sofosbuvir (with or without ribavirin) are presented in **Table 3.**

Table 3: Adverse Reactions of at Least Moderate Severity Reported in ≥3% of Patients in the Clinical Trial of DAKLINZA in Combination with Sofosbuvir (DCV+SOF) With or Without Ribavirin

Adverse Reaction	Percent with Adverse Reactions[a]	
	DCV+SOF (- Ribavirin) N=476	DCV+SOF (+ Ribavirin) N=203
Blood and Lymphatic System Disorders		
Anemia	0	7%
Nervous System Disorders		
Headache	1%	4%
General Disorders and Aministration Site Conditions		
Fatigue	3%	5%

[a] Events of at least moderate severity (Grades 2-4) with at least a possible relationship to study drug (investigator attribution) and occurring in at least 3% of the 203 patients treated with DAKLINZA and sofosbuvir with ribavirin or the 476 patients treated with DAKLINZA and sofosbuvir without ribavirin in studies AI444040, ALLY-3, ALLY-2 and ALLY-1.

Less Common Clinical Trial Adverse Drug Reactions

Adverse reactions of at least moderate severity (Grades 2-4) reported in clinical studies of DAKLINZA administered in combination with sofosbuvir, with or without ribavirin, for the treatment of HCV infection at a frequency of <3% are listed below by body system.

***General Disorders and Administration Site Conditions*:** malaise, non-cardiac chest pain.

Gastrointestinal Disorders: diarrhea, nausea, gastroesophageal reflux disease, abdominal pain upper, dry mouth.

***Nervous System Disorders*:** dizziness, migraine, amnesia, cognitive disorder, disturbance in attention, dysgeusia, syncope.

Psychiatric Disorders: insomnia, anxiety, depression, irritability, nightmare, thinking abnormal.

Skin and Subcutaneous Tissue Disorders: rash, erythema, pruritus.

***Investigations*:** blood creatinine increased, creatinine renal clearance decreased.

***Musculoskeletal and Connective Tissue Disorders*:** arthralgia, back pain, fibromyalgia, joint swelling, muscle spasms, myalgia, pain in extremity.

***Metabolism and Nutrition Disorders*:** decreased appetite, gout.

***Renal and Urinary Disorders*:** renal failure.

***Cardiac Disorders*:** diastolic dysfunction.

***Respiratory, Thoracic, and Mediastinal Disorders*:** cough.

***Vascular disorders*:** hypertension.

Abnormal Clinical Chemistry Findings

Selected Grade 2-4 laboratory elevations observed in HCV-infected patients treated with DAKLINZA combination therapy and occurring at a frequency of 3% or greater from phase 2 and 3 clinical trial data are presented in **Table 4** by regimen.

Table 4: Selected Grade 2-4 Laboratory Abnormalities Reported in ≥3% in Clinical Trials of DAKLINZA in Combination with Other Oral Agents

Parameter[a]	Percent with Abnormality	
	DCV+SOF (- Ribavirin) N=476	DCV+SOF (+ Ribavirin) N=203
Hemoglobin (≤9.9 g/dL)	<1%	15%
Alanine aminotransferase (ALT) increased (≥2.6 x ULN)	5%	3%
Aspartate aminotransferase (AST) increased (≥2.6 x ULN)	4%	5%
Total bilirubin increased (≥1.6 x ULN)	5%	20%[b]
Lipase increased (≥1.6 x ULN)	13%	18%

ULN= Upper Limit of Normal

[a] Laboratory results were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0.

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

Post-Market Adverse Drug Reactions

Because postmarketing adverse 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.

The following additional adverse reactions were identified during post approval use of DAKLINZA:

Cardiac Disorders

Cardiac arrhythmias including severe bradycardia and heart block have been observed in patients receiving amiodarone who initiate treatment with sofosbuvir in combination with another HCV direct-acting antiviral, including DAKLINZA (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular** and **DRUG INTERACTIONS**).

DRUG INTERACTIONS

Overview

Refer to the corresponding Product Monographs of other drugs in the regimen for drug interaction information. The most conservative recommendation among all the components of the regimen should be followed.

The concomitant use of DAKLINZA and other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of DAKLINZA and possible development of resistance, dosage adjustments of concomitant medications, or clinically significant adverse reactions from greater exposures of concomitant drugs.

Drugs contraindicated with DAKLINZA due to loss of efficacy and possible development of resistance are summarized in **Table 5**. Clinical guidance for preventing or managing other possible and known significant drug interactions is presented in **Table 6**. 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.

Drug-Drug Interactions

Potential for Other Drugs to Affect DAKLINZA

Daclatasvir is a substrate of CYP3A4, P-gp, and organic cation transporter (OCT) 1. Moderate or strong inducers of CYP3A4 or P-gp may decrease the plasma levels and therapeutic effect of daclatasvir; strong inducers of CYP3A4 are contraindicated with DAKLINZA and dose increases to 90 mg once daily (three 30 mg tablets or one 60 mg and one 30 mg tablet) are recommended with moderate inducers (see **CONTRAINDICATIONS** and **Table 5**, **Table 6** and **Table 8**). Strong inhibitors of CYP3A4 (eg, clarithromycin, erythromycin, itraconazole, ketoconazole, ritonavir) may result in significant changes in the plasma exposure of daclatasvir and dose reductions to 30 mg once daily (using the 30 mg tablet; DAKLINZA tablets should not be broken) are recommended (see **Table 6** and **Table 8**). P-gp may play roles in both limiting the oral absorption of daclatasvir and mediating daclatasvir excretion, and OCT 1 may play a role in mediating liver uptake of daclatasvir. Coadministration of medicines that inhibit P-gp or OCT1 activity is likely to have a limited effect on daclatasvir exposure. A drug interaction study with cyclosporine, which is a strong P-gp inhibitor and a weak CYP3A inhibitor resulted in a 40% increase in daclatasvir AUC suggesting that inhibition of P-gp alone with no or minimal inhibition of CYP3A is not expected to significantly increase daclatasvir exposure.

Potential for DAKLINZA to Affect Other Drugs

In vitro, daclatasvir inhibited efflux transporters (P-gp, breast cancer resistance protein [BCRP]), hepatic uptake transporters (OATP 1B1, 1B3 and 2B1), organic anion transporters (OAT1, OAT3), and OCT1 and OCT2. *In vivo,* daclatasvir has been shown to be a weak-to-moderate inhibitor of P-gp, and a weak inhibitor of OATP1B1, OATP1B3, and BCRP. Administration of DAKLINZA may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B1 or 1B3, or BCRP (eg, digoxin, rosuvastatin), which could increase or prolong their therapeutic effect

and adverse reactions (see **Table 6** and **Table 7**). Caution should be used if the medicinal product has a narrow therapeutic range (eg, digoxin, **Table 6**). Daclatasvir is not expected to have a clinical effect on the pharmacokinetics of substrates of OATP2B1, OAT1, OAT3, or OCT2. Daclatasvir, *in vitro*, did not inhibit (IC_{50} >40 μM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6. Daclatasvir did not have a clinically meaningful effect on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate.

Drugs Contraindicated with DAKLINZA

DAKLINZA is contraindicated in combination with drugs that strongly induce CYP3A4 and P-gp (see **Table 5**), and thus, may lead to lower exposure and loss of efficacy of DAKLINZA (see **CONTRAINDICATIONS**).

Table 5 Drugs that are Contraindicated with DAKLINZA

Drug Class/Drug Name[a]	Mechanism of Interaction	Clinical Comment
Anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Strong induction of CYP3A4 by coadministered drug	Coadministration of DAKLINZA with these drugs may decrease the plasma exposures of the active substances and lead to loss of virologic response to DAKLINZA.
Antimycobacterial agents rifabutin, rifampin, rifapentine[b]		
Glucocorticoid, systemic dexamethasone		
Herbal products St. John's wort (*Hypericum perforatum*)		

a This table is not a comprehensive list of all drugs that strongly induce CYP3A4.

b Not marketed in Canada.

Established and Potentially Significant Drug Interactions

Table 6 provides clinical recommendations for established or potentially significant drug interactions between DAKLINZA and other drugs (see **Table 7** and **Table 8** for pharmacokinetic data from drug-drug interaction studies).

Table 6: Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
HCV antiviral agents		
Simeprevir[c]	↑ Daclatasvir	No dose adjustment is necessary with simeprevir. Although increased daclatasvir concentrations were observed in a drug-drug interaction study in healthy subjects, data from HCV-infected patients indicate that no dose adjustment of either drug is needed if simeprevir and daclatasvir are coadministered.
Telaprevir[c]	↑ Daclatasvir	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with telaprevir or other strong inhibitors of CYP3A4.
Boceprevir	↑ Daclatasvir	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with boceprevir or other strong inhibitors of CYP3A4.
HIV-1 antiviral agents		
Protease inhibitor: Atazanavir/ritonavir[c] Atazanavir/cobicistat	↑ Daclatasvir	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with atazanavir/ritonavir, atazanavir/cobicistat, or other strong inhibitors[d] of CYP3A4.
Non-nucleoside reverse transcriptase inhibitor (NNRTI): Efavirenz[c] Etravirine Nevirapine	↓ Daclatasvir	The dose of DAKLINZA should be increased to 90 mg once daily when coadministered with efavirenz, etravirine, nevirapine or other moderate inducers of CYP3A4.
Integrase inhibitor: Elvitegravir/cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	↑ Daclatasvir	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with cobicistat or other strong inhibitors of CYP3A4.
Antibacterials		
Clarithromycin	↑ Daclatasvir	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with clarithromycin or other strong inhibitors of CYP3A4.
Erythromycin	↑ Daclatasvir	Administration of DAKLINZA with erythromycin may result in increased concentrations of daclatasvir. Caution is advised.
Anticoagulants		
Dabigatran etexilate	↑ Dabigatran etexilate	Safety monitoring is advised when initiating treatment with DAKLINZA in patients receiving dabigatran etexilate or other intestinal P-gp substrates that have a narrow therapeutic range.
Antifungals		
Itraconazole Ketoconazole[c]	↑ Daclatasvir	The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with

Table 6: Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Posaconazole Voriconazole		ketoconazole, itraconazole, posaconazole, voriconazole, or other strong inhibitors of CYP3A4.
Fluconazole	↑ Daclatasvir	Modest increases in concentrations of daclatasvir are expected, but no dose adjustment of DAKLINZA or fluconazole is required.
Cardiovascular agents		
Antiarrhythmic:		
Amiodarone	Interaction not studied.	Co-administration of amiodarone with DAKLINZA may result in serious symptomatic bradycardia. Consider an alternative antiarrhythmic. For patients with no alternative antiarrhythmic option, close monitoring is recommended if amiodarone is administered with DAKLINZA in combination with sofosbuvir. Refer to amiodarone and sofosbuvir Product Monographs (See **WARNINGS AND PRECAUTIONS**;**Drug Interactions** and **ADVERSE REACTIONS; Post-Market Adverse Drug Reactions**)
Digoxin[c]	↑ Digoxin	Digoxin and other P-gp substrates with a narrow therapeutic range should be used with caution when coadministered with DAKLINZA. The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Calcium channel blockers: Diltiazem Verapamil	↑ Daclatasvir	Administration of DAKLINZA with diltiazem or verapamil may result in increased concentrations of daclatasvir. Caution is advised.
Endothelin receptor antagonist		
Bosentan	↓ Daclatasvir	The dose of DAKLINZA should be increased to 90 mg once daily when coadministered with bosentan or other moderate inducers of CYP3A4.
Lipid-lowering agents		
HMG-CoA reductase inhibitor: Atorvastatin Fluvastatin Pravastatin Rosuvastatin[c] Simvastatin	↑ statins	Based on a clinical study with rosuvastatin (10 mg dose), an increase in plasma exposure of rosuvastatin (a substrate of OATP 1B1/1B3 and BCRP) was observed when coadministered with DCV. Treatment with rosuvastatin and other OATP 1B1/1B3 and/or BCRP substrates can be initiated at the recommended dose when coadministered with DAKLINZA. Close clinical monitoring for both desired therapeutic outcomes and side effects of the OATP and/or BCRP substrate is recommended.

