# DEVAZO™ Tablets

(Daclatasvir)

DESCRIPTION:

**DEVAZO™** (Daclatasvir) is an inhibitor of HCV nonstructural protein 5A (NS5A). The chemical name for drug substance Daclatasvir dihydrochloride is carbamic acid, N,N′-[[1,1′-biphenyl]-4,4′-diylbis[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 its molecular weight is 738.88 (free base). Daclatasvir dihydrochloride drug substance is white to yellow. Daclatasvir is freely soluble in water (>700mg/mL)

COMPOSITION:

**DEVAZO™** 30mg Tablets
Each film-coated tablet contains: Daclatasvir Dihydrochloride MS equivalent to Daclatasvir…….....30mg

**DEVAZO™** 60mg Tablets
Each film-coated tablet contains: Daclatasvir Dihydrochloride MS equivalent to Daclatasvir……....60mg

CLINICAL PHARMACOLOGY:

Mechanism of Action: Daclatasvir is a direct-acting antiviral agent (DAA) against the hepatitis C virus

Pharmacodynamics: *Cardiac Electrophysiology*

At a dose 3 times the maximum recommended dose, Daclatasvir did not prolong the QT interval to any clinically relevant extent

Pharmacokinetics: The pharmacokinetic properties of Daclatasvir were evaluated in healthy adult subjects and in subjects with chronic HCV. Administration of Daclatasvir tablets in HCV-infected subjects resulted in approximately dose-proportional increases in $C_{max}$, AUC, and $C_{min}$ up to 60mg 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 60mg once daily in chronic HCV-infected subjects are shown in Table 1

Table 1: Population Pharmacokinetic Estimates for Daclatasvir in Chronic HCV-Infected Subjects Receiving Daclatasvir 60mg Once Daily and Sofosbuvir 400mg Once Daily

| Parameters | Daclatasvir 60mg Once daily (n=152) |
|---|---|
| AUC0-24h (ng•h/mL)<br>Mean ± standard deviation<br>Median (range) | <br>10973 ± 5288<br>9680 (3807 - 41243) |
| $C_{24h}$ (ng/mL)<br>Mean ± standard deviation<br>Median (range) | <br>182 ± 137<br>148 (21 - 1050) |

Absorption and Bioavailability: In HCV-infected subjects following multiple oral doses of Daclatasvir tablet ranging from 1mg to 100mg once daily, peak plasma concentrations occurred within 2 hours post dose In vitro studies with human Caco-2 cells indicated that Daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%

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

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

Metabolism: Daclatasvir is a substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism. Following single-dose oral administration of 25mg $^{14}C$-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 25mg $^{14}C$-Daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% of the dose as unchanged Daclatasvir) and 6.6% of the dose was excreted in the urine (primarily as unchanged Daclatasvir). Following multiple-dose administration of Daclatasvir in HCV-infected subjects, with doses ranging from 1mg to 100mg once daily, the terminal elimination half-life of Daclatasvir ranged from approximately 12 to 15 hours. In subjects who received Daclatasvir 60 mg tablet orally followed by 100•g [$^{13}C$,$^{15}N$]-Daclatasvir intravenous dose, the total clearance was 4.2 L/h.

Specific Populations

*Renal Impairment:* The pharmacokinetics of Daclatasvir following a single 60mg oral dose was studied in non–HCV-infected subjects with renal impairment. Using a regression analysis, the predicted AUC(0-inf) of Daclatasvir was estimated to be 26%, 60%, and 80% higher in subjects with creatinine clearance (CLcr) values of 60, 30, and 15mL/min, respectively, relative to subjects with normal renal function (CLcr of 90mL/min, defined using the Cockcroft-Gault CLcr formula), and Daclatasvir unbound AUC(0-inf) was predicted to be 18%, 39%, and 51% higher for subjects with CLcr values of 60, 30, and 15mL/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-inf) compared to 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

*Hepatic Impairment:* The pharmacokinetics of Daclatasvir following a single 30mg oral dose was studied in non–HCV-infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared to a corresponding matched control group. The $C_{max}$ and AUC(0-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-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 (18-79 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 to male subjects. This difference in Daclatasvir AUC is not considered clinically relevant.

