**PRESCRIBING INFORMATION**

*To be sold by retail on the prescription of a Hepatologist only*

# ℞ Daclatasvir Tablets 60 mg

## DACLAGEN-60

**GENERIC NAME**

Daclatasvir Tablets 60 mg

**BLACK BOX WARNING**

**WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS CO-INFECTED WITH HCV AND HBV**

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with **DACLAHEP Tablets**. HBV reactivation has been reported in HCV/HBV co-infected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV co-infected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate management for HBV infection as clinically indicated.

**QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains:

Daclatasvir Dihydrochloride IP eq. to Daclatasvir.....60 mg

Excipients .....q.s.

Colours: Ferric oxide USP-NF Yellow and Titanium dioxide IP

**DOSAGE FORM(S) AND STRENGTH(S)**

Film-coated tablet containing 60 mg of daclatasvir

**CLINICAL PARTICULARS**

**Therapeutic Indication**

**DACLAHEP Tablets** are indicated for use with sofosbuvir in the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection.

**Dosage and Administration**

***Testing for HBV Infection***

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with daclatasvir dihydrochloride.

Treatment with Daclatasvir should be initiated and monitored by a hepatologist or a physician experienced in the management of chronic hepatitis C under the guidance of a hepatologist.

The recommended dose of Daclatasvir is 60 mg once daily, to be taken orally with or without meals. Daclatasvir must be administered in combination with other medicinal products.

**Table 1: Recommended Regimens and Treatment Duration for Daclatasvir Combination Therapy**

| HCV Genotype and Patient Population | Treatment | Duration |
|---|---|---|
| Genotype 3 without cirrhosis | Daclatasvir + Sofosbuvir | 12 weeks |
| Genotype 3 HCV infection post-liver transplant | Daclatasvir + Sofosbuvir + Ribavirin | 12 weeks |
| Genotype 3 with Compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis | | |

***Dose Modification, Interruption and Discontinuation***

Dose modification of daclatasvir to manage adverse reactions is not recommended. If treatment interruption of components in the regimen is necessary because of adverse reactions, daclatasvir must not be given as monotherapy.

There are no virologic treatment-stoppage rules that apply to the combination of daclatasvir with sofosbuvir.

***Dose Recommendation for Concomitant Medicines***

***Strong Inhibitors of Cytochrome P450 Enzyme 3A(CYP3A)***

The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A.

***Moderate Inducers of CYP3A***

The dose of daclatasvir should be increased to 90 mg once daily when co-administered with moderate inducers of CYP3A.

***Strong Inducers of CYP3A***

Daclatasvir dose is contraindicated.

***Method of Administration***

Daclatasvir is to be taken orally with or without meals. Patients should be instructed to swallow the tablet whole. The film-coated tablet should not be chewed or crushed due to the unpleasant taste of the active substance.

***Missed Doses***

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

**Contraindications**

The use of Daclatasvir is contraindicated in the following cases:

- Patients with hypersensitivity to any of the active or inactive ingredients of this formulation
- Co-administration with medicinal products that strongly induce cytochrome P450 3A (CYP3A) and P-glycoprotein transporter (P-gp) and, thus, may lead to lower exposure and loss of efficacy of daclatasvir. These active substances include but are not limited to phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, rifapentine, systemic dexamethasone, and the herbal product St. John's wort *(Hypericum perforatum).*

**Table 2: Drugs that are Contraindicated with Daclatasvir Dihydrochloride**

| Drug Class | Drugs within Class that are Contraindicated with Daclatasvir Dihydrochloride[a] | Clinical Comments |
|---|---|---|
| Anticonvulsants | phenytoin, carbamazepine | May lead to loss of virologic response to daclatasvir dihydrochloride |
| Antimycobacterial agents | Rifampin | |
| Herbal products | St. John's wort (*Hypericum perforatum*) | |

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

**Special Warnings and Precautions for Use**

Daclatasvir must not be administered as monotherapy. Daclatasvir must be administered in combination with other medicinal products for the treatment of chronic HCV infection.

***Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone***

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

Co-administration of amiodarone with daclatasvir dihydrochloride in combination with sofosbuvir is not recommended. In patients taking amiodarone who have no alternative treatment options and who will be co-administered daclatasvir dihydrochloride and sofosbuvir, the following needs to be noted:

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

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

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

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or light-headedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion, or memory problems.