Table 6: Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Wakefulness promoting agent		
Modafinil	↓ Daclatasvir	The dose of DAKLINZA should be increased to 90 mg once daily when coadministered with modafinal or other moderate inducers of CYP3A4.

[a] This table is not all inclusive.

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

[c] These interactions have been studied (see **Table 7** and **Table 8**).

d Refer to section **Drugs without Significant Interactions with DAKLINZA**, for other protease inhibitors where no dose adjustment is required

Assessment of Drug Interactions

Drug interaction studies were conducted with daclatasvir and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of daclatasvir on the C_{max}, AUC, and C_{min} of the coadministered drug are summarized in **Table 7**. The effects of the coadministered drug on the C_{max}, AUC, and C_{min} of daclatasvir are summarized in **Table 8**. All studies were conducted in healthy adults unless otherwise noted.

Table 7: Effect of DAKLINZA on the Pharmacokinetic Parameter Values of Co-Administered Drugs

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	N	Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug With/Without Daclatasvir. No Effect = 1.00		
				C_{max}	AUC	C_{min}
Antidepressants						
Escitalopram	10 mg QD	60 mg QD	15	1.00 (0.92, 1.08)	1.05 (1.02, 1.08)	1.10 (1.04, 1.16)
Antiviral Agents, HCV						
Peginterferon alfa/ribavirin[a]	180 µg once weekly 1000 or 1200 mg/day	60 mg QD	9	Ribavirin: 0.94 (0.79, 1.11)	Ribavirin: 0.94 (0.80, 1.11)	Ribavirin: 0.98 (0.82, 1.17)
Simeprevir	150 mg QD	60 mg QD	24	1.39 (1.27, 1.52)	1.44 (1.32, 1.56)	1.49 (1.33, 1.67)
Sofosbuvir[a]	400 mg QD	60 mg QD	30	GS-331007: 0.8 (0.77, 0.90)[b]	GS-331007: 1.0 (0.95, 1.08)[b]	GS-331007: 1.4 (1.35, 15.3)[b]

Table 7: Effect of DAKLINZA on the Pharmacokinetic Parameter Values of Co-Administered Drugs

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	N	Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug With/Without Daclatasvir. No Effect = 1.00		
				C_{max}	AUC	C_{min}
Telaprevir	500 mg q12h	20 mg QD	15	1.01 (0.89, 1.14)	0.94 (0.84, 1.04)	NA
	750 mg q8h	20 mg QD	14	1.02 (0.95, 1.09)	0.99 (0.95, 1.03)	NA
Antiviral Agents, HIV-1 or HBV						
Tenofovir disoproxil fumarate	300 mg QD	60 mg QD	20	0.95 (0.89, 1.02)	1.10 (1.05, 1.15)	1.17 (1.10, 1.24)
Darunavir + ritonavir	600 mg/ritonavir 100 mg b.i.d	30 mg QD	11	0.97 (0.80, 1.17)	0.90 (0.73, 1.11)	0.98 (0.67, 1.44)
Lopinavir + ritonavir	400 mg/ritonavir 100 mg b.i.d	30 mg QD	5	1.22 (1.06, 1.41)	1.15 (0.77, 1.72)	1.54 (0.46, 5.07)
Dolutegravir	50 mg QD	60 mg QD	12	1.29 (1.07, 1.57)	1.33 (1.11, 1.59)	1.45 (1.25, 1.68)
Cardiovascular agents						
Digoxin	0.125 mg QD	60 mg QD	15	1.65 (1.52, 1.80)	1.27 (1.20, 1.34)	1.18 (1.09, 1.28)
Hormonal Contraceptives						
Ethinyl estradiol/ norgestimate	35 μg QD for 21 days/norgestimate 0.180/0.215/ 0.250 mg QD for 7/7/7 days	60 mg QD	20	Ethinyl estradiol: 1.11 (1.02, 1.20) Norelgestromin: 1.06 (0.99, 1.14) Norgestrel: 1.07 (0.99, 1.16)	Ethinyl estradiol: 1.01 (0.95, 1.07) Norelgestromin: 1.12 (1.06, 1.17) Norgestrel: 1.12 (1.02, 1.23)	NA
Immunosuppressants						
Cyclosporine	500 mg single dose	60 mg QD	14	0.96 (0.91, 1.02)	1.03 (0.97, 1.09)	NA
Tacrolimus	5 mg single dose	60 mg QD	14	1.05 (0.90, 1.23)	1.00 (0.88, 1.13)	NA
Lipid-lowering Agents						
Rosuvastatin	10 mg single dose	60 mg QD	22	2.04 (1.83, 2.26)	1.58 (1.44, 1.74)	NA

Table 7: Effect of DAKLINZA on the Pharmacokinetic Parameter Values of Co-Administered Drugs

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	N	Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug With/Without Daclatasvir. No Effect = 1.00		
				C_{max}	AUC	C_{min}
Narcotic Analgesics						
Methadone	40-120 mg QD individualized dose[c]	60 mg QD	14	R-methadone: 1.07 (0.97, 1.18)	R-methadone: 1.08 (0.94, 1.24)	R-methadone: 1.08 (0.93, 1.26)
Buprenorphine + naloxone	8/2 mg to 24/6 mg QD	60 mg QD	9	Buprenorphine: 1.40 (1.03, 1.64) Norbuprenor-phine 1.65 (1.38, 1.99)	Buprenorphine 1.37 (1.24, 1.52) Norbuprenor-phine 1.62 (1.30, 2.02)	Buprenorphine 1.17 (1.03, 1.32) Norbuprenor-phine 1.46 (1.12, 1.89)
Sedatives						
Midazolam	5 mg single dose	60 mg QD	18	0.95 (0.88, 1.04)	0.87 (0.83, 0.92)	NA

[a] Study conducted in patients with chronic HCV infection.

[b] GS-331007 is the major circulating metabolite of the prodrug sofosbuvir.

[c] Evaluated in opioid-dependent adults on stable methadone maintenance therapy.

NA = not available.

Table 8: Effect of Coadministered Drugs on the Pharmacokinetic Parameter Values of DAKLINZA

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	N	Mean Ratio (90% CI) of Pharmacokinetic Parameters of Daclatasvir With/Without Coadministered Drug. No Effect = 1.00		
				C_{max}	AUC	C_{min}
Acid-reducing Agents						
Famotidine	40 mg single dose	60 mg single dose	18	0.56 (0.46, 0.87)	0.82 (0.70, 0.96)	0.89 (0.75, 1.06)
Omeprazole	40 mg QD	60 mg single dose	12	0.64 (0.54, 0.77)	0.84 (0.73, 0.96)	0.92 (0.80, 1.05)

Table 8: Effect of Coadministered Drugs on the Pharmacokinetic Parameter Values of DAKLINZA

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	N	Mean Ratio (90% CI) of Pharmacokinetic Parameters of Daclatasvir With/Without Coadministered Drug. No Effect = 1.00		
				C_{max}	AUC	C_{min}
Antidepressants						
Escitalopram	10 mg QD	60 mg QD	15	1.14 (0.98, 1.32)	1.12 (1.01, 1.26)	1.23 (1.09, 1.38)
Antifungals						
Ketoconazole	400 mg QD	10 mg single dose	14	1.57 (1.31, 1.88)	3.00 (2.62, 3.44)	NA
Antimycobacterials						
Rifampin	600 mg QD	60 mg single dose	14	0.44 (0.40, 0.48)	0.21 (0.19, 0.23)	NA
Antiviral Agents, HCV						
Peginterferon alfa/ribavirin[b]	180 µg once weekly/ 1000 or 1200 mg/day	60 mg QD	10	↔[c]	↔[c]	↔[c]
Simeprevir	150 mg QD	60 mg QD	17	1.50 (1.39, 1.62)	1.96 (1.84, 2.10)	2.68 (2.42, 2.98)
Sofosbuvir[e]	400 mg QD	60 mg QD	30	0.88[c] (0.78, 0.99)	0.95[c] (0.82, 1.10)	0.91[c] (0.71, 1.16)
Telaprevir [a]	500 mg q12h	20 mg QD	15	1.46 (1.28, 1.66)	2.32 (2.06, 2.62)	NA
	750 mg q8h	20 mg QD	15	1.22 (1.04, 1.44)	2.15 (1.87, 2.48)	NA
Antiviral Agents, HIV-1 or HBV						
Atazanavir/ ritonavir [a]	300 mg/100 mg QD	20 mg QD	14	1.35 (1.24, 1.47)	2.10 (1.95, 2.26)	3.65 (3.25, 4.11)
Efavirenz [a]	600 mg QD	60 mg QD for 9 days/120 mg QD for 5 days	15	0.83 (0.76, 0.92)	0.68 (0.60, 0.78)	0.41 (0.34, 0.50)
Tenofovir disoproxil fumarate	300 mg QD	60 mg QD	20	1.06 (0.98, 1.15)	1.10 (1.01, 1.21)	1.15 (1.02, 1.30)
Darunavir + ritonavir[a]	800 mg/ ritonavir 100 mg QD	30 mg QD	11	0.77 (0.70, 0.85)	1.41 (1.32, 1.50)	NA

Table 8: Effect of Coadministered Drugs on the Pharmacokinetic Parameter Values of DAKLINZA

Concomitant Drug	Coadministered Drug Dose	DAKLINZA Dose	N	Mean Ratio (90% CI) of Pharmacokinetic Parameters of Daclatasvir With/Without Coadministered Drug. No Effect = 1.00		
				C_{max}	AUC	C_{min}
Lopinavir + ritonavir[a]	400 mg/ritonavir 100 mg b.i.d	30 mg QD	5	0.67 (0.61, 0.74)	1.15 (1.07, 1.24)	NA
Dolutegravir	50 mg QD	60 mg QD	12	1.03 (0.84, 1.25)	0.98 (0.83, 1.15)	1.06 (0.88, 1.29)
Immunosuppressants						
Cyclosporine	400 mg single dose	60 mg QD	14	1.04 (0.94, 1.15)	1.40 (1.29, 1.53)	1.56 (1.41, 1.71)
Tacrolimus	5 mg single dose	60 mg QD	14	1.07 (1.02, 1.12)	1.05 (1.03, 1.07)	1.10 (1.03, 1.19)
Narcotic Analgesics						
Methadone	40-120 mg QD individualized dose[d]	60 mg QD	14	↔[e]	↔[e]	↔[e]
Buprenorphine + naloxone	8/2 mg to 24/6 mg QD	60 mg QD	9	↔[e]	↔[e]	↔[e]

[a] Daclatasvir pharmacokinetic results are dose-normalized to 60 mg dose.