*Race:* Population pharmacokinetic analyses in HCV-infected subjects indicated that race had no clinically relevant effect on Daclatasvir exposure

Drug Interactions

*Cytochrome P450 (CYP) Enzymes:* Daclatasvir is a substrate of CYP3A. In vitro, Daclatasvir did not inhibit ($IC_{50}$ 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 coadministered or drugs used as probes to evaluate potential drug-drug interactions. The effects of Daclatasvir on the $C_{max}$, AUC, and $C_{min}$ of the coadministered drug are summarized in Table 2, and the effects of the coadministered drug on the $C_{max}$, AUC, and $C_{min}$ of Daclatasvir are summarized in Table 3

Table 2: Effect of Daclatasvir on the Pharmacokinetics of Concomitant Drugs

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

Note: In Table 2, for the concomitant medication, drug-drug interaction data were not included if 90% CIs for $C_{max}$, AUC, and $C_{min}$ (if applicable for $C_{min}$) were within 80% to 125%. These concomitant medications include cyclosporine, escitalopram, ethinyl estradiol/norgestimate, midazolam, tacrolimus, and tenofovir disoproxil fumarate

a $C_{min}$ was defined as either the $C_{tau}$ or the $C_{trough}$ concentration value. b The buprenorphine and norbuprenorphine pharmacokinetic parameters were dose normalized to 8mg

c Samples up to 6 hours collected; $C_{0h}$ substituted for $C_{12h}$ concentration value. d The methadone pharmacokinetic parameters were dose normalized to 40mg

NA = Not available

Table 3: Effect of Co-administered Drugs on Daclatasvir Pharmacokinetics

| Concomitant Drug | Co-Administered Drug Dose | Daclatasvir Dose | Ratio of Pharmacokinetic Parameters of Daclatasvir Combination / No Combination (90% CI) | | |
|---|---|---|---|---|---|
| | | | $C_{max}$ | AUC | $C_{min}$ [a] |
| Atazanavir / ritonavir | 300mg/100mg QD | 20mg 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 | 400mg single dose | 60mg QD | 1.04 (0.94, 1.15) | 1.40 (1.29, 1.53) | 1.56 (1.41, 1.71) |
| Darunavir / ritonavir | 800mg/100mg QD | 30mg QD (test arm) | 0.38 (0.35, 0.42)[b] | 0.70 (0.66, 0.75) | NA |
| Dolutegravir | 50mg QD | 60mg QD | 1.03 (0.84, 1.25) | 0.98 (0.83, 1.15) | 1.06 (0.88, 1.29) |

| | | | | | |
|---|---|---|---|---|---|
| Efavirenz | 600mg QD | 120mg 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 | 10mg QD | 60mg QD | 1.14 (0.98, 1.38) | 1.12 (1.01, 1.26) | 1.23 (1.09, 1.38) |
| Famotidine | 40mg single dose | 60mg QD single dose (2 hrs. after famotidine administration) | 0.56 (0.46, 0.67) | 0.82 (0.70, 0.96) | 0.89 (0.75, 1.06) |
| Ketoconazole | 400mg QD | 10mg single dose | 1.57 (1.31, 1.88) | 3.00 (2.62, 3.44) | NA |
| Lopinavir / ritonavir | 400mg/100mg BID | 30mg QD (test arm) | 0.34 (0.31, 0.37)[b] | 0.58 (0.54, 0.62)[b] | NA |
| Omeprazole | 40mg single dose | 60mg single dose | 0.64 (0.54, 0.77) | 0.84 (0.73, 0.96) | 0.92 (0.80, 1.05) |
| Rifampin | 600mg QD | 60mg single dose | 0.44 (0.40, 0.48) | 0.21 (0.19, 0.23) | NA |
| Simeprevir | 150mg QD | 60mg QD | 1.50 (1.39, 1.62) | 1.96 (1.84, 2.10) | 2.68 (2.42, 2.98) |
| Tenofovir disoproxil fumarate | 300mg QD | 60mg QD | 1.06 (0.98, 1.15) | 1.10 (1.01, 1.21) | 1.15 (1.02, 1.30) |

