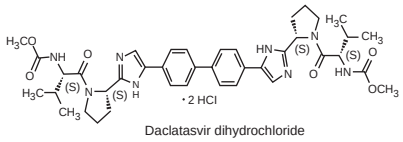
Daclavia™

[Daclatasvir Tablets]

30mg & 60mg

DESCRIPTION

Daclavia (Daclatasvir) is a highly selective inhibitor of HCV nonstructural protein 5A (NS5A) replication complex. The chemical name for Daclatasvir dihydrochloride is carbamic acid, N,N'-[[1,1'-biphenyl]-4,4'-diylbis[1H-imidazole-5,2-diyl-(2S)- 2,1- pyrrolidinediyl[(1S)-1-(1-methylethyl)-2-oxo-2,1-ethanediyl]]]bis-, C,C'-dimethyl ester, hydrochloride (1:2). Its molecular formula is $C_{40}H_{50}N_8O_6.2HCl$ and the structural formula is:



• 2 HCl

Daclatasvir dihydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Daclavia (Daclatasvir) Tablets are available for oral administration as:

Daclavia Tablets 30mg
Each film-coated tablet contains:
Daclatasvir dihydrochloride equivalent to Daclatasvir… 30mg

Daclavia Tablets 60mg
Each film-coated tablet contains:
Daclatasvir dihydrochloride equivalent to Daclatasvir… 60mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Daclatasvir is a direct acting antiviral agent (DAA) against the hepatitis C virus. Daclatasvir is an inhibitor of nonstructural protein 5A (NS5A), a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir inhibits both viral RNA replication and virion assembly. Daclatasvir interacts with the N-terminus within Domain 1 of the protein, which may cause structural distortions that interfere with NS5A functions.

Pharmacokinetics

Absorption

Daclatasvir is readily absorbed following multiple oral doses with peak plasma concentrations occurring between 1 and 2 hours after tablet intake. The absolute bioavailability of Daclatasvir tablet is 67%. Steady state is achieved after 4 days of once daily administration.

Effect of Food

Administration of Daclatasvir 60mg tablet with high fat and high caloric meal decreases peak plasma concentration and AUC by 28% and 23% respectively as compared to fasted state. Food effect was not observed with administration of Daclatasvir 60mg tablet after low fat and low caloric meal as compared to fasted state.

Distribution

Plasma protein binding of Daclatasvir in HCV-infected subjects is approximately 99% and independent of dose at the dose range studied (1mg to 100 mg). *In vitro* studies indicate that Daclatasvir is actively and passively transported into hepatocytes. The active transport is mediated by OCT1 and other unidentified uptake transporters, but not by organic anion transporter (OAT) 2, sodium-taurocholate cotransporting polypeptide (NTCP), or OATPs.

Metabolism

Daclatasvir is a substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism. No metabolites circulated at levels more than 5% of the parent concentration.

Elimination

Following single-dose oral administration of Daclatasvir in healthy volunteers, 88% of total radioactivity recovered in feces (53% as unchanged drug) and 6.6% excreted in the urine (primarily as unchanged drug). Following multiple-dose administration of Daclatasvir in HCV-infected patients, the terminal elimination half-life of Daclatasvir ranged from 12- 15 hours.

Special Population

Patients with hepatic impairment

The C_{max} and AUC of total Daclatasvir (free and protein-bound drug) were lower in patients with hepatic impairment.

Patients with renal impairment

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

THERAPEUTIC INDICATIONS

Daclavia (Daclatasvir) is indicated in combination with sofosbuvir, with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) infections in adults.

DOSAGE AND ADMINISTRATION

Recommended dosage of Daclavia (Daclatasvir) is 60mg taken orally, once daily, with or without food.

Recommended treatment for Daclavia (Daclatasvir) interferon-free combination therapy:

Patient Population	Regimen and Duration
HCV Genotype 1 or 4	
Patients without cirrhosis	Daclavia + sofosbuvir for 12 weeks
Patients with cirrhosis Child-Pugh A or B	Daclavia + sofosbuvir + ribavirin for 12 weeks or Daclavia + sofosbuvir (without ribavirin) for 24 weeks
Patients with cirrhosis Child-Pugh C	Daclavia + sofosbuvir +/- ribavirin for 24 weeks
HCV Genotype 3	
Patients without cirrhosis	Daclavia + sofosbuvir for 12 weeks
Patients with cirrhosis	Daclavia + sofosbuvir +/- ribavirin for 24 weeks
Recurrent HCV Infection post-liver transplant (Genotype 1, 3 or 4)	
Patients without cirrhosis	Daclavia + sofosbuvir + ribavirin for 12 weeks
Patients with Child Pugh A or B cirrhosis Genotype 1 or 4	Daclavia + sofosbuvir + ribavirin for 12 weeks
Genotype 3	Daclavia + sofosbuvir +/- ribavirin for 24 weeks
Patients with Child Pugh C cirrhosis	Daclavia + sofosbuvir +/- ribavirin for 24 weeks

Daclatasvir with peginterferon alfa and ribavirin

This regimen is an alternative recommended regimen for patients with genotype 4 infections, without cirrhosis or with compensated cirrhosis. Daclavia (Daclatasvir) is given for 24weeks, in combination with 24-48 weeks of peginterferon alfa and ribavirin.