[b] Study conducted in patients with chronic HCV infection.

[c] Comparison for daclatasvir was to a historical reference (data from 3 studies of daclatasvir 60 mg once daily with peginterferon alfa and ribavirin).

[d] Evaluated in opioid-dependent adults on stable methadone maintenance therapy.

[e] Compared to historical data.

NA = not available.

Drugs without Significant Interactions with DAKLINZA

Based on the results of drug interaction studies and expected interaction potential, no dose adjustment is recommended when DAKLINZA is given with buprenorphine + naloxone, cyclosporine, escitalopram, ethinyl estradiol + norgestimate, darunavir + ritonavir, dolutegravir, famotidine, lopinavir + ritonavir, methadone, midazolam (parenteral), omeprazole, peginterferon alfa, raltegravir, rilpivirine, ribavirin, simeprevir, sofosbuvir, tacrolimus, tenofovir disoproxil fumarate or tenofovir.

Drug-Food Interactions

DAKLINZA may be taken with or without food (See **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**; **Pharmacokinetics**).

Drug-Herb Interactions

Coadministration of St. John's wort (*Hypericum perforatum*), a strong inducer of CYP3A4 and P-gp, may decrease DAKLINZA plasma concentrations, which may result in loss of therapeutic effect.

St. John's wort is contraindicated with DAKLINZA (See **CONTRAINDICATIONS**).

Drug-Laboratory Interactions

Interactions of DAKLINZA with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

DAKLINZA must be administered in combination with other drugs for the treatment of HCV (see **Table 9** and **CLINICAL TRIALS**).

Treatment regimen and duration are dependent on both viral genotype and patient population.

NS5A Resistance Testing in HCV Genotype 1a-Infected Patients with Cirrhosis

Consider screening for the presence of NS5A polymorphisms at amino acid positions M28T, 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**).

Recommended Dose

The recommended dose of DAKLINZA is 60 mg, taken orally, once daily with or without food.

For co-infected patients (HCV-HIV-1) follow the dosage recommendation of DAKLINZA with certain antiretroviral agents (see **DRUG INTERACTIONS**).

For specific dose recommendations for sofosbuvir, refer to the corresponding Product Monograph.

For patients with Child-Pugh A, B or C cirrhosis or recurrence of HCV infection after liver transplant, the recommended initial dose of ribavirin is 600 mg daily with food, modified based on hemoglobin and creatinine clearance measurements (see **Dose Modification and Interruption, Table 10**).

The recommended regimens and treatment duration of the combination therapies are provided in **Table 9**

Table 9: Recommended Treatment Regimen and Duration in Monoinfected and Co-infected (HCV-HIV-1)a Treatment-Naive and Treatment-Experiencedb Populations with Genotypes 1, 2 or 3 HCV.

HCV Genotype	Patient Population	Treatment Regimen	Treatment Duration (weeks)
Genotype 1 Genotype 2[c] Genotype 3	Without Cirrhosis	DAKLINZA + sofosbuvir	12
	With Cirrhosis compensated (CP A)[d] decompensated (CP B or C[e])	DAKLINZA + sofosbuvir + ribavirin	12
	Post-Liver Transplant		12

[a] Daclatasvir dose is required to be adjusted based on the antiretroviral regimen (see **DRUG INTERACTIONS**, **Table 6**).

[b] Excludes patients with previous exposure to NS5A inhibitors.

[c] The treatment regimen and duration recommendations for GT-2 (Child-Pugh Class A, B or C) are based on a limited number of patients . No GT-2 post-liver transplant patients were enrolled in the clinical studies (see **CLINICAL TRIALS, Table 17**).

[d] For GT-1 patients with compensated cirrhosis (Child-Pugh Class A), DAKLINZA + sofosbuvir without ribavirin may be considered.

[e] Lower SVR12 rates have been reported with decompensated cirrhotic patients (Child-Pugh Class C) treated for 12 weeks with DAKLINZA + sofosbuvir + ribavirin. Consider extending treatment duration to 24 weeks with or without ribavirin. Ribavirin may be added based on clinical assessment of individual patient (see **Dose Modification and Interruption** and **CLINICAL TRIALS**).

Dose Modification and Interruption

Daklinza

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

Ribavirin

If tolerated, the ribavirin dose can be titrated up to 1000 mg/day. If the starting dose is not well-tolerated, the dose should be reduced as clinically indicated, based on haemoglobin and creatinine measurements (see **Table 10**).

Table 10 Ribavirin dosing guidelines for coadministration with Daklinza regimen for patients with cirrhosis or post-transplant

Laboratory Value/Clinical Criteria	Ribavirin Dosing Guideline
Haemoglobin	
>12 g/dL	600 mg daily
>10 to ≤12 g/dL	400 mg daily
>8.5 to ≤10 g/dL	200 mg daily
≤8.5 g/dL	Discontinue ribavirin
Creatinine Clearance	
>50 mL/min	Follow guidelines above for haemoglobin
>30 to ≤50 mL/min	200 mg every other day
≤30 mL/min or haemodialysis	Discontinue ribavirin

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

Special Populations

Pediatrics (<18 years of age)

DAKLINZA has not been studied in pediatric patients <18 years of age.

Geriatrics (≥65 years of age)

No dose adjustment of DAKLINZA is required for elderly patients.

Renal Impairment

No dose adjustment of DAKLINZA is required for patients with any degree of renal impairment.

Refer to the Product Monograph for SOVALDI for information on use of those products in patients with renal impairment.

Hepatic Impairment

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

Missed Dose

Patients should be instructed that if they miss a dose of DAKLINZA, the dose should be taken as soon as possible if remembered within 20 hours of the scheduled dose time. However, if the missed dose is remembered more than 20 hours after the scheduled dose, 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 corresponding Product Monographs.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

There is no known antidote for overdose of DAKLINZA. Treatment of overdose with DAKLINZA should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Because daclatasvir is highly protein bound (>99%) and has a molecular weight greater than 500 $g \cdot mol^{-1}$, dialysis is unlikely to significantly reduce plasma concentrations of the drug.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Daclatasvir, a direct-acting antiviral agent (DAA) against the hepatitis C virus, is a highly selective inhibitor of the NS5A replication complex (see **MICROBIOLOGY**).

Pharmacodynamics

Effect on the Electrocardiogram

The effect of daclatasvir 60 mg tablet and 180 mg tablet on the QTc interval was evaluated in a randomized, partially blinded, placebo-controlled, positive-controlled, 4-period, 4-treatment, single-dose, crossover study in 56 healthy subjects. Subjects were randomized to receive daclatasvir (60 mg or 180 mg) or matching placebo under blinded conditions; moxifloxacin 400 mg, the positive control, was administered as an open-label treatment. Daclatasvir plasma exposures after a single 180 mg dose, as measured by Cmax, AUC(0-T), AUC(INF), were approximately 2.5, 2.9, and 3.0 times the exposures after a single 60 mg dose. These exposures are expected to bracket the highest plasma concentrations expected clinically. Neither 60 mg nor 180 mg of daclatasvir resulted in clinically relevant ΔQTcF prolongations. At every time point (1 to >22 hours), the upper bound of the two-sided 90% confidence interval for ΔΔQTcF (daclatasvir minus placebo) was less than 5 msec. The concentration-response analysis of QTcF revealed no apparent trend of ΔΔQTcF with increased plasma concentration. Daclatasvir 60 mg and 180 mg had no effect on heart rate, QRS or PR intervals.

Pharmacokinetics

The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in patients with chronic HCV (see **Table 11**).

Table 11: Summary of Once-Daily Administration of DAKLINZA in Healthy Adults and HCV Infected Patients.

PK Parameters	Healthy Subjects Geometric Mean (CV%)	HCV-Infected Patients[a] Geometric Mean (CV%)
AUC_{TAU} (ng●h/mL)	13203 (29)	14122 (70)
C_{max} (ng/mL)	1549 (29)	1534 (58)
C_{min} (ng/mL)	231 (48)	232 (83)

[a] Daclatasvir 60 mg once daily in combination with peginterferon alfa and ribavirin.

Overall, exposure to daclatasvir in patients infected with HCV and in healthy subjects was similar at the 60 mg dose. Daclatasvir exposures are comparable when co-administered with either peginterferon alfa/ribavirin or sofosbuvir.

Absorption

Daclatasvir is rapidly absorbed with a maximum concentration appearing 1-2 hours after ingestion of the tablet formulation. In normal healthy volunteers, daclatasvir C_{max} and AUC_{INF} are proportional to dose in the 20 mg to 60 mg dose range. In both healthy subjects and patients with HCV at doses ranging from 1 to 100 mg once daily for 14 days, steady state was achieved in approximately 4 days of once-daily dosing with a mean T-HALF of 12 to 15 hours and a median T_{max} of 1 to 2 hours.

In Caco-2 cells, daclatasvir exhibited an efflux ratio of > 24 suggesting that daclatasvir is likely to be a substrate of the efflux transporter P-gp. Daclatasvir is not a substrate of breast cancer resistance protein (BCRP). Despite being a P-gp substrate, daclatasvir was well absorbed with an absolute bioavailability of 67% observed in humans, suggesting that intestinal efflux is not a substantial barrier for daclatasvir absorption *in vivo*.

Effect of Food on Oral Absorption

In healthy subjects, administration of a daclatasvir 60 mg tablet after a high-fat meal (approximately 1000 kcal, approximately 50% from fat) decreased daclatasvir C_{max} and AUC by 28% and 23%, respectively, compared with administration under fasting conditions. Administration of a daclatasvir 60 mg tablet after a light meal (approximately 275 kcal, approximately 15% from fat) did not reduce daclatasvir exposure. The change in exposure when daclatasvir is coadministered with a high fat meal is not considered clinically significant and is not expected to alter the efficacy of daclatasvir based on an exposure-response analysis (see **DOSAGE AND ADMINISTRATION**).

Distribution

At steady state, protein binding of daclatasvir in HCV-infected patients was approximately 99% and independent of dose at the dose range studied (1-100 mg). In patients 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 (Vss) was 47.1 L (6.22 L/kg).

In vitro studies indicate that daclatasvir is actively and passively transported into hepatocytes, with active transport being the major contributor. The active transport is mediated by OCT1 and other unidentified uptake transporters, but not by OAT2, sodium-taurocholate cotransporting polypeptide (NTCP), or OATPs. *In vitro,* daclatasvir inhibited efflux transporters (P-gp, BCRP), hepatic uptake transporters (OATP 1B1, 1B3 and 2B1), organic anion transporter (OAT) 1 and OAT3, and organic cation transporter (OCT)1 and OCT2.