Note: In Table 3, drug-drug interaction data for Daclatasvir were not included for a study with tacrolimus because the 90% CIs for $C_{max}$, AUC, and $C_{min}$ were within 80% to 125%
a $C_{min}$ was defined as either the $C_{tau}$ or the $C_{trough}$ Daclatasvir concentration value
b Observed, non-dose normalized data. 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: peginterferon alfa, ribavirin, or antacids. No clinically relevant interaction is anticipated for Daclatasvir with concomitant use of rilpivirine

Microbiology
*Mechanism of Action:* Daclatasvir is an inhibitor of NS5A, a nonstructural protein encoded by HCV. Daclatasvir binds to the N- terminus of NS5A and inhibits both viral RNA replication and virion assembly. Characterization of Daclatasvir-resistant viruses, biochemical studies, and computer modeling data indicate that Daclatasvir interacts with the N-terminus within Domain 1 of the protein, which may cause structural distortions that interfere with NS5A functions
*Antiviral Activity:* Daclatasvir had 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 • 3620 nM.

INDICATIONS AND USAGE
Daclatasvir is indicated for use with sofosbuvir, with or without ribavirin, for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1 or genotype 3 infection
*Limitations of Use:* Sustained virologic response (SVR12) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving Daclatasvir in combination with sofosbuvir for 12 weeks

DOSAGE AND ADMINISTRATION
Testing Prior to the Initiation of Therapy: 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. NS5A Resistance Testing in HCV Genotype 1a-Infected Patients with Cirrhosis: Consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93 in patients with cirrhosis who are infected with HCV genotype 1a prior to the initiation of treatment with Daclatasvir and sofosbuvir with or without ribavirin

Recommended Dosage: The recommended dosage of Daclatasvir is 60mg, taken orally, once daily, with or without food. Table 4 provides the recommended Daclatasvir-containing treatment regimens and duration based on HCV genotype and patient population. The optimal duration of Daclatasvir and sofosbuvir with or without ribavirin has not been established for HCV genotype 3 patients with cirrhosis or for HCV genotype 1 patients with Child-Pugh C cirrhosis. For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 4. For specific dosage recommendations for sofosbuvir, refer to the prescribing information
For HCV genotype 1 or 3 patients with Child-Pugh B or C cirrhosis or post-transplantation patients, the starting dose of ribavirin is 600mg once daily, increasing up to 1000mg daily as tolerated. The starting dose and on-treatment dose of ribavirin can be decreased based on hemoglobin and creatinine clearance. For HCV genotype 3 patients with compensated cirrhosis (Child-Pugh A), the recommended dosing of ribavirin is based on weight (1000mg for patients weighing less than 75kg and 1200 mg for those weighing at least 75kg administered orally in two divided doses with food)

Table 4: Recommended Treatment Regimen and Duration for Daclatasvir in Patients with Genotype 1 or 3 HCV

| | Patient Population | Treatment and Duration |
|---|---|---|
| Genotype 1 | Without cirrhosis | Daclatasvir + sofosbuvir for 12 weeks |
| | Compensated (Child-pugh A) cirrhosis | |
| | Decompensated (Child-pugh B or C) cirrhosis | Daclatasvir + sofosbuvir + ribavirin for 12 weeks |
| | Post-transplant | |
| Genotype 3 | Without cirrhosis | Daclatasvir + sofosbuvir for 12 weeks |
| | Compensated (Child-pugh A) or decompensated (Child-pugh B or C) cirrhosis | Daclatasvir + sofosbuvir + ribavirin for 12 weeks |
| | Post-transplant | |

Dosage Modification Due to Drug Interactions
Refer to the drug interactions and contraindications sections for other drugs before coadministration with Daclatasvir

Table 5: Recommended Daclatasvir Dosage Modification with CYP3A Inhibitors and Inducers

| Concomitant Drugs | Daclatasvir Dosage |
|---|---|
| Strong CYP3A inhibitors and certain HIV antiviral agents | 30mg once daily |
| Moderate CYP3A inducers and nevirapine | 90mg once daily |
| Strong CYP3A inducers | Contraindicated |