- If HCV RNA is undetectable at treatment weeks 4 and 12, all 3 components of the regimen should be continued for duration of 24 weeks.
- If undetectable HCV RNA is achieved, but not at treatment weeks 4 and 12, Daclavia (Daclatasvir) should be discontinued at 24 weeks, but peginterferon alfa and ribavirin should be continued for duration of 48 weeks.

Ribavirin Dosing Guidelines

The dose of ribavirin, when combined with Daclavia (Daclatasvir) is weight-based (1000 or 1200mg in patients <75 kg or •75 kg) respectively.

For patients with Child-Pugh A, B, or C cirrhosis or recurrence of HCV infection after liver transplantation, the recommended initial dose of ribavirin is 600mg daily with food. If the starting dose is well-tolerated, the dose can be titrated up to a maximum of 1000 - 1200mg daily (breakpoint 75 kg). If the starting dose is not well-tolerated, the dose should be reduced as clinically indicated, based on hemoglobin and creatinine clearance measurements in the table below:

Laboratory Value	Ribavirin Dosing Guideline
Hemoglobin	
>12 g/dL	600mg daily
> 10 to -12 g/dL	400mg daily
> 8.5 to -10 g/dL	200mg daily
-8.5 g/dL	Discontinue ribavirin
Creatinine Clearance	
>50 mL/min	Follow guidelines above for hemoglobin
>30 to -50 mL/min	200mg every other day
-30 mL/min or hemodialysis	Discontinue ribavirin

Dose modification, interruption and discontinuation

Dose modification of Daclavia (Daclatasvir) to manage adverse reactions is not recommended. If treatment interruption of components in the regimen is necessary because of adverse reactions, Daclavia (Daclatasvir) must not be given as monotherapy. There are no virologic treatment stopping rules that apply to the combination of Daclavia (Daclatasvir) with sofosbuvir.

Treatment discontinuation in patients with inadequate on-treatment virologic response during treatment with Daclatasvir, peginterferon alfa and ribavirin

It is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR) therefore discontinuation of treatment is recommended in these patients. The HCV RNA thresholds that trigger discontinuation of treatment (i.e. treatment stopping rules) are presented in table below:

HCV RNA	Action
Treatment week 4: >1000 IU/ml	Discontinue Daclavia, peginterferon alfa and ribavirin
Treatment week 12: •25 IU/ml	Discontinue Daclavia, peginterferon alfa and ribavirin
Treatment week 24: •25 IU/ml	Discontinue peginterferon alfa and ribavirin (treatment with Daclavia is complete at week 24)

Dose recommendation for concomitant medicines

Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)

The dose of Daclavia (Daclatasvir) should be reduced to 30mg once daily when co-administered with strong inhibitors of CYP3A4.

Moderate inducers of CYP3A4

The dose of Daclavia (Daclatasvir) should be increased to 90mg once daily when co-administered with moderate inducers of cytochrome P450 3A4 (CYP3A4).

Missed Doses

Patients should be instructed that, if they miss a dose of Daclavia (Daclatasvir), 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.

Special Population

Patients with Renal Impairment

No dose adjustment of Daclavia (Daclatasvir) is necessary for patients with any degree of renal impairment.

Patients with Hepatic Impairment

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

Pediatric Population

Daclavia (Daclatasvir) is not recommended for use in children and adolescents aged below 18 years.

CONTRAINDICATIONS

Daclatasvir is contraindicated:

- In patients with hypersensitivity to Daclatasvir or to any excipients of the product.
- In combination drugs that strongly induce cytochrome P450 3A4 and thus may lead to lower exposure and loss of efficacy of Daclatasvir.

- The combination of Daclatasvir with peginterferon alfa and ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant because of the risks of birth defects and fetal death associated with ribavirin.
- Since Daclatasvir is used in combination with other medicinal products, the contraindications applicable to those medicinal products are applicable to the combination regimen.

ADVERSE REACTIONS
Very Common
Anemia, headache, nausea and fatigue.

Common
Decreased appetite, depression, anxiety, insomnia, dizziness, migraine, hot flush, cough, dyspnea, dyspnea exertional, nasal congestion, diarrhea, abdominal pain upper, constipation, flatulence, gastroesophageal reflux disease, dry mouth, vomiting, pruritus, dry skin, alopecia, rash, arthralgia, myalgia and irritability.

PRECAUTIONS
General
Daclatasvir must not be administered as monotherapy. Daclatasvir must be administered in combination with other medicinal products for the treatment of chronic HCV infection. Warnings and precautions for other medicinal products in the regimen also apply when coadministered with Daclatasvir.

Loss of Virologic Response Due to Drug Interactions
The concomitant use of Daclatasvir and other drugs may result in known or potentially significant drug interactions, some may lead to:
- Therapeutic effect loss of Daclatasvir and development of resistance.
- Dose adjustment of concomitant drugs or Daclatasvir.
- Clinically significant adverse reactions possibly from greater exposures of concomitant drugs or Daclatasvir.