***Risk of Hepatitis B Virus Reactivation in Patients Co-infected with HCV and HBV***

Cases of HBV reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation and should, therefore, be monitored and managed according to current clinical guidelines.

Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg-positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg-negative and anti-HBc-positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increases in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with daclatasvir dihydrochloride. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with daclatasvir dihydrochloride and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

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

The concomitant use of daclatasvir dihydrochloride and other drugs may result in known or potentially significant drug interactions, some of which may lead to

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

Consider the potential for drug interactions before and during daclatasvir dihydrochloride therapy, review concomitant medications during daclatasvir dihydrochloride therapy, and monitor for the adverse reactions associated with the concomitant drugs.

***Risks Associated with Ribavirin Combination Treatment***

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

**Drug Interactions**

***Contraindications of Concomitant Use***

Daclatasvir is contraindicated in combination with medicinal products that strongly induce CYP3A and P-gp, e.g., phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, rifapentine, systemic dexamethasone, and the herbal product St. John's wort *(Hypericum perforatum)* and, thus, may lead to lower exposure and loss of efficacy of daclatasvir.

***Potential for Other Drugs to Affect Daclatasvir Dihydrochloride***

Daclatasvir is a substrate of CYP3A4. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of daclatasvir. Strong inhibitors of CYP3A (e.g., clarithromycin, itraconazole, ketoconazole, ritonavir) may increase the plasma levels of daclatasvir.

***Potential for Daclatasvir Dihydrochloride to Affect Other Drugs***

Daclatasvir is an inhibitor of P-glycoprotein transporter (P-gp), organic anion transporting polypeptide (OATP) 1B1 and 1B3, and breast cancer resistance protein (BCRP). Administration of daclatasvir dihydrochloride 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***

Clearance of HCV infection with direct-acting antivirals may lead to changes in hepatic function, which may impact the safe and effective use of concomitant medications. For example, altered blood glucose control resulting in serious symptomatic hypoglycemia has been reported in diabetic patients in postmarketing case reports and published epidemiological studies. Management of hypoglycemia in these cases required either discontinuation or dose modification of concomitant medications used for diabetes treatment. Frequent monitoring of relevant laboratory parameters (e.g., International Normalized Ratio [INR] in patients taking warfarin, blood glucose levels in diabetic patients) or drug concentrations of concomitant medications such as cytochrome P450 substrates with a narrow therapeutic index (e.g., certain immunosuppressants) is recommended to ensure safe and effective use. Dose adjustments of concomitant medications may be necessary. Refer to the prescribing information for other agents in the regimen for drug interaction information. The most conservative recommendation should be followed.

Table 3 provides clinical recommendations for established or potentially significant drug interactions between daclatasvir dihydrochloride and other drugs. Clinically relevant increase in concentration is indicated as "↑" and clinically relevant decrease as "↓" for drug interaction data.