Metabolism

Following a single oral dose (60 mg) administration of ^{14}C-DCV in healthy adult subjects (n = 6), the systemic exposure of the parent drug or unmodified daclatasvir was 94.3%. Minimal metabolites were present in plasma (< 5%). Overall, 8 metabolites (7 products of oxidation and 1 product of hydration) were formed in humans. Daclatasvir was the predominant radioactive component in human plasma, accounting for 97% to 100% of the plasma radioactivity. BMS-805215 was the only metabolite detected in human plasma, accounting for trace amounts to 2% of the plasma radioactivity. BMS-805215 is an active metabolite, but it is more than 100-fold less potent than daclatasvir. *In vitro* studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 the major CYP isoform responsible for the metabolism of daclatasvir and in the formation of BMS-805215.

Excretion

Following a single-dose of oral ^{14}C-daclatasvir in healthy subjects, approximately 88% of total radioactivity was recovered in the feces, primarily as parent drug (approximately 53% of the dose), and some as the predominant metabolite in humans, BMS-805215 (approximately 15% of the dose); approximately 6.6% was recovered in urine predominantly as parent drug. These data indicate that the liver is the major clearance organ for daclatasvir in humans. *In vitro* studies indicate that daclatasvir is actively and passively transporter into hepatocytes. The active transport is mediated by OCT1 and other unidentified uptake transporters.

Following multiple-dose administration of daclatasvir, the terminal elimination half-life of daclatasvir ranged from 9 to 15 hours in healthy subjects and 10 to 15 hours in HCV-infected patients. In subjects who received daclatasvir 60 mg tablet orally followed by 100 μg [^{13}C,^{15}N]-daclatasvir intravenous dose, the total clearance was 4.24 L/h.

Special Populations and Conditions

Pediatrics

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

Geriatrics

Population pharmacokinetic analysis of data from clinical trials indicated that age had no apparent effect on the pharmacokinetics of daclatasvir (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

Gender

Based on population pharmacokinetic analysis of data from clinical trials, AUC values at steady state in male and female HCV-infected patients were 9940 ng.h/mL and 13243 ng.h/mL, respectively. Overall, the difference between male and female patients are minor and not considered clinically meaningful.

Race

Based on population pharmacokinetic analysis of data from clinical trials, AUC values at steady state in white, black, and Asian HCV-infected patients were 11097 ng.h/mL, 12104 ng.h/mL, and 10951 ng.h/mL, respectively. Overall, the differences between these groups are minor and not considered clinically meaningful.

Hepatic Insufficiency

The pharmacokinetics of daclatasvir 30 mg single dose was investigated in an open-label, parallel-group study of 18 non-HCV infected subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment and compared to 12 matched control subjects with normal hepatic function. For total daclatasvir, the C_{max} decreased by 46%, 45%, and 55% and AUC_{INF} decreased by 43%, 38%, and 36%, respectively, in subjects with mild, moderate, and severe hepatic impairment compared to normal subjects. The exposure for free (unbound) daclatasvir was 14% to 43% lower for C_{max} and 2% to 40% lower for AUC_{INF} in hepatically impaired subjects; hepatic impairment did not have a clinically significant effect on the free drug concentration of daclatasvir. There was no clear association between daclatasvir exposures and Child-Pugh scores. Patients with any degree of hepatic impairment may receive the recommended 60 mg dose of DAKLINZA.

Renal Insufficiency

The pharmacokinetics of daclatasvir was studied with a single 60 mg dose of daclatasvir in non-HCV infected subjects with normal renal function (creatinine clearance [CLcr] ≥ 90 mL/min, defined by the Cockcroft-Gault CLcr formula), with mild (≥ 60 to <90 mL/min), moderate (≥ 30 to <60 mL/min), or severe (CLcr < 30 mL/min) renal impairment not on hemodialysis, and in patients with end-stage renal disease (ESRD) on hemodialysis. Compared to non-HCV-infected subjects with normal renal function, the AUC of daclatasvir was estimated to be 26.4%, 59.8%, and 79.6% higher in subjects with CLcr values of 60, 30, and 15 mL/min, respectively. Daclatasvir unbound AUC was estimated to be 18.0%, 39.2%, and 51.2% higher for subjects with CLcr values of 60, 30, and 15 mL/min, respectively, relative to subjects with normal renal function. Subjects with end-stage renal disease requiring hemodialysis had a 26.9% increase in daclatasvir AUC and a 20.1% increase in unbound AUC compared to subjects with normal renal function. No dosage adjustment of DAKLINZA is necessary for patients with any degree of renal impairment.

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

STORAGE AND STABILITY

Store at room temperature (15° to 30°C) and store in the original container.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DAKLINZA tablets are available for oral administration in strengths 30 mg and 60 mg daclatasvir containing the following non-medicinal ingredients for the tablet core: anhydrous lactose, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry Green and silicon dioxide. The Opadry green contains the following inactive ingredients: FD & C blue #2 / indigo carmine aluminum lake, hypromellose, iron oxide (yellow), polyethylene glycol 400 and titanium dioxide.

DAKLINZA 30 mg daclatasvir (equivalent to 33 mg daclatasvir dihydrochloride) tablets are green, biconvex, pentagonal, and debossed with "BMS" on one side and "213" on the other side.

DAKLINZA 60 mg daclatasvir (equivalent to 66 mg daclatasvir dihydrochloride) tablets are light green, biconvex, pentagonal, and debossed with "BMS" on one side and "215" on the other side.

DAKLINZA tablets, 30 mg and 60 mg are supplied in HDPE bottles containing 28 tablets.

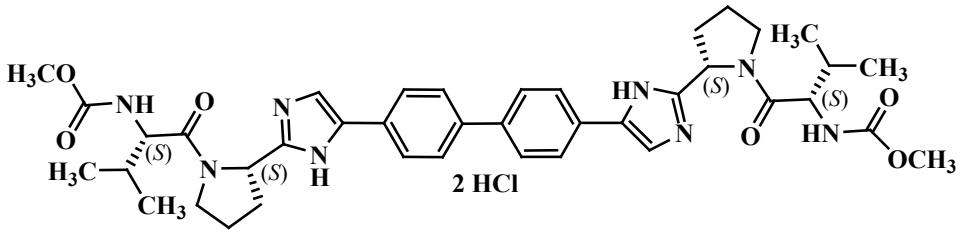
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	daclatasvir dihydrochloride
Chemical name:	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).
Molecular formula:	$C_{40}H_{50}N_8O_6 \bullet 2HCl$
Molecular mass:	811.80 $g \cdot mol^{-1}$ (HCl salt), 738.88 $g \cdot mol^{-1}$ (free base)

Structural formula:



Physicochemical properties:

Appearance:	Daclatasvir drug substance is a white to yellow powder.
Solubility:	Daclatasvir has poor solubility in water and ethanol at neutral pH. The solubility is strongly pH-dependent and the solubility is high at low pH values.

CLINICAL TRIALS

The efficacy and safety of DAKLINZA in combination with sofosbuvir, with or without ribavirin were evaluated in a phase 2 study (AI444040) and three phase 3 clinical trials: ALLY-1 (AI444215) in patients with Child-Pugh A, B or C cirrhosis or recurrence of chronic HCV infection after liver transplant, ALLY-2 (AI444216) in patients with HCV/HIV-1 coinfection and ALLY-3 (AI444218) in patients with chronic HCV genotype 3 infection and compensated liver disease (see **Table 12** for details of the study design). In these studies, sustained virologic response (SVR, virologic cure) was defined as HCV RNA below the lower limit of quantification (LLOQ) at post-treatment week 12.

Table 12: Summary of Study Design for Trial of DAKLINZA Combination Therapy for Chronic Hepatitis C Infection

Trial	Treatment Regimens and Dosage	Genotype/Population	Duration of Treatment
AI444040 (open-label)	DAKLINZA (60 mg QD) and sofosbuvir (400 mg QD) ± ribavirin[a], n=211 (90 patients received ribavirin[a])	GT-1, 2, 3 treatment-naive, without cirrhosis GT-1, failed prior protease inhibitor (PI) therapy, without cirrhosis	GT-1 treatment-naive (n=82), 12 weeks GT-1, 2, 3 treatment-naive (n=88) and GT-1 failed prior PI therapy (n=41), 24 weeks
AI444215 (ALLY-1) open-label	DAKLINZA (60 mg QD), sofosbuvir (400 mg QD) and ribavirin[b] n=113	GT-1, 2, 3, 4 [c] treatment naive and treatment experienced	12 weeks
AI444216 (ALLY-2) open-label	DAKLINZA (60 mg QD-dose adjusted for concomitant antiretroviral use) and sofosbuvir (400 mg QD) n=153	GT-1,2,3,4 treatment naive and treatment experienced	12 weeks
AI444218 (ALLY-3) Open-label	DAKLINZA (60 mg QD) and sofosbuvir (400 mg QD), n=152	GT-3 treatment-naive and treatment experienced	12 weeks

[a] For patients with HCV genotype 1 infection, the dose of ribavirin in AI444040 for patients less than 75 kg was 1000 mg/day (400 mg in the morning and 600 mg in the evening) and for patients weighing 75 kg or more, 600 mg twice daily. For patients with HCV genotype 2 or 3 infection, the dose of ribavirin was 400 mg/day twice daily. Ribavirin was to be taken with a meal.

[b] The recommended initial dose of ribavirin was 600 mg daily with food, modified based on hemoglobin and creatinine clearance measurements. If tolerated, the ribavirin dose could be titrated up to 1000 mg/day (see **DOSAGE AND ADMINISTRATION, Table 10**).

[c] Includes 1 patient with HCV genotype 6. Due to this small sample size, data for patients with HCV genotype 6 infection are not further presented.

DAKLINZA in Combination with Sofosbuvir for the Treatment of Patients Infected with HCV Genotypes 1, 2, or 3 (Study AI444040)

The demographic and other baseline characteristics of the population are summarized in **Table 13**.