Patients with Child-Pugh C Liver Disease
A moderate treatment regimen of Daclatasvir and sofosbuvir or ribavirin for 24 weeks is proposed for patients with Child-Pugh C. Ribavirin may be added based on clinical assessment of an individual patient.

Severe Bradycardia and Heart Block
It is recommended that patients are closely monitored when initiating Daclatasvir in combination with sofosbuvir. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.
All patients receiving Daclatasvir and sofosbuvir in combination with amiodarone with or without other drugs that lower heart rate should also be warned of the symptoms of bradycardia and heart block.

Effects on ability to drive and use machines
Dizziness is reported during treatment with Daclatasvir in combination with sofosbuvir. While dizziness, disturbance in attention, blurred vision and reduced visual acuity have been reported during treatment with Daclatasvir in combination with peginterferon alfa and ribavirin.

Pregnancy
Daclatasvir should not be used during pregnancy or in women of childbearing potential not using contraception. Use of highly effective contraception should be continued for 5 weeks after completion of Daclatasvir therapy.

Nursing Mothers
It is not known whether Daclatasvir is present in human milk, affects human milk production, or has effects on the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Daclatasvir and any potential adverse effects on the breastfed child from Daclatasvir or from the underlying maternal condition.

Drug Interaction
Other Drugs Affecting Daclatasvir
Daclatasvir is a substrate of CYP3A. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of daclatasvir. Strong inhibitors of CYP3A (eg, clarithromycin, itraconazole, ketoconazole, ritonavir) may increase the plasma levels of Daclatasvir.

Daclatasvir affecting other Drugs
Daclatasvir is an inhibitor of P-glycoprotein transporter (P-gp), organic anion transporting polypeptide (OATP) 1B1 and 1B3, and breast cancer resistance protein (BCRP). Administration of Daclatasvir may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B1 or 1B3, or BCRP, which could increase or prolong their therapeutic effect or adverse reactions.

Established and other Potentially Significant Drug Interactions

Concomitant Drug Name	Effect on concentration	Comment
Antivirals		
Protease inhibitors: Atazanavir with ritonavir, Atazanavir with cobicistat Indinavir, Nelfinavir, Saquinavir, Telaprevir, Boceprevir.	Increase Daclatasvir	Decrease Daclatasvir dose to 30mg once daily
Other antiretrovirals: Cobicistat-containing antiretroviral regimens Examples: atazanavir/cobicistat, elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate	Increase Daclatasvir	Decrease Daclatasvir dose to 30mg once daily except with darunavir combined with cobicistat.
Non-nucleoside reverse transcriptase inhibitors (NNRTI): Efavirenz, Etravirine, Nevirapine	Decrease Daclatasvir	Increase Daclatasvir dose to 90mg once daily.
Strong CYP3A inhibitors (see also antiviral agents)		
Examples: clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole	Increase Daclatasvir	Decrease Daclatasvir dose to 30mg once daily when coadministered with strong inhibitors of CYP3A.
Moderate CYP3A inducers (see also antiviral agents)		
Examples: bosentan, dexamethasone, modafinil, nafcillin, rifapentine	Decrease Daclatasvir	Increase Daclatasvir dose to 90mg once daily when coadministered with moderate inducers of CYP3A.
Anticoagulants		
Dabigatran etexilate mesylate	Increase Dabigatran	Use of Daclatasvir with dabigatran etexilate is not recommended in specific renal impairment groups, depending on the indication.
Cardiovascular Agents		
Antiarrhythmic: Amiodarone	Amiodarone: effects unknown	Coadministration of amiodarone with Daclatasvir in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia.
Antiarrhythmic: Digoxin	Increase Daclatasvir	Patients already receiving daclatasvir initiating digoxin: Initiate treatment using the lowest appropriate digoxin dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. Patients already receiving digoxin prior to initiating daclatasvir: Measure serum digoxin concentrations before initiating daclatasvir. Reduce digoxin concentrations by decreasing digoxin dosage by approximately 15% to 30% or by modifying the dosing frequency and continue monitoring.
Lipid Lowering Agents		
HMG-CoA Reductase inhibitors: Atorvastatin, Fluvastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin	Increase concentration of HMG-CoA Reductase Inhibitors	Monitoring for HMG-CoA Reductase Inhibitor associated adverse events such as myopathy.
Narcotic Analgesic / Treatment of Opioid Dependence		
Buprenorphine, Buprenorphine/ naloxone	Increase Buprenorphine Increase norbuprenorphine	Clinical monitoring for buprenorphine-associated adverse events is recommended.

OVERDOSAGE
There is no known antidote for overdose of Daclatasvir. Treatment of overdose with Daclatasvir should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Because Daclatasvir is highly protein bound (>99%), dialysis is unlikely to significantly reduce plasma concentrations of daclatasvir.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Daclavia (Daclatasvir) Tablets 30mg are available in pack of 28's.
Daclavia (Daclatasvir) Tablets 60mg are available in pack of 28's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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