**Table 3: Established and Other Potentially Significant Drug Interactions**

| Concomitant Drug Class: Drug Name | Effect on Concentration[a] | Clinical Comment |
|---|---|---|
| ***HIV antiviral agents*** | | |
| Protease inhibitors: Atazanavir with ritonavir[b]<br>Indinavir, nelfinavir, saquinavir | ↑ Daclatasvir | Decrease daclatasvir dihydrochloride dose to 30 mg once daily. |
| Other antiretrovirals: Cobicistat-containing antiretroviral regimens Examples: atazanavir/cobicistat, elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate | ↑ Daclatasvir | Decrease daclatasvir dihydrochloride dose to 30 mg once daily except with darunavir combined with cobicistat. |
| Non-nucleoside reverse transcriptase inhibitors (NNRTI): Efavirenz[b]<br>Etravirine<br>Nevirapine | ↓ Daclatasvir | Increase daclatasvir dihydrochloride dose to 90 mg once daily. |
| ***Strong CYP3A inhibitors*** *(see also HIV antiviral agents)* | | |
| Examples: clarithromycin, itraconazole, ketoconazole[b], nefazodone, posaconazole, telithromycin, voriconazole | ↑ Daclatasvir | Decrease daclatasvir dihydrochloride dose to 30 mg once daily when co-administered with strong inhibitors of CYP3A. |
| ***Moderate CYP3A inducers*** *(see also HIV antiviral agents)* | | |
| Examples: bosentan, dexamethasone, modafinil, nafcillin, rifapentine | ↓ Daclatasvir | Increase daclatasvir dihydrochloride dose to 90 mg once daily when co-administered with moderate inducers of CYP3A. |
| ***Anticoagulants*** | | |
| Dabigatran etexilate mesylate | ↑ Dabigatran | Use of daclatasvir dihydrochloride with dabigatran etexilate is not recommended in specific renal impairment groups, depending on the indication. Please see the dabigatran prescribing information for specific recommendations. |
| ***Cardiovascular agents*** | | |
| Antiarrhythmic: Amiodarone | Amiodarone: effects unknown | Co-administration of amiodarone with daclatasvir dihydrochloride in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If co-administration is required, cardiac monitoring is recommended. |
| Antiarrhythmic: Digoxin[b] | ↑ Digoxin | Patients already receiving daclatasvir and initiating digoxin: Initiate treatment using the lowest appropriate digoxin dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring.<br>Patients already receiving digoxin prior to initiating daclatasvir: Measure serum digoxin concentrations before initiating daclatasvir. Reduce digoxin concentrations by decreasing digoxin dosage by approximately 15–30% or by modifying the dosing frequency and continue monitoring. |
| ***Lipid-lowering agents*** | | |
| HMG-CoA reductase inhibitors:<br>Atorvastatin<br>Fluvastatin<br>Pitavastatin<br>Pravastatin<br>Rosuvastatin[b]<br>Simvastatin | ↑ Atorvastatin<br>↑ Fluvastatin<br>↑ Pitavastatin<br>↑ Pravastatin<br>↑ Rosuvastatin<br>↑ Simvastatin | Monitor for HMG- CoA reductase inhibitor-associated adverse events such as myopathy. |
| ***Narcotic analgesic/treatment of opioid dependence*** | | |
| Buprenorphine<br>Buprenorphine/naloxone | ↑ Buprenorphine<br>↑ Norbuprenorphine | For buprenorphine or buprenorphine/naloxone, no adjustment is needed, but clinical monitoring for buprenorphine-associated adverse events is recommended. |

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

[b] These interactions have been studied.

***Drugs without Clinically Significant Interactions with Daclatasvir Dihydrochloride***

Based on the results of drug interaction trials Cytochrome P450 (CYP) Enzymes.

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

***Transporters***

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

Drug interaction studies were conducted with daclatasvir and other drugs likely to be co-administered or drugs used as probes to evaluate potential drug–drug interactions. The effects of daclatasvir on the $C_{max}$, AUC, and $C_{min}$ of the co-administered drug are summarized in Table 4, and the effects of the co-administered drug on the $C_{max}$, AUC, and $C_{min}$ of daclatasvir are summarized in Table 5. For information regarding clinical recommendations. Drug interaction studies were conducted in healthy adults unless otherwise noted.

**Table 4: Effect of Daclatasvir Dihydrochloride on the Pharmacokinetics of Concomitant Drugs**

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

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

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

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

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

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

NA = Not available.