Table 13: Demographic and Other Baseline Characteristics of HCV Genotype 1, 2, or 3 Infected Patients Treated with DAKLINZA and Sofosbuvir ± Ribavirin in Study AI444040

Characteristic	Genotype 1 Treatment-Naive 12 or 24 weeks[a] N= 126 n (%)	Genotype 1 Prior Non-Responders to Telaprevir or Boceprevir 24 weeks N=41 n (%)	Genotype 2/3 Treatment-Naive 24 weeks N= 44 n (%)
Age (years)			
Mean (range)	52.0 (20-69)	54.7 (23-70)	49.7 (24-67)
Gender			
Male	64 (50.8%)	25 (61.0%)	22 (50.0%)
Female	62 (49.2%)	16 (39.0%)	22 (50.0%)
Race			
White	100 (79.4%)	37 (90.2%)	38 (86.4%)
Black	21 (16.7%)	3 (7.3%)	2 (4.5%)
Asian	1 (0.8%)	1 (2.4%)	3 (6.8%)
Other	4 (3.2%)	0 (0.0%)	1 (2.3%)
Genotype			
1a	99 (78.6%)	33 (80.5%)	-
1b	27 (21.4%)	8 (19.5%)	-
2	0 (0.0%)	0 (0.0%)	26 (59.1%)
3	0 (0.0%)	0 (0.0%)	18 (40.9%)
HCV RNA[b]			
Mean $\log_{10}$ IU/mL	6.40	6.33	6.63
<800,000 IU/mL	28 (22.2%)	5 (12.2%)	9 (20.5%)
≥800,000 IU/mL	98 (77.8%)	36 (87.8%)	35 (79.5%)
Mean score (range) on FibroTest[c]	0.446 (0.03-0.89)	0.564 (0.08-0.87)	0.406 (0.04-0.88)
IL28B rs12979860 genotype			
CC	40 (31.7%)	1 (2.4%)	20 (45.5%)
CT	67 (53.2%)	27 (65.9%)	20 (45.5%)
TT	18 (14.3%)	13 (31.7%)	4 (9.1%)

a All treatment-naive patients with HCV genotype 1 infection in AI444040 were without cirrhosis, and were randomized to a treatment duration of 12 (n=82) or 24 (n=44) weeks.

b RNA values were measured 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.

c a validated non-invasive diagnostic assay for liver fibrosis status.

Conversion of the FibroTest score to the corresponding METAVIR score suggests that 15% of all patients (22% of patients with prior PI failure, 14% of patients with genotype 2 or 3) had F3/F4 or F4 liver fibrosis.

Study Results

Treatment Outcomes in AI444040 Using Daclatasvir-Sofosbuvir +/- RBV

SVR and outcomes in patients without SVR in AI444040 are shown by patient population in **Table 14**.

Table 14: Treatment Outcomes: DAKLINZA in Combination with Sofosbuvir with or without Ribavirin in Patients with HCV Genotype 1, 2, or 3 in Study AI444040

	Genotype 1		Genotype 2	Genotype 3
Treatment Outcomes	**Treatment Naive 12 or 24 weeks[a] N=126 n (%)**	**Prior Telaprevir or Boceprevir Failures 24 weeks N=41 n (%)**	**Treatment Naive 24 weeks N=26 n (%)**	**Treatment Naive 24 weeks N=18 n (%)**
SVR12 [b,c,d]	125 (99%)	41 (100%)	25 (96%)	16 (89%)
Week 4[e]	124 (98%)	40 (98%)	26 (100%)	18 (100%)
EOTR [f]	126 (100%)	38 (93%)	26 (100%)	16 (89%)
Outcomes for patients without SVR[a]				
Overall virologic failure	1 (1%)	0	1 (4%)	2 (12%)
On treatment virologic failure	0	0	0	1 (6%)
Virologic breakthrough[g]	0	0	0	1 (6%)
Relapse[g]	0	0	0	1/16 (6%)
Missing post-treatment data	1 (1%)	0	1 (4%)	0
Discontinuation				
Due to adverse event	1 (1%)	0	1 (4%)	0
Other[h]	0	0	1 (4%)	1 (6%)

[a] All treatment-naive patients with HCV genotype 1 infection in AI444040 were without cirrhosis, and were randomized to a treatment duration of 12 (n=82) or 24 (n=44) weeks. For treatment-naive and treatment-experienced HCV genotype 1 infected patients with cirrhosis, 24 weeks of treatment with DCV+SOF is recommended (see **Table 9**).

[b] SVR12: Sustained virologic response with HCV RNA <LLOQ at follow-up Week 12. Missing post-treatment Week 12 HCV RNA was imputed using the using the NVCB approach, ie, using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA visit window.

[c] In study AI444040, 31 patients received a 7-day lead-in with sofosbuvir monotherapy. When these patients are excluded, SVR rates for treatment-naive patients are 99% (110/111) in patients with HCV genotype 1, 94% (16/17) in patients with HCV genotype 2, and 100% (11/11) in patients with HCV genotype 3.

[d] SVR12 rates were not influenced by the inclusion of ribavirin in the regimen.

[e] Week 4: HCV RNA <LLOQ at treatment Week 4.

[f] EOTR: HCV RNA undetectable at End of Treatment.

[g] Virologic breakthrough was defined as confirmed increase in viral load of at least 1 $\log_{10}$ IU/mL from nadir or any confirmed HCV RNA ≥LLOQ if previously declined to <LLOQ during treatment. Relapse was defined as HCV RNA ≥LLOQ during follow-up after HCV RNA undetectable at end of treatment.

[h] No deaths were observed in study AI444040.

SVR12 was achieved by 99% of patients with HCV genotype 1, 96% of those with genotype 2, and 89% of those with genotype 3. Response was rapid (more than 97% of patients had HCV RNA <LLOQ at Week 4) Treatment-naive patients with HCV genotype 1 who received 12 weeks of treatment had a similar response (SVR12=99%) as those treated for 24 weeks (SVR12=100%). While the addition of ribavirin to the regimen did not result in an increase in efficacy, the frequencies of adverse reactions commonly associated with ribavirin therapy (rash, cough, anemia, dyspnea, insomnia, and anxiety) were higher for patients in this study who received ribavirin than for patients who did not.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. The response rates for these subgroups are summarized in **Table 15**.

Table 15: SVR[a] with DAKLINZA and Sofosbuvir in Selected Subgroups of HCV Genotype 1 Patients who Were Treatment Naive or Failed Prior Treatment with Telaprevir/Boceprevir and HCV Genotype 2 or 3 Patients who Were Treatment Naive in Study AI444040

Characteristic	Genotype 1 Treatment-Naive 12 or 24 weeks N= 126 n/N (%)	Genotype 1 Prior Non-Responders to Telaprevir or Boceprevir 24 weeks N=41 n/N (%)	Genotype 2/3 Treatment-Naive 24 weeks N= 44 n/N (%)
HCV Genotype			
1a	97/99 (98%)	32/33 (97%)	NA
1b	27/27 (100%)	8/8 (100%)	
HCV RNA			
<800,000 IU/mL	28/28 (100%)	5/5 (100%)	8/9 (89%)
≥800,000 IU/mL	96/98 (98%)	35/36 (97%)	32/35 (91%)
Patients with multiple risk factors: METAVIR F3/F4 fibrosis, IL28B non-CC, HCV RNA >800,000 IU/mL	17/17 (100%)		1/1 (100%)

[a] Modified Intent to Treat analysis. Patients with missing follow-up Week 12 data were considered nonresponders at this timepoint.

Response was not influenced by HCV subtype (1a/1b), IL28B genotype, presence or absence of baseline NS5A polymorphisms, or use of ribavirin.

Outcomes in Study AI444040 are expected to be applicable to a broader patient population because patients who failed peginterferon alfa and ribavirin, with or without telaprevir or boceprevir, are treatment naive to DAKLINZA and sofosbuvir, and would be expected to achieve similar SVR rates as treatment-naive patients treated with DAKLINZA and sofosbuvir. These patient populations include:

- HCV genotype 1 patients who failed prior treatment with peginterferon alfa and ribavirin: Among the 167 HCV genotype 1 patients in the study, 17 fit the profile associated with difficult-to-treat patients who typically fail treatment with peginterferon alfa and ribavirin (METAVIR F3/F4 fibrosis, IL28B non-CC, and HCV RNA >800,000 IU/mL); all 17 patients achieved SVR with DAKLINZA and sofosbuvir. Among the 41 HCV genotype 1 patients who failed prior treatment with telaprevir or boceprevir in combination with peginterferon alfa and ribavirin, all 41 achieved SVR with DAKLINZA and sofosbuvir +/- ribavirin.
- HCV genotype 2 or 3 patients who failed peginterferon alfa and ribavirin: Among 44 treatment-naive patients with HCV genotype 2 or 3 who received DAKLINZA and sofosbuvir +/- ribavirin, 41 (93%) achieved SVR.

Outcomes in Study AI444040 with a regimen given for 24 weeks are also expected to be applicable to a duration of 12 weeks for most patients. Of 82 treatment-naive patients with HCV genotype 1 who received 12 weeks of treatment, 99% achieved SVR with DAKLINZA and sofosbuvir +/- ribavirin. It is expected that similar outcomes would be applicable in patients with HCV genotype 1 infection who failed prior treatment with peginterferon alfa and ribavirin with or without telaprevir or boceprevir, since they are treatment naive to DAKLINZA and sofosbuvir. While 12 weeks of treatment is also expected to result in a similar response as 24 weeks of treatment in patients with HCV genotype 2 and genotype 3 infection, longer treatment (24 weeks) should be considered for treatment-experienced HCV genotype 3-infected patients with cirrhosis.

DAKLINZA in Combination with Sofosbuvir and Ribavirin for Patients with Child-Pugh A, B or C Cirrhosis or with HCV Recurrence after Liver Transplant (ALLY-1) and DAKLINZA in Combination with Sofosbuvir +/- Ribavirin for Patients with HCV/HIV-1 coinfection (ALLY-2) and Genotype 3 (ALLY-3)

The demographic and other baseline characteristics of the populations included in ALLY-1, 2 and 3 are summarized in **Table 16**.

Table 16: Demographic and Other Baseline Characteristics of HCV Genotypes 1, 2, 3 and 4 Infected Patients Treated with DAKLINZA in ALLY-1, 2 and 3

Characteristic	ALLY-1 12 weeks N= 112 n (%)	ALLY-2[a] 12 weeks N= 153 n (%)	ALLY-3 12 weeks N= 152 n (%)
Age (years)			
Median (range)	59.0 (19-82)	53.0 (24-71)	55.0 (24-73)
Gender			
Male	76 (67.9%)	135 (88%)	90 (59.2%)
Female	36 (32.1%)	18 (12%)	62 (40.8%)
Race			
White	107 (95.5%)	97 (63%)	137 (90.1%)
Black	4 (3.6%)	50 (33%)	6 (3.9%)
Other	1 (0.9%)	6 (4%)	9 (5.9%)
Genotype			
1a	65 (58%)	104 (68%)	-
1b	21 (18.8%)	23 (15%)	-
2	5 (4.5%)	13 (8%)	-
3	17 (15.2%)	10 (7%)	152 (100.0%)
4	4 (3.6%)	3 (2%)	-
HCV RNA[b]			
Mean $\log_{10}$ IU/mL	6.28	6.51	6.27
<800,000 IU/mL	33 (29.5%)	30 (20%)	44 (28.9%)
≥800,000 IU/mL	79 (70.5%)	123 (80%)	108 (71.1%)
IL28B rs12979860 genotype			
CC	25 (22.3%)	41 (27%)	60 (39.5%)
CT	64 (57.1%)	78 (51%)	68 (44.7%)
TT	23 (20.5%)	34 (22%)	24 (15.8%)

a Concomitant HIV-1 therapy included PI-based regimens (darunavir + ritonavir, atazanavir + ritonavir, or lopinavir/ritonavir) for 46% of patients, NNRTI-based (efavirenz, nevirapine, or rilpivirine) regimens for 26% of patients, integrase–based regimens (raltegravir or dolutegravir) for 26%, and nucleoside only (abacavir + emtricitabine + zidovudine) regimens for 1%. Two patients were not receiving treatment for HIV-1.

b RNA values were measured 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.