Dosage reduction of Daclatasvir for adverse reactions is not recommended
*Discontinuation of Therapy*
If sofosbuvir is permanently discontinued in a patient receiving Daclatasvir with sofosbuvir, then Daclatasvir should also be discontinued

CONTRAINDICATIONS
[1] When Daclatasvir is used in combination with other agents, the contraindications applicable to those agents are applicable to the combination regimen. Refer to the respective prescribing information for a list of contraindications
[1] Daclatasvir is contraindicated in combination with drugs that strongly induce CYP3A and, thus, may lead to lower exposure and loss of efficacy of Daclatasvir. Contraindicated drugs include, but are not limited to those listed in Table 6

Table 6: Drugs that are contraindicated with Daclatasvir

| Drug Class | Drug within Class that are Contraindicated with Daclatasvirs a | Clinical Comments |
|---|---|---|
| Anticonvulsants | phenytoin, carbamazepine | May lead to loss of virologic response to daclatasvir |
| Antimycobacterial agents | rifampin | |
| Herbal products | St. John's wort (Hypericum perforatum) | |

a This table is not a comprehensive list of all durgs that strongly induce CYP3A

WARNINGS AND PRECAUTIONS

PRECAUTIONS FOR USE IN PATIENTS CURRENTLY INFECTED OR HAVE A HISTORY OF HEPATITIS-B VIRUS (HBV), BECAUSE OF REACTIVATION OF HEPATITIS-B VIRUS

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV
Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals, and who were not receiving HBV antiviral therapy. 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. 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 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 and other drugs may result in known or potentially significant drug interactions, some of which may lead to (see Contraindications and Drug Interaction):

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

See Table 6 for drugs contraindicated with Daclatasvir due to loss of efficacy and possible development of resistance [see Contraindications]. See Table 10 for steps to prevent or manage other possible and known significant drug interactions [see Drug Interactions]. Consider the potential for drug interactions before and during Daclatasvir therapy, review concomitant medications during Daclatasvir therapy, and monitor for the adverse reactions associated with the concomitant drugs.

Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with another HCV direct-acting antiviral, including Daclatasvir. A fatal cardiac arrest was reported in a patient receiving a sofosbuvir-containing regimen (ledipasvir/sofosbuvir). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this bradycardia effect is unknown. Coadministration of amiodarone with Daclatasvir in combination with sofosbuvir is not recommended. For patients taking amiodarone who have no alternative treatment options and who will be coadministered Daclatasvir and sofosbuvir:

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

Patients who are taking sofosbuvir in combination with Daclatasvir 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 should also undergo similar cardiac monitoring as outlined above. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion, or memory problems [see Adverse Reactions and Drug Interactions, Table 10]

Risks Associated with Ribavirin Combination Treatment

If Daclatasvir 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

ADVERSE REACTIONS

If Daclatasvir 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 labeling:

- Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone [see Warnings and Precautions]

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Approximately 2400 subjects with chronic HCV infection have been treated with the recommended dose of Daclatasvir in combination with other anti-HCV drugs in clinical trials. Six hundred seventy-nine subjects have received a Daclatasvir and sofosbuvir based regimen. Safety experience from three clinical trials of Daclatasvir and sofosbuvir with or without ribavirin is presented.

Daclatasvir and Sofosbuvir

In the ALLY-3 trial, 152 treatment-naive and treatment-experienced subjects with HCV genotype 3 infection were treated with Daclatasvir 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-naive and treatment experienced subjects with HCV/HIV-1 coinfection were treated with Daclatasvir 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 7

Table 7: Adverse Reactions (All Severity) Reported at • 5% Frequency, Daclatasvir + Sofosbuvir, Studies ALLY-3 and ALLY-2

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

Daclatasvir, 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 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 8.

Table 8: Adverse Reactions (All Severity) Reported at • 5% Frequency in Either Treatment Cohort, Daclatasvir + 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 Grade 3 and 4 treatment-emergent laboratory abnormalities observed in clinical trials of Daclatasvir in combination with sofosbuvir with or without ribavirin are presented in Table 9

Table 9: Selected Grade 3 and 4 Laboratory Abnormalities in Clinical Trials of Daclatasvir + Sofosbuvir ± Ribavirin, Studies ALLY-3, ALLY-2