**Table 5: Effect of Co-administered Drugs on Daclatasvir Dihydrochloride Pharmacokinetics**

| Concomitant Drug | Co-administered Drug Dose | Daclatasvir Dihydrochloride Dose | Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI) | | |
|---|---|---|---|---|---|
| | | | $C_{max}$ | AUC | $C_{min}$[a] |
| Atazanavir/ Ritonavir | 300 mg/ 100 mg QD | 20 mg QD (test arm) | 0.45 (0.41, 0.49)[b] | 0.70 (0.65, 0.75)[b] | 1.22 (1.08, 1.37)[b] |
| Cyclosporine | 400 mg single Dose | 60 mg QD | 1.04 (0.94, 1.15) | 1.40 (1.29, 1.53) | 1.56 (1.41, 1.71) |
| Darunavir/ Ritonavir | 800 mg/100 mg QD | 30 mg QD (test arm) | 0.38 (0.35, 0.42)[b] | 0.70 (0.66, 0.75)[b] | NA |
| Dolutegravir | 50 mg QD | 60 mg QD | 1.03 (0.84, 1.25) | 0.98 (0.83, 1.15) | 1.06 (0.88, 1.29) |
| Efavirenz | 600 mg QD | 120 mg QD (test arm) | 1.67 (1.51, 1.84)[b] | 1.37 (1.21, 1.55)[b] | 0.83 (0.69, 1.00)[b] |
| Escitalopram | 10 mg QD | 60 mg QD | 1.14 (0.98, 1.32) | 1.12 (1.01, 1.26) | 1.23 (1.09, 1.38) |
| Famotidine | 40 mg single dose | 60 mg single dose (2 hours after famotidine administration) | 0.56 (0.46, 0.67) | 0.82 (0.70, 0.96) | 0.89 (0.75, 1.06) |
| Ketoconazole | 400 mg QD | 10 mg single dose | 1.57 (1.31, 1.88) | 3.00 (2.62, 3.44) | NA |
| Lopinavir/ Ritonavir | 400 mg/100 mg BID | 30 mg QD (test arm) | 0.34 (0.31, 0.37)[b] | 0.58 (0.54, 0.62)[b] | NA |
| Omeprazole | 40 mg single dose | 60 mg single dose | 0.64 (0.54, 0.77) | 0.84 (0.73, 0.96) | 0.92 (0.80, 1.05) |
| Rifampin | 600 mg QD | 60 mg single dose | 0.44 (0.40, 0.48) | 0.21 (0.19, 0.23) | NA |
| Simeprevir | 150 mg QD | 60 mg QD | 1.50 (1.39, 1.62) | 1.96 (1.84, 2.10) | 2.68 (2.42, 2.98) |
| Tenofovir disoproxil fumarate | 300 mg QD | 60 mg QD | 1.06 (0.98, 1.15) | 1.10 (1.01, 1.21) | 1.15 (1.02, 1.30) |

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

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

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

NA = Not available.

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

**Use in Special Populations**

***Patients with Renal Impairment***

No dosage adjustment of daclatasvir is required for patients with any degree of renal impairment.

***Patients with Hepatic impairment***

Based on a hepatic impairment study in non–HCV-infected subjects, no dosage adjustment of daclatasvir is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment.

***Pregnant Women***

***Risk Summary***

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

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

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

*ANIMAL DATA*

Daclatasvir was administered orally to pregnant rats at doses of 0, 50, 200, or 1,000 mg/kg/day on gestation days 6 to 15. Maternal toxicity (mortality, adverse clinical signs, body-weight losses, and reduced food consumption) was noted at doses of 200 and 1,000 mg/kg/day. In the offspring, malformations of the fetal brain, skull, eyes, ears, nose, lip, palate, or limbs were observed at doses of 200 and 1,000 mg/kg. The dose of 1,000 mg/kg was associated with profound embryo lethality and lower fetal body weight. No malformations were noted at 50 mg/kg/day. Systemic exposure (AUC) at 50 mg/kg/day in pregnant females was 6 times higher than exposures at the RHD.

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

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

***Lactating Women***

***Risk Summary***

It is not known whether daclatasvir dihydrochloride is present in human milk, affects human milk production, or has effects on the breastfed infant. Daclatasvir was present in the milk of lactating rats.

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

If daclatasvir dihydrochloride is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

***Data***

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

***Females and Males of Reproductive Potential***

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

***Pediatric Patients***

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

***Geriatric Patients***

Of 1,184 subjects treated with the recommended dose of daclatasvir dihydrochloride in ten clinical trials, 7% of subjects were 65 years of age or older. Safety was similar across older and younger subjects and there were no safety findings unique to subjects 65 years and older. SVR12 rates were comparable among older and younger subjects. No dosage adjustment of daclatasvir dihydrochloride is required for elderly patients.

**Effect on Ability to Drive and Use Machines**

The effect on ability to drive and use machines has not been established for daclatasvir.

**Dimension:** 325x535 mm
**Colour:** Black
**Spec.:** 40 ± 15% Gsm Bible Paper
**Folding size:** 40.62x66.87 mm
**Reason for change:** PIL text matter updated, dimension changed and artwork code revised

**Undesirable Effects**

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

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

- Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone

***Clinical Trials Experience***

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

Approximately 2,400 subjects with chronic HCV infection have been treated with the recommended dose of daclatasvir dihydrochloride in combination with other anti-HCV drugs in clinical trials. A total of 679 subjects have received a daclatasvir dihydrochloride- and sofosbuvir-based regimen. Safety experience from three clinical trials of daclatasvir dihydrochloride and sofosbuvir with or without ribavirin is presented.