Treatment Outcomes in ALLY-1, 2 and 3

ALLY-1; Study Results in Patients with Compensated (Child-Pugh A) and Decompensated (Child-Pugh B, C) Cirrhosis and Post-Liver Transplant.

The SVR12 rates and outcomes in patients without SVR12 in ALLY-1 are reported for patients infected with different genotypes and different levels of cirrhosis in **Table 17**. SVR12 rates were comparable regardless of age, race, gender, IL28B allele status or baseline HCV RNA level. In the cirrhosis cohort, 4 patients with hepatocellular carcinoma underwent liver transplantation after 1 to 71 days of treatment; 3 of the 4 patients received 12 weeks of post-liver transplant treatment extension and 1 patient, treated for 23 days before transplantation, did not receive treatment extension. All 4 patients achieved SVR12.

Table 17: Treatment Outcomes of DAKLINZA in Combination with Sofosbuvir and Ribavirin for 12 weeks in Patients with Cirrhosis or HCV Recurrence after Liver Transplant (ALLY-1)

Treatment Outcomes	Advanced Cirrhosis 12 Weeks N=60 %(n/N)	Post-Transplant 12 Weeks N=52 %(n/N)
SVR12		
All	83% (50/60)	94% (49/52)
Child-Pugh A	92% (11/12)	-
Child-Pugh B	94% (30/32)	-
Child-Pugh C	56% (9/16)	-
MELD score		
≥15	67% (14/21)	-
<15	87% (34/39)	-
Genotype 1	82% (37/45)	95% (39/41)
1a	76% (26/34)	97% (30/31)
1b	100% (11/11)	90% (9/10)
Genotype 2	80% (4/5)	-
Genotype 3	83% (5/6)	91% (10/11)
Genotype 4	100% (4/4)	-
Outcomes for patients without SVR		
On-treatment virologic failure[b]	2% (1/60)	0
Relapse[c]	16% (9/58)	6% (3/52)

[a] Among patients with HCV genotype 1 infection and advanced cirrhosis, SVR12 was 91% (10/11) for Child-Pugh A, 92% (22/24) for Child-Pugh B, and 50% (5/10) for Child-Pugh C.

[b] One patient had detectable HCV RNA at end of treatment.

[c] Relapse rates are calculated with a denominator of patients with HCV RNA not detected at the end of treatment.

ALLY-2; Study Results in HCV-HIV-1 Co-infected Patients

The SVR12 rates and outcomes in patients without SVR12 in ALLY-2 are reported for patients with HCV/HIV-1 coinfection in **Table 18**. SVR12 rates were high regardless of combination antiretroviral therapy (CART). Among HCV treatment-naive patients, 98% (46/47) of those receiving a PI-based regimen, 100% (28/28) of those receiving an NNRTI-based regimen, 92% (23/25) of those receiving an integrase inhibitor-based regimen, and the 1 patient not receiving concomitant antiretroviral therapy achieved SVR. Among HCV treatment-experienced patients, 96% (22/23) of those receiving a PI-based regimen, 100% (12/12) of those receiving an NNRTI regimen, 100% (14/14) of those receiving an integrase inhibitor-based regimen achieved SVR as did the 2 patients receiving nucleoside analogs only and the 1 patient not on concomitant antiretroviral therapy.

SVR12 rates were comparable regardless of age, race, gender, IL28B allele status, or baseline HCV RNA level.

Table 18: Treatment Outcomes of DAKLINZA in Combination with Sofosbuvir in Patients with HCV/HIV-1 Coinfection (ALLY-2)

Treatment Outcomes	HCV Treatment-Naive 12 Weeks N=101 %(n/N)	HCV Treatment-Experienced[a] 12 Weeks N=52 %(n/N)
SVR12		
All	97% (98/101)	98% (51/52)
No cirrhosis[b]	98% (88/90)	100% (34/34)
With cirrhosis[b]	89% (8/9)	93% (14/15)
Outcomes for patients without SVR12		
On-treatment virologic failure[c]	1% (1/101)	0
Relapse[d]	1% (1/100)	2% (1/52)
Missing post-treatment data	1% (1/100)	0

[a] Prior treatment was interferon-based for 49 patients, and 3 patients received sofosbuvir and ribavirin.

[b] Cirrhosis status was indeterminate for 5 patients.

[c] One patient had detectable HCV RNA at end of treatment.

[d] Relapse rates are calculated with a denominator of patients with HCV RNA not detected at the end of treatment.

The SVR12 rates in ALLY-2 are shown by patient population and HCV genotype in **Table 19**. 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**.

Table 19: SVR12 Rates by Patient Population and HCV Genotypes Treated with DAKLINZA in Combination with Sofosbuvir in HIV-HCV Co-infected Patients (ALLY-2).

Genotype[a]	SVR12	
	HCV Treatment-Naive n=101	HCV Treatment-Experienced n=52
Genotype 1	96% (80/83)	98% (43/44)
1a	96 % (68/71)	97 %(32/33)
1b	100 (12/12)	100%(11/11)
Genotype 2	100% (11/11)	100% (2/2)
Genotype 3	100% (6/6)	100% (4/4)
Genotype 4	100% (1/1)	100% (2/2)

[a] Cirrhosis was present in 22/127 patients with HCV genotype 1, 1/13 patients with genotype 2, 1/10 patients with genotype 3, and no patients with genotype 4.

ALLY-3; Study Results in GT-3 Patients

The SVR12 and outcomes in patients without SVR12 for GT-3 patients in ALLY-3 are shown by patient population in **Table 20**. SVR12 rates in ALLY-3 were higher (93%; 111/119) in patients with F0 to F3 baseline fibrosis score by FibroTest compared with patients with F4 baseline fibrosis score (70% 21/30). SVR12 rates were higher in Treatment Naive patients than in Treatment Experienced patients. SVR12 rates were comparable regardless of age, race, gender, IL28B allele status, or baseline HCV RNA level

Table 20: Treatment Outcomes of DAKLINZA in Combination with Sofosbuvir in Patients with HCV Genotype 3 Infection (ALLY-3)

Treatment Outcomes	Treatment-Naive n=101	Treatment-Experienced n=51	Total n=152
SVR12			
All	90% (91/101)	86% (44/51)	89% (135/152)
No cirrhosis	97% (73/75)	94% (32/34)	96% (105/109)
With cirrhosis	58% (11/19)	69% (9/13)	63% (20/32)
Outcomes for patients without SVR12			
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] Cirrhosis status was missing or inconclusive for 11 patients.

[b] One patient had detectable HCV RNA at end of treatment.

[c] Relapse rates are calculated with a denominator of patients with HCV RNA not detected at the end of treatment.

Long-term Follow-up

In an ongoing follow-up study to assess durability of response up to 3 years after treatment with DAKLINZA in phase 2 and 3 studies, no relapses occurred among 28 patients who achieved

SVR12 with DAKLINZA and sofosbuvir (± ribavirin) with a median duration of post-SVR12 follow-up of approximately 14.5 months.

MICROBIOLOGY

Mechanism of Action

Daclatasvir is an inhibitor of NS5A, a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir inhibits both viral RNA replication and virion assembly. *In vitro* and computer 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

In Vitro

Daclatasvir is a pan-genotypic inhibitor of full-length and chimeric replicons encoding NS5A sequences from clinical isolates representing HCV genotypes 1-6. 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), 0.008 nM (range, 0.005-0.02 nM, n=5), 0.2 nM (range, 0.006-3.2 nM, n=17), and 0.003 nM (range, 0.001-0.007 nM, n=4) against hybrid replicons containing genotypes 1a, 1b, 2, 3, and 4 patient-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, 2, 3, and 4 patient-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), 17.5 nM (range, 0.3-60 nM, n=16), 1835 nM (range, 1.3->5000 nM, n=8), and 0.035 nM (range, 0.007-158 nM, n=10).

The median EC_{50} values of daclatasvir for genotype 5 patient-derived NS5A hybrid replicons was 0.004 nM (range, 0.003-0.019 nM, n=3) while the EC_{50} value against a single HCV genotype 6 derived replicon was 0.054 nM.

Daclatasvir showed additive to synergistic interactions with interferon alfa, HCV NS3 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.

In Vivo

In HCV genotype 1a-infected treatment-naive patients, a single 60 mg dose of daclatasvir resulted in a 3.2 $\log_{10}$ IU/mL mean reduction in viral load measured after 24 hours.

Resistance

See the Product Monograph for the cell culture and clinical resistance profile for sofosbuvir.

In Cell Culture

Substitutions conferring daclatasvir resistance in HCV genotypes 1-6 were selected in the cell-based replicon system and observed in the N-terminal 100 amino acid region of NS5A.

In stable genotype 1a replicon cell lines, M28T, Q30H, Q30R, L31V, and Y93C substitutions were identified and exhibited ≥500-fold reduced susceptibility to daclatasvir. For genotype 1b, the L31M/Y93H and L31V/Y93H combinations exhibited >8000-fold reduced susceptibility to daclatasvir.

In stable genotype 2a replicon cell lines, F28S, C92R, and Y93H substitutions exhibited ≥470-fold reduced susceptibility to daclatasvir, whereas for genotype 3a, Y93H exhibited 2738-fold reduced susceptibility to daclatasvir.

In stable genotype 4a replicon cell lines, R30G/S or L30H/R or Y93H/R identified in genotype 4a replicons exhibited ≥143-fold reduced susceptibility to daclatasvir. For genotype 5a, the L31F/K56R and L31V/K56R combinations exhibited >6000-fold reduced susceptibility to daclatasvir. For genotype 6a, L31M, P32L, P32S, and T58N exhibited ≥382-fold reduced susceptibility to daclatasvir.

In Clinical Studies

The resistance profile of DAKLINZA has been evaluated in a phase 2 clinical trial with sofosbuvir. Results for baseline NS5A polymorphisms and treatment-emergent substitutions are provided below.

Effect of Baseline HCV Polymorphisms on Treatment Response

In a pooled analysis of 605 available baseline NS5A sequences from patients who received daclatasvir and sofosbuvir with or without ribavirin for 12 or 24 weeks, baseline NS5A polymorphisms at amino acid positions associated with daclatasvir resistance (28, 30, 31 or 93) were detected in 19% (116/605) of patients (32/295 genotype 1a, 15/75 genotype 1b, 33/36 genotype 2, 31/192 genotype 3, 4/6 genotype 4, and 1/1 genotype 6) with available baseline NS5A sequence. These NS5A polymorphisms included M28T/V, Q30E/H/L/R, L31M or Y93C/H/L/N/S in patients with genotype 1a; R30K/M/Q, L31M or Y93H in patients with genotype 1b; F28L or L31M in patients with genotype 2; M28V, A30E/K/S/T/V, L31M or Y93H in patients with genotype 3; L28M or L30R in patients with genotype 4; and F28M/V and R30S in patients with genotype 6.

