

# DASAVIR<sup>TM</sup> Tablets (Daclatasvir)

ڈیساویر ٹیبلٹس

## QUALITATIVE AND QUANTITATIVE COMPOSITION

### Dasavir Tablets 30mg

Each film-coated tablet contains: Daclatasvir dihydrochloride equivalent to Daclatasvir... 30mg

### Dasavir Tablets 60mg

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## CLINICAL PARTICULARS

### Therapeutic Indications

Dasavir (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 Dasavir (Daclatasvir) is 60mg taken orally, once daily, with or without food.

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

Patient Population	Regimen and Duration
<b>HCV Genotype 1 or 4</b>	
Patients without cirrhosis	Dasavir + sofosbuvir for 12 weeks
Patients with cirrhosis Child-Pugh A or B	Dasavir + sofosbuvir + ribavirin for 12 weeks or Dasavir + sofosbuvir (without ribavirin) for 24 weeks
Patients with cirrhosis Child-Pugh C	Dasavir + sofosbuvir +/- ribavirin for 24 weeks
<b>HCV Genotype 3</b>	
Patients without cirrhosis	Dasavir + sofosbuvir for 12 weeks
Patients with cirrhosis	Dasavir + sofosbuvir +/- ribavirin for 24 weeks

### Recurrent HCV Infection post-liver transplant (Genotype 1, 3 or 4)

Patients without cirrhosis	Dasavir + sofosbuvir + ribavirin for 12 weeks
Patients with Child Pugh A or B cirrhosis Genotype 1 or 4	Dasavir + sofosbuvir + ribavirin for 12 weeks Dasavir + sofosbuvir +/- ribavirin for 24 weeks
Patients with Child Pugh C cirrhosis Genotype 3	Dasavir + 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. Dasavir (Daclatasvir) is given for 24 weeks, 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, Dasavir (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 Dasavir (Daclatasvir) is weight-based (1,000 or 1,200mg 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 1,000 - 1,200mg 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 values	Ribavirin Dosing Guideline
<b>Hemoglobin</b>	
>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
<b>Creatinine Clearance</b>	
>50 mL/min	Follow guidelines above for hemoglobin
>30 to ≤ 50 mL/min	200mg every other day
≤ 30 mL/min or haemodialysis	Discontinue ribavirin

### Dose modification, interruption and discontinuation

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

### Treatment discontinuation in patients with inadequate on-treatment virologic response during treatment with Dasavir, 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 Dasavir, peginterferon alfa and ribavirin
Treatment week 12: ≥ 25 IU/ml	Discontinue Dasavir, peginterferon alfa and ribavirin
Treatment week 24: ≥ 25 IU/ml	Discontinue peginterferon alfa and ribavirin (treatment with Dasavir is complete at week 24)

### Dose recommendation for concomitant medicines

Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)

The dose of Dasavir (Daclatasvir) should be reduced to 30mg once daily when coadministered with strong inhibitors of CYP3A4.

### Moderate inducers of CYP3A4

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

### Missed Doses

Patients should be instructed that, if they miss a dose of Dasavir (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 Populations

#### Elderly

No dose adjustment of Dasavir (Daclatasvir) is required for patients aged ≥ 65 years

#### Renal Impairment

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

#### Hepatic Impairment

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

#### Pediatric Population

Dasavir (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.

### WARNINGS AND 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 bradycardia 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.

### INTERACTIONS

#### 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
<b>Protease Inhibitors:</b>		
Atazanavir with ritonavir, Atazanavir with cobicistat, Indinavir, Nelfinavir, Saquinavir, Telaprevir, Boceprevir.	Increase Daclatasvir	Decrease Daclatasvir dose to 30mg once daily
<b>Other antiretrovirals:</b>		
Cobicistat-containing antiretroviral regimens Examples: atazanavir/cobicistat, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	Increase Daclatasvir	Decrease Daclatasvir dose to 30mg once daily when coadministered with darunavir combined with cobicistat.
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTI):</b> Efavirenz, Etravirine, Nevirapine		
	Decrease Daclatasvir	Increase Daclatasvir dose to 50mg once daily.
<b>Strong CYP3A inhibitors (see also antiviral agents)</b>		
Examples: clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, voriconazole, voriconazole	Increase Daclatasvir	Decrease Daclatasvir dose to 30mg once daily when coadministered with strong inhibitors of CYP3A.
<b>Moderate CYP3A inducers (see also antiviral agents)</b>		
Examples: bosentan, dexamethasone, modafinil, rifampin, rifampetin	Decrease Daclatasvir	Increase Daclatasvir dose to 50mg once daily when coadministered with moderate inducers of CYP3A
<b>Anticoagulants</b>		
Dabigatran etexilate mesylate	Increase Dabigatran	Use of Daclatasvir with dabigatran etexilate is not recommended in specific renal impairment groups, depending on the indication.
<b>Cardiovascular Agents</b>		
Coadministration of amilorone with Daclatasvir in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia.		
<b>Antiarrhythmic: Amiodarone</b> Amiodarone: effects unknown		
Patients already receiving 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		
Antiarrhythmic: Digoxin	Increase Daclatasvir	
<b>Lipid Lowering Agents</b>		
HMG-CoA Reducease inhibitors: Atorvastatin, Fluvastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin	Increase concentration of HMG-CoA Reducease Inhibitors	Monitoring for HMG-CoA Reducease Inhibitor associated adverse events such as myopathy.
<b>Narcotic Analgesic / Treatment of Opioid Dependence</b>		
Buprenorphine, Buprenorphine/naloxone	Increase Buprenorphine Increase nortuprenorphine	Clinical monitoring for buprenorphine-associated adverse events is recommended.

## PREGNANCY AND BREAST FEEDING

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.

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.

## 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.

## 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, upper abdominal pain, constipation, flatulence, gastroesophageal reflux disease, dry mouth, vomiting, pruritus, dry skin, alopecia, rash, arthralgia, myalgia and irritability.

### OVERDOSE

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.

## PHARMACOLOGICAL PROPERTIES

### 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-terminals within Domain 1 of the protein, which may cause structural distortions that interfere with NS5A functions.

### Pharmacokinetic Properties

#### 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 (NTPC), or OATPs.

#### Metabolism

Daclatasvir is a substrate of CYP3A, with CYP3A4 being the primary CYP isozyme 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 POPULATIONS

### Hepatic Impairment

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

### Renal Impairment

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

## PHARMACEUTICAL PARTICULARS

### Shelf life

Observe expiry date on the outer pack.

### Dosage & Instructions:

As prescribed by the Physician. For details see enclosed leaflet. Keep out of the reach of children. Protect from sunlight and moisture. Do not store above 30°C. Do not use if seal over bottle is broken. To be sold on the prescription of a registered medical practitioner only.

خوراک و احتیاط :  
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ طبیعت کے لئے کھدوموجردوہولناہیچہاظرہفرا کریں۔  
بچوں کی ناک سے دور رکھیں۔ زائب رہنے سے بچاؤ رکھیں۔ ۳۰ سے زیادہ گرمیوں سے بچاؤ رکھیں۔  
بچوں کی سانس لینی ٹیگ ہٹائی ہوتے ہوئے استعمال نہ کریں۔ صرف صفحہ ڈاکٹر کے نسخے پر فرسٹ کریں۔

### Nature and Contents of Container

DASAVIR (Daclatasvir) Tablets 30mg are available in a HDPE bottle pack of 28's. DASAVIR (Daclatasvir) Tablets 60mg are available in a HDPE bottle pack of 28's.

## Manufactured by:

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