***Daclatasvir Dihydrochloride and Sofosbuvir***

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

In the ALLY-2 trial, 153 treatment-naïve and treatment-experienced subjects with HCV/HIV-1 co-infection were treated with daclatasvir dihydrochloride 60 mg once daily (dose-adjusted for concomitant antiretroviral use) in combination with sofosbuvir for 12 weeks. The most common adverse reaction (frequency of 10% or greater) was fatigue. The majority of adverse reactions were mild to moderate in severity. No subjects discontinued therapy for adverse events. Adverse reactions considered at least possibly related to treatment and occurring at a frequency of 5% or greater in ALLY-3 or ALLY-2 are presented in Table 6.

**Table 6: Adverse Reactions (All Severity) Reported at ≥5% Frequency, Daclatasvir Dihydrochloride + Sofosbuvir, Studies ALLY-3 and ALLY-2**

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

***Daclatasvir Dihydrochloride, Sofosbuvir, and Ribavirin***

In the ALLY-1 trial, 113 subjects with chronic HCV infection, including 60 subjects with Child-Pugh A, B, or C cirrhosis and 53 subjects with recurrence of HCV after liver transplantation, were treated with daclatasvir dihydrochloride 60 mg once daily in combination with sofosbuvir and ribavirin for 12 weeks. The most common adverse reactions (frequency of 10% or greater) among the 113 subjects were headache, anemia, fatigue, and nausea. The majority of adverse reactions were mild to moderate in severity. Of the 15 (13%) subjects who discontinued study drug for adverse events, 13 (12%) subjects discontinued ribavirin only and 2 (2%) subjects discontinued all study drugs. During treatment, 4 subjects in the cirrhotic cohort underwent liver transplantation. Adverse reactions considered at least possibly related to treatment and occurring at a frequency of 5% or greater in either treatment cohort in ALLY-1 are presented in Table 7.

**Table 7: Adverse Reactions (All Severity) Reported at ≥5% Frequency in Either Treatment Cohort, Daclatasvir Dihydrochloride + Sofosbuvir + Ribavirin, Study ALLY-1**

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

***Laboratory Abnormalities***

Selected Grades 3 and 4 treatment-emergent laboratory abnormalities observed in clinical trials of daclatasvir dihydrochloride in combination with sofosbuvir with or without ribavirin are presented in Table 8.

**Table 8: Selected Grades 3 and 4 Laboratory Abnormalities in Clinical Trials of Daclatasvir Dihydrochloride + Sofosbuvir ± Ribavirin, Studies ALLY-3, ALLY- 2, and ALLY-1**

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

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

***Postmarketing Experience***

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

***Cardiac Disorders****:* Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with a sofosbuvir-containing regimen.

***Reporting of Suspected Adverse Reactions***

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form (form.heteroworld.com) or by Hetero Helpline No. 1800-120-8689. Also for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.com.

**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 the drug.

**PHARMACOLOGICAL PROPERTIES**

**Mechanism of Action**

Daclatasvir is a direct-acting antiviral agent (DAA) against the hepatitis C virus. Daclatasvir is an inhibitor of NS5A, a nonstructural protein encoded by HCV. Daclatasvir binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly. Characterization of daclatasvir-resistant viruses, biochemical studies, and computer modelling 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.

**Pharmacodynamic Properties**

***Antiviral Activity***

Daclatasvir had median $EC_{50}$ values of 0.008 nM (range, 0.002–0.03 nM; n=35), 0.002 nM (range, 0.0007–0.006 nM; n=30), and 0.2 nM (range, 0.006–3.2 nM; n=17) against hybrid replicons containing genotypes 1a, 1b, and 3a subject-derived NS5A sequences, respectively, without detectable daclatasvir resistance-associated polymorphisms at NS5A amino acid positions 28, 30, 31, or 93. Daclatasvir activity was reduced against genotypes 1a, 1b, and 3a subject-derived replicons with resistance-associated polymorphisms at positions 28, 30, 31, or 93, with median $EC_{50}$ values of 76 nM (range, 4.6–2409 nM; n=5), 0.05 nM (range, 0.002–10 nM; n=12), and 13.5 nM (range, 1.3–50 nM; n=4), respectively. Similarly, the $EC_{50}$ values of daclatasvir against 3 genotype 3b and 1 genotype 3i subject derived NS5A sequences with polymorphisms (relative to a genotype 3a reference) at positions 30+31 (genotype 3b) or 30+62 (genotype 3i) were ≥3,620 nM.