Overall SVR12 rates for patients with or without baseline NS5A polymorphisms at 28, 30, 31 or 93 were 88% (102/116) and 96% (469/489), respectively (see **Table 21**). In patients without cirrhosis, the SVR12 rates in patients with and without baseline NS5A polymorphisms were high: 95% (83/87) and 99% (350/353), respectively. In patients with cirrhosis, SVR12 rates with and without baseline NS5A polymorphisms were 52% (11/21) and 85% (77/91), respectively. Specific baseline NS5A polymorphisms in the 10 patients with cirrhosis who failed were: M28T (n = 1), L31M (n = 2, both Child-Pugh B) and Y93N (n = 1) in patients with genotype 1a; A30K (n = 1), Y93H (n = 3) and A30T (n = 1) in patients with genotype 3; and L31M (n = 1, Child-Pugh C) in a patient with genotype 2. All of the described genotype 1a, genotype 2, and genotype 3 NS5A

substitutions confer a greater than 100-fold reduction in daclatasvir activity *in vitro*, except for A30T which was only detected at baseline and not at failure. For the 14 patients with cirrhosis who failed without noted baseline NS5A polymorphisms, 6 patients had Child-Pugh C liver disease.

The sofosbuvir resistance-associated substitution S282T was not detected in the baseline NS5B sequence of any patient in Phase 2 or 3 studies by population-based sequencing.

Table 21: Impact of Baseline NS5A Polymorphisms (at Amino Acid Positions 28, 30 31 Or 93) on SVR12 Response in Patients Infected with Genotypes 1-4 With/Without Baseline Cirrhosis Treated With Daclatasvir And Sofosbuvir With/Without Ribavirin for 12 or 24 Weeks

	SVR12 Rates in Patients with NS5A Sequences	
	With Noted Baseline NS5A Polymorphisms[a] % (n/N)	**Without Noted Baseline NS5A Polymorphisms % (n/N)**
Overall[b]	**88% (102/116)**	**96% (469/489)**
Patients with Cirrhosis (Child-Pugh A, B, C)[c]	**52% (11/21)**	**85% (77/91)**
Genotype 1a	33% (2/6)	88% (42/48)
Genotype 1b	0	100% (12/12)
Genotype 2	83% (5/6)	0
Genotype 3	29% (2/7)[a]	73% (22/30)
Genotype 4	100% (2/2)[a]	100% (1/1)
Patients without Cirrhosis	**95% (83/87)**	**99% (350/353)**
Genotype 1a	100% (24/24)	100% (186/186)
Genotype 1b	100% (11/11)	100% (42/42)
Genotype 2	100% (27/27)	100% (3/3)
Genotype 3	83% (19/23)	98% (118/121)
Genotype 4	100% (2/2)	100% (1/1)

[a] Two patients with cirrhosis (1 genotype 3, 1 genotype 4) each with Child-Pugh C cirrhosis who received daclatasvir and sofosbuvir with ribavirin were classified as nonvirologic failures due to data not being available for the integrated analysis although they achieved SVR12; both patients had noted baseline NS5A polymorphisms (genotype 3: A30K; genotype 4: L28M) and are not included in this analysis.

[b] For 53 post-liver transplant patients treated with daclatasvir and sofosbuvir ± ribavirin for 12 weeks, the presence of baseline NS5A polymorphisms (at 28, 30, 31 or 93) did not appear to impact response rates since all patients (n = 8) with these polymorphisms achieved SVR12. The overall total row in the table includes this patient population, but they are not included in the rows for patients with and without cirrhosis, as cirrhosis status was not determined.

[c] Patients with cirrhosis were only treated for 12 weeks

Resistance Substitutions in Patients Not Achieving SVR

In a pooled analysis of 679 patients who received daclatasvir/sofosbuvir with or without ribavirin in Phase 2 and 3 studies for 8, 12, or 24 weeks, 44 patients (19 with genotype 1a, 2 with genotype 1b, 2 with genotype 2, and 21 with genotype 3) qualified for resistance analysis due to virologic

failure or early study discontinuation and having HCV RNA greater than 1000 IU/mL. Post-baseline NS5A and NS5B sequencing (assay cut-off of 20%) were available for 44/44 and 39/44 patients, respectively.

NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 37/44 patients (13/19 with genotype 1a, 1/2 with genotype 1b, 2/2 with genotype 2, and 21/21 with genotype 3) not achieving SVR. Treatment-emergent NS5A RAVs are shown in **Table 22**.

Table 22: Treatment-Emergent NS5A Substitutions in Pooled Data from Phase 2 and 3 Clinical Trials[a] for Patients Infected with HCV Genotypes 1-3 Not Achieving SVR12 with DAKLINZA and Sofosbuvir

Category	DAKLINZA and Sofosbuvir			
	Genotype 1a % (n/N)	**Genotype 1b % (n/N)**	**Genotype 2 % (n/N)**	**Genotype 3 % (n/N)**
Treated patients	336	85	50	200
Non-responders (non-SVR12 or Treatment Failures)	21[b]	4[b]	3[b]	22[b]
Non-responders with available NS5A sequence.	19	2	2	21
Emergent substitution at NS5A position 28, 29, 30, 31, 32, 58, 62, 93	58% (11/19)	50% (1/2)	0	76% (16/21)
M28: T	11% (2/19)	NA	NA	NA
R30: G, H, P, Q	NA	0	NA	NA
Q30: E, H, K, R	53% (10/19)	NA	NA	NA
L31: M, V	11% (2/19)	0	NA	NA
P32X[c]	NA	50% (1/2)	NA	NA
H58: D, P	11% (2/19)	NA	NA	NA
P58: A, G, S	NA	0	NA	NA
Y93: C, H, N	11% (2/19)	0	0	52% (11/21)
Y93H	0	0	0	52% (11/21)
GT-3: L31I, S62L	Less than 10%			

[a] Treatment-emergent NS5A RAVs were observed in studies AI444215, AI444216 and AI44218.

[b] Six patients (2 GT-1a, 2 GT-1b, 1 GT-2, and 1 GT-3) without NS5A sequence post-baseline either died or were lost to follow-up after achieving SVR4 [N=2], were lost to follow-up during the treatment phase [N=1], were incarcerated during treatment [N=2], or achieved SVR12 but had HCV RNA < LLOQ TD on treatment [N=1].

[c] X represents a deletion of the designated amino acid. NS5A-P32X reduced daclatasvir susceptibility by >1,000,000-fold resistance when tested *in-vitro*.

NA= not applicable

Thirteen (68%) of the 19 patients with HCV genotype 1a who qualified for resistance testing harbored one or more NS5A RAVs at positions M28, Q30, L31, H58 or Y93 of which 11 were treatment-emergent (**Table 22**). Five of the patients with genotype 1a also had Child-Pugh C liver disease. Two patients had the same NS5A RAVs at baseline and post-baseline (M28T or Y93N). Substitutions at Q30 were most frequently observed (Q30E/H/K/R; 10/19 [52.6%]). Of the 2 patients with genotype 1b who qualified for resistance testing, a deletion at NS5A-P32 was observed in 1 patient.

The 2 patients with genotype 2 who qualified for resistance testing had the same NS5A RAVs at baseline and post-baseline (L31M).

Of the 21 patients with genotype 3 who qualified for resistance testing, 21 (100%) patients harbored one or more NS5A RAVs at positions 30, 31, 62 or 93. Substitutions at Y93 were most frequently observed (17/21 [81%]) and were observed at baseline in 6 patients and only post-baseline in 11 patients. Among the 7 patients who had no NS5A RAVs at failure, all received daclatasvir/sofosbuvir for 8 weeks.

All of the described genotype 1a Q30 substitutions, genotype 1b P32 deletion, genotype 2 L31M, and genotype 3 Y93H conferred reduced susceptibility to daclatasvir *in vitro* (fold-change in EC50 values of 900 or greater).

Persistence of Resistance-Associated Substitutions

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

Cross Resistance

Daclatasvir was fully active against sofosbuvir resistance-associated substitutions while daclatasvir-resistant substitutions remained fully sensitive to sofosbuvir.

Cytotoxicity

Daclatasvir showed no cytotoxicity in multiple cell lines derived from liver, lymphoid or endothelial tissue. The CC50 values ranged from 11 to 38 μM in HuH7 and from 17 to 90 μM in HuH7, Vero, MDBK, MRC5, and MT2 cell lines.

NON-CLINICAL TOXICOLOGY

Acute Toxicity

Daclatasvir has a very low potential for acute toxicity. Single doses ≤ 150 mg/kg in dogs and monkeys, and ≤ 1000 mg/kg in mice and rats produced no mortality and were well tolerated.

Chronic Toxicity

In repeat-dose toxicity studies in dogs, Daclatasvir was not tolerated at a dose of 100 mg/kg/day (AUC 158 μg•h/mL, 10.5× RHD AUC), which was associated with mortality due to bone marrow and hepatic toxicity. In contrast, with the exception of a single monkey (150 mg/kg/day; AUC 80.3 μg•h/mL, 5.3× RHD AUC) euthanized with signs of hepatic and bone marrow toxicity, monkeys tolerated Daclatasvir dosed for ≤ 9 months (≤ 300 mg/kg/day; AUC ≤ 41.2 μg•h/mL, 2.7× RHD AUC). The findings for the 1 decedent monkey were not consistent with findings in other monkeys dosed for ≤ 9 months (see study description below), and based on the overall weight of evidence from completed monkey and clinical studies, are unlikely to be related to daclatasvir although a relationship cannot be discounted.

In repeat-dose toxicity studies in rats (≤ 6 months) and monkeys (≤ 9 months), the main target organs included the liver (monkeys) and adrenal gland (rats and monkeys). In monkeys dosed for 9 months, the most robust monkey study (i.e., longest duration and greatest number of monkeys assessed), hepatic effects at 30 mg/kg/day (AUC 11.6 μg•h/mL, 0.8× RHD AUC) included minimal Kupffer-cell hypertrophy/hyperplasia. At 150 mg/kg/day (AUC 38.8 μg•h/mL, 2.7× RHD AUC), additional hepatic findings included minimal to slight mononuclear cell infiltrates, increases in liver-associated serum biomarkers (ALT, AST, CRP), and slight bile duct hyperplasia. All these changes were reversible following a 2-month recovery period, with the exception of minimal to slight Kupffer cell hypertrophy/hyperplasia, which was not considered adverse. Adrenal effects in rats included reversible adrenal cortical hypertrophy associated with increased urine corticosterone levels at 100 mg/kg/day (AUC 107 μg•h/mL, 7.1× RHD AUC). Adrenal gland changes in monkeys were characterized as reversible minimal to marked decreases in cytoplasmic vacuolation in the cortical zona fasciculata, and in males, increases in adrenal-gland weight at ≥ 30 mg/kg/day (AUC ≥ 11.6 μg•h/mL, ≥ 0.8× RHD AUC), and at a dose of 300 mg/kg/day (AUC 41.2 μg•h/mL, 2.7× RHD AUC) slight cortical hyperplasia in the zona reticularis.

Overall, with repeat dosing across species and study durations ≤ 9 months, no observed effect level (NOEL) or no observable adverse effect level (NOAEL) doses and AUC values were generally consistent indicating little potential for cumulative or new toxicities to emerge with long-term administration.