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

***Resistance***

***In Cell Culture***

HCV genotype 1a, 1b, and 3a replicon variants with reduced susceptibility to daclatasvir were selected in cell culture, and the genotype and phenotype of daclatasvir-resistant NS5A amino acid variants were characterized. Phenotypic analysis of genotype 1a replicons expressing single NS5A M28T, Q30E, Q30H, Q30R, L31V, Y93C, Y93H, and Y93N substitutions exhibited 500-, 18,500-, 1,083-, 900-, 2,500-, 1,367-, 8,500-, and 34,833-fold reduced susceptibility to daclatasvir, respectively. For genotype 1b, L31V and Y93H single substitutions and L31M/Y93H and L31V/Y93H combinations exhibited 33-, 30-, 16,000-, and 33,667-fold reduced susceptibility to daclatasvir, respectively. A P32-deletion (P32X) in genotype 1b reduced daclatasvir susceptibility by >1,000,000-fold. For genotype 3a, single A30K, L31F, L31I, and Y93H substitutions exhibited 117-, 320-, 240-, and 3,733-fold reduced susceptibility to daclatasvir, respectively.

***In Clinical Studies***

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

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

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

***Persistence of Resistance-associated Substitutions***

In a long-term follow-up study that included HCV genotype 1-and genotype 3-infected subjects treated with daclatasvir-containing regimens in Phase 2/3 clinical trials, viral populations with treatment-emergent NS5A resistance-associated substitutions persisted at detectable levels for more than 1 year in most subjects.

***Effect of Baseline HCV Amino Acid Polymorphisms on Treatment Response***

*Genotype 1A NS5A Polymorphisms:* In HCV genotype 1a-infected subjects with cirrhosis, the presence of an NS5A amino acid polymorphism at position M28, Q30, L31, or Y93 (defined as any change from reference identified by population-based nucleotide sequencing) was associated with reduced efficacy of daclatasvir and sofosbuvir with or without ribavirin for 12 weeks in the ALLY-1 and ALLY-2 trials. Due to the limited sample size, insufficient data are available to determine the impact of specific NS5A polymorphisms at these positions on SVR12 rates in subjects with cirrhosis. In 6 of 54 subjects (11%) with cirrhosis, one of the following specific NS5A polymorphisms was seen at baseline: M28V/T (n=2), Q30R (n=1), L31M (n=2), or Y93N (n=1); 2 subjects with M28V or Q30R achieved SVR12 while 4 subjects with M28T, L31M, or Y93N did not achieve SVR. In 11 of 112 subjects (10%) without cirrhosis, one or more of the following specific NS5A polymorphisms was seen at baseline: M28T/V (n=3), Q30H/L/R (n=5), L31M (n=1), and Y93C/H/S (n=4); all noncirrhotic subjects with these baseline NS5A polymorphisms achieved SVR12. Based on an analysis of 1,026 HCV genotype 1a NS5A amino acid sequences from pooled clinical trials, the prevalence of polymorphisms at these positions was 11% overall, and 11% in the U.S.

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

*Genotype 3 NS5A Polymorphisms:* In the ALLY-3 trial in which HCV genotype 3-infected subjects received daclatasvir and sofosbuvir for 12 weeks, the presence of an NS5A Y93H polymorphism was associated with a reduced SVR12 rate (see Table 9). In a pooled analysis of 175 subjects infected with HCV genotype 3 with available baseline nucleotide sequence data in the ALLY-1, -2, and -3 trials, virus isolates from 7% (13/175) of subjects had the NS5A Y93H polymorphism, and all 13 of these subjects were in the ALLY-3 trial. Phylogenetic analysis of NS5A sequences indicated that all genotype 3 subjects with available data in the ALLY-1, -2, and -3 trials (n=175) were infected with HCV subtype 3a.

**Table 9: Impact of NS5A Amino Acid Polymorphisms on SVR12 Rates in Subjects with HCV Genotype 1a or Genotype 3 Infection in Phase 3 Trials of Daclatasvir + Sofosbuvir ± Ribavirin**

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

[a] HCV genotype 1a-infected subjects received daclatasvir + sofosbuvir ± ribavirin for 12 weeks in the ALLY-1 and ALLY-2 trials. HCV genotype 3-infected subjects received daclatasvir + sofosbuvir for 12 weeks in the ALLY-3 trial; no data on the impact of Y93H are available for HCV genotype 3-infected subjects treated with daclatasvir + sofosbuvir ± ribavirin in ALLY-1 and ALLY-2 trials.

[b] None of the 11 subjects with Child-Pugh C cirrhosis had an indicated NS5A polymorphism; 5 achieved SVR (genotype 1a: 4/9; genotype 3a: 1/2).

[c] Any change from genotype 1a reference.

[d] Includes subjects who were post-transplant with undefined cirrhosis status.

***Cross-Resistance***

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

***Cardiac Electrophysiology***

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

**Pharmacokinetic Properties**

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

Population pharmacokinetic estimates for daclatasvir 60 mg once daily in chronic HCV-infected subjects are shown in Table 10.

**Table 10: Population Pharmacokinetic Estimates for Daclatasvir in Chronic HCV-Infected Subjects Receiving Daclatasvir 60 mg Once Daily and Sofosbuvir 400 mg Once Daily**

| Parameters | Daclatasvir 60 mg Once Daily (n=152) |
|---|---|
| **$AUC_{0\text{-}24h}$ (ng•h/mL)** | |
| Mean ± standard deviation | 1,0973 ± 5,288 |
| Median (range) | 9,680 (3,807–41,243) |
| **$C_{24h}$ (ng/mL)** | |
| Mean ± standard deviation | 182 ± 137 |
| Median (range) | 148 (21–1,050) |

***Absorption and Bioavailability***

Daclatasvir administered as a tablet was readily absorbed following multiple oral doses, with peak plasma concentrations occurring between 1 and 2 hours.

Daclatasvir $C_{max}$, AUC, and $C_{min}$ increased in a near dose-proportional manner. Steady state was achieved after 4 days of once-daily administration. At the 60 mg dose, exposure to daclatasvir was similar between healthy and HCV-infected subjects.

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

*In vivo* and *In vitro* studies with human Caco-2 cells indicated that daclatasvir is a substrate of P-gp. Studies showed that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.

***Effect of Food on Oral Absorption***

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

***Distribution***

With multiple dosing, protein-binding of daclatasvir in HCV-infected subjects was approximately 99% and independent of dose at the dose range studied (1–100 mg). In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [$^{13}C$, $^{15}N$]-daclatasvir intravenous dose, estimated volume of distribution at steady state was 47 l.

***Metabolism***

Daclatasvir is a substrate of CYP3, with CYP3A4 being the major CYP isoform responsible for the metabolism. Following single-dose oral administration of 25 mg $^{14}C$-daclatasvir in healthy subjects, the majority of radioactivity in plasma was predominately attributed to parent drug (97% or greater).

***Elimination***

Following single-dose oral administration of 25 mg $^{14}C$–daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% as unchanged drug) and 6.6% was excreted in the urine (primarily as unchanged daclatasvir). Following multiple-dose administration of daclatasvir in HCV-infected subjects, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [$^{13}C$, $^{15}N$]-daclatasvir intravenous dose, the total clearance was 4.24 l/h.

***Use in Special Populations***

***Patients with Renal Impairment***

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

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

***Patients with Hepatic Impairment***

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

***Pediatric Patients***

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

***Geriatric Patients***

Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18 to 79 years) analyzed, age did not have a clinically relevant effect on the pharmacokinetics of daclatasvir.

***Gender***

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

***Race***

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

**NONCLINICAL PROPERTIES**

***Animal Toxicology or Pharmacology***

***Carcinogenesis and Mutagenesis***

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

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

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

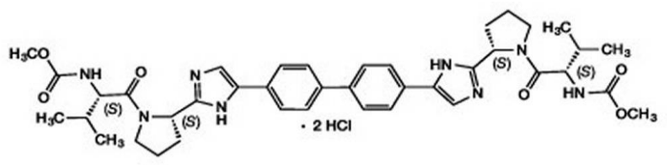
***Impairment of Fertility***

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

If daclatasvir and sofosbuvir are administered with ribavirin, the information for ribavirin on impairment of fertility also applies to this combination regimen.

**DESCRIPTION**

Daclatasvir is an inhibitor of HCV nonstructural protein 5A (NS5A). The chemical name of daclatasvir dihydrochloride is carbamic acid *N*,*N*'-[[1,1'-biphenyl]-4,4'-diylbis[1*H*-imidazole-5,2-diyl-(2*S*)-2,1-pyrrolidinediyl[(1*S*)-1-(1-methylethyl)-2-oxo-2,1-ethanediyl]]]bis-, *C*,*C*'-dimethyl ester, hydrochloride (1:2). Its molecular formula is $C_{40}H_{50}N_8O_6$•2HCl and its molecular weight is 738.88. Its structural formula is as follows:




**PHARMACEUTICAL PARTICULARS**

**Incompatibilities**

Not applicable.

**Shelf-Life**

As on the pack.

**Packaging Information**

HDPE Container pack of 28 Tablets

**Storage and Handling Instructions**

- **Store protected from moisture at a temperature not exceeding 30°C.**
- KEEP OUT OF THE REACH OF CHILDREN
- Keep container tightly closed. Dispense in original container.
- Do not use if seal over container opening is broken or missing.

**PATIENT COUNSELING INFORMATION**

**1. What are DACLAHEP Tablets?**

**DACLAHEP Tablets** are indicated for use with sofosbuvir in the treatment of patients with chronic HCV genotype 3 infection.

- Take **DACLAHEP Tablets** with sofosbuvir or with sofosbuvir and ribavirin.
- You should not take **DACLAHEP Tablets** without a prescription.

It is not known if **DACLAHEP Tablets** are safe and effective in children under 18 years of age.

**2. What is the most important information I should know about DACLAHEP Tablets?**

**DACLAHEP Tablets** can cause serious side effects, including the following:

- Hepatitis B virus reactivation: Before starting treatment with **DACLAHEP Tablets**, your healthcare provider will do blood tests to check for hepatitis B virus infection. If you have ever had hepatitis B virus infection, the hepatitis B virus could become active again during or after treatment of the hepatitis C virus with **DACLAHEP Tablets**. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems, including liver failure and death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop taking **DACLAHEP Tablets.**

For more information about side effects, see the section "What are the possible side effects of DACLAHEP Tablets?"

**Before taking DACLAHEP, tell your healthcare provider about all of your medical conditions, including the following**:

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

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

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

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

**3. How should I take DACLAHEP Tablets?**

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

**4. What are the possible side effects of DACLAHEP Tablets?**

**DACLAHEP Tablets** can cause serious side effects, including

- Hepatitis B virus reactivation. See "What is the most important information I should know about DACLAHEP Tablets?"

Daclatasvir dihydrochloride in combination with sofosbuvir and amiodarone may cause serious side effects, including the following:

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

The most common side effects of daclatasvir dihydrochloride when used in combination with sofosbuvir include

- headache; and,
- tiredness

The most common side effects of daclatasvir dihydrochloride when used in combination with sofosbuvir and ribavirin include

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

***Reporting of Suspected Adverse Reactions***

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form (form.heteroworld.com) or by Hetero Helpline No. 1800-120-8689. Also for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.com.

**5. How should I store DACLAHEP Tablets?**

- Store protected from moisture at a temperature not exceeding 30°C.
- Keep **DACLAHEP Tablets** and all medicines out of the reach of children.
- Keep the container tightly closed.
- Dispense in the original container.

**6. General information about the safe and effective use of DACLAHEP Tablets**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use **DACLAHEP Tablets** for a condition for which it was not prescribed. Do not give **DACLAHEP Tablets** to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about **DACLAHEP Tablets** that is written for health professionals.

**7. What are the ingredients in DACLAHEP Tablets?**

Active ingredient: Daclatasvir Dihydrochloride

Inactive ingredients: Ferric oxide USP-NF Yellow and Titanium dioxide IP

**DETAILS OF THE MANUFACTURER**

Hetero Labs Limited (Unit-II),
Village: Kalyanpur, Chakkan Road,
Tehsil: Baddi, Distt.: Solan,
Himachal Pradesh-173205

**DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE**

MNB/09/780 dated 18-03-2020

**DATE OF REVISION**

07/09/2022

The product is sold under license from BMS and Medicines Patent Pool.

**For sale in India only, not for Export.**

**GENYGI**

Marketed by:
**Genygi Life Sciences Private Limited**
SS - 29, Second Floor, Aditya Mega Mall,
Plot # 9D, Delhi - 110032

xxxxx-00

**Dimension:** 325x535 mm
**Colour:** Black
**Spec.:** 40 ± 15% Gsm Bible Paper
**Folding size:** 40.62x66.87 mm
**Reason for change:** PIL text matter updated, dimension changed and artwork code revised