Juvenile Toxicology

In juvenile rats administered daclatasvir for 10 weeks, there were no new toxicities relative to those observed in adult rats. The highest dose tested was associated with adrenal gland hypertrophy at AUC values 7.8-fold the RHD AUC. The AUC value at the no observed adverse effect level (NOAEL) for juvenile toxicity was 3.1-fold the RHD AUC.

Carcinogenesis and Mutagenesis

Daclatasvir was not carcinogenic in mice at AUC values 8.7-fold the RHD AUC or in rats at 4.7-fold the RHD AUC. No evidence of mutagenic or clastogenic activity was observed in *in vitro*

mutagenesis (Ames) tests, mammalian mutation assays in Chinese hamster ovary cells, or in an *in vivo* oral micronucleus study in rats.

Impairment of Fertility

Daclatasvir had no effects on fertility in male or female rats at any dose tested. The highest AUC value in unaffected females was 18-fold the RHD AUC. In male rats, effects on reproductive endpoints were limited to reduced prostate/seminal vesicle weights, and minimally increased dysmorphic sperm at 200 mg/kg/day; however, neither finding adversely affected fertility or the number of viable conceptuses sired. The AUC associated with this dose in males is 19-fold the RHD AUC.

Reproductive Toxicology

Daclatasvir was not a selective developmental toxicant when administered to pregnant rats or rabbits during organogenesis. Neither maternal nor developmental toxicities were observed at maternal daclatasvir doses associated with AUC values 4.6-fold (rat) and 16-fold (rabbit) the RHD AUC. At higher doses, concomitant maternal and developmental toxicities were noted in both species; AUC values associated with these doses were 25-fold (rat) and 72-fold (rabbit) RHD AUC values.

Maternal toxicity included mortality, adverse clinical signs, and decreases in body weight and food consumption. Developmental toxicity consisted of increases in embryofetal lethality, reduced fetal body weights, and increased incidence of fetal malformations of the ribs and variations, notably affecting the developing head and skull. In a study of prenatal and postnatal development in rats, there was neither maternal nor developmental toxicity at doses up to 50 mg/kg/day, associated with AUC values 2.6-fold the RHD AUC. At the highest dose (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. The AUC value associated with this dose is 4.7-fold the RHD AUC.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrDAKLINZA™
(daclatasvir tablets)

Read this carefully before you start taking **DAKLINZA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DAKLINZA**.

What is DAKLINZA used for?

PrDAKLINZA is used to treat chronic (long-lasting) infection with the hepatitis C virus (HCV) genotypes 1, 2 and 3. DAKLINZA is used with other medicines that also treat chronic HCV infection.

People with hepatitis C infection have the virus in their blood and in their liver.

DAKLINZA should not be taken alone.

DAKLINZA has not been studied in children under 18 years of age.

How does DAKLINZA work?

PrDAKLINZA used with other medicines has been shown to cure chronic HCV infection in most patients. Cure means the HCV is removed from your blood (remains at an undetectable level) for 3 months after finishing all treatment.

DAKLINZA blocks a protein from the virus that is needed to make new virus, and this helps to lower the virus level in your body.

What are the ingredients in DAKLINZA?

Medicinal ingredients: Daclatasvir tablets, 30, 60 mg (as daclatasvir dihydrochloride).

Non-medicinal ingredients: Anhydrous lactose, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry Green and silicon dioxide. The Opadry Green contains the following inactive ingredients: FD & C blue #2 / indigo carmine aluminum lake, hypromellose, iron oxide (yellow), polyethylene glycol 400 and titanium dioxide.

DAKLINZA comes in the following dosage forms:

PrDAKLINZA is available as tablets. Each tablet contains daclatasvir as the active ingredient. Tablets are available in two strengths. DAKLINZA 60 mg tablets are light green, biconvex, pentagonal and debossed with “BMS” on one side and “215” on the other. DAKLINZA 30 mg tablets are green, biconvex, pentagonal and debossed with “BMS” on one side and “213” on the other.

Do not use DAKLINZA if:

- you are allergic to daclatasvir or any other ingredients in this product (see "**What are the ingredients in DAKLINZA**")
- you are taking certain medicines **(**see **"Do not take DAKLINZA if you take a medicine that contains:")**

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DAKLINZA. Talk about any health conditions or problems you may have, including if you:

- have liver problems other than hepatitis C infection.
- have hepatitis B. Hepatitis B activity may increase when medicines like DAKLINZA are used to treat hepatitis C infections. Your doctor will monitor your hepatitis B levels and may do blood tests before, during and after hepatitis C treatment. Your doctor may prescribe hepatitis B treatment.
- have HIV-1.
- have had a liver transplant.
- have any other medical condition.
- are pregnant or plan to become pregnant (see **Pregnancy**).
- are breastfeeding or plan to breastfeed. It is not known if DAKLINZA passes into your breast milk. You and your healthcare provider should decide if you will take DAKLINZA or breastfeed. You should not do both.
- are taking any medications (see **Tell your healthcare professional about all medicines you take**).
- have a rare hereditary problem of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption) as this product contains lactose.

Heart block and a severe lowering of the heart beat have occurred in patients taking amiodarone with DAKLINZA and sofosbuvir. Your doctor will decide if amiodarone can be used with DAKLINZA and sofosbuvir. Contact your doctor if you suffer certain side effects while taking this combination (see "**What are the possible side effects from using DAKLINZA?**" section).

If you are taking DAKLINZA with sofosbuvir (SOVALDI), do not take other medicines that contain sofosbuvir, such as HARVONI.

Pregnancy

Pregnancy when DAKLINZA is taken with ribavirin:

Ribavirin may cause birth defects or death of your unborn baby. If you are pregnant or your sexual partner is pregnant or plans to become pregnant, do not take these medicines. You or your sexual partner should not become pregnant during treatment and for 6 months after treatment ends.

-Females and males must use 2 effective forms of birth control during treatment and for the 6 months after treatment with ribavirin. Talk with your healthcare provider about forms of birth control that may be used during this time.

-Females must have a negative pregnancy test before starting treatment with ribavirin, every month while being treated, and every month for 6 months after your treatment ends.

Pregnancy when DAKLINZA is <u>NOT</u> taken with ribavirin:

If you are NOT taking ribavirin with DAKLINZA, the following information about pregnancy applies:

- The effects of DAKLINZA on pregnancy and the unborn child are not known. DAKLINZA should not be used during pregnancy. **If you can become pregnant, use effective birth control during and for 5 weeks after** your treatment with DAKLINZA ends.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DAKLINZA:

PrDAKLINZA and other medicines may affect each other. This can cause you to have too much or too little DAKLINZA or the other medicines in your body. The medicines may not work well or you may have side effects. Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

Do not take DAKLINZA if you take a medicine that contains:

- carbamazepine (Carbatrol♦, Epitol♦, Equetro♦, Tegretol) or oxcarbazepine (Oxtellar XR♦, Trileptal)
- dexamethasone (when administered by injection or taken by mouth)
- phenobarbital (Luminal♦)
- phenytoin (Dilantin, Phenytek♦)
- rifabutin (Mycobutin)
- rifampin (Rifadin, Rifamate♦, Rifater, Rimactane♦)
- rifapentine (Priftin♦)
- St. John's wort (*Hypericum perforatum*) or a product that contains St. John's wort

Other drugs that may interact with DAKLINZA include:

- amiodarone (Cordarone, Pacerone♦)
- atazanavir (Reyataz)/ritonavir (Norvir), and atazanavir/cobicistat (Evotaz). You may need a lower dose of DAKLINZA.
- atorvastatin (Caduet, Lipitor, Liptruzet♦)
- boceprevir (Victrelis)

- bosentan (Tracleer)
- clarithromycin (Biaxin, Prevpac♦)
- combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild). You may need a lower dose of DAKLINZA.
- dabigatran etexilate mesylate (Pradaxa)
- digoxin (Digifab, Digox, Lanoxin)
- ditiazem (Cardizem♦, Cardizem CD, Cardizem LA♦, Tiazac, Cartia XT♦, Dilacor XR♦, Dilt-CD♦, Diltzac♦, Taztia XT♦)
- efavirenz (Sustiva, Atripla). You may need a higher dose of DAKLINZA.
- etravirine (Intelence)
- erythromycin
- fluvastatin (Lescol)
- itraconazole (Sporanox, Onmel♦)
- ketoconazole (when taken by mouth) (Nizoral). You may need a lower dose of DAKLINZA.
- modafinil (Provigil)
- nafcillin♦
- nevirapine (Viramune)
- pitavastatin (Livalo♦)
- posaconazole (Noxafil♦)
- pravastatin (Pravachol)
- rosuvastatin (Crestor)
- simvastatin (Simcor♦, Vytorin♦, Zocor)
- telaprevir (Incivek)
- telithromycin (Ketek♦)
- verapamil (Covera-HS♦, Calan♦, Verelan)
- voriconazole

♦ Not marketed in Canada

This is **not** a complete list of medicines that could interact with DAKLINZA. Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How to take DAKLINZA:

Do not take [Pr]DAKLINZA alone to treat chronic hepatitis C infection. DAKLINZA should be used together with other medicines for chronic HCV infection such as sofosbuvir (with or without ribavirin).

Take DAKLINZA exactly as your healthcare provider tells you to take it. Do not take more or fewer tablets than what your healthcare provider tells you to take.

Do not stop taking DAKLINZA without first talking with your healthcare provider.

Usual adult dose:

The usual dose is one 60 mg tablet once each day with or without food. A 30 mg tablet is available if your doctor prescribes a lower or higher dose.

Overdose:

If you think you have taken too much DAKLINZA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is important not to miss a dose of [Pr]DAKLINZA. If you do miss a dose and it is:

- less than 20 hours from the time you usually take DAKLINZA, take the missed dose as soon as possible. Take the next dose at the usual time.
- more than 20 hours from the time you usually take DAKLINZA, skip the missed dose. Take the next dose at the usual time.

Do not take 2 doses of DAKLINZA at the same time to make up for the missed dose.

What are possible side effects from using DAKLINZA?

These are not all the possible side effects you may feel when taking [Pr]DAKLINZA. If you have any side effects not listed here, contact your healthcare professional. Please also see section "**Do not use DAKLINZA if**".

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

- **Slow heart rate (bradycardia).** 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

When DAKLINZA is used in conjunction with sofosbuvir and ribavirin, common or very common side effects include headache, fatigue, nausea, rash, diarrhea and difficulty in sleeping.

The following serious side effects have occurred:

Serious side effects and what to do about them			
Symptom / effect*	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON **Effect: Low red blood cell counts (anemia)** **Symptoms:** -Tiredness -Headache -Shortness of breath -Dizziness -Looking pale		√	

*These side effects are commonly associated with ribavirin therapy.

This is not a complete list of side effects. If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store PrDAKLINZA at room temperature (15° to 30°C) in the original container.

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

If you want more information about DAKLINZA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.bmscanada.ca, or by calling 1-866-463-6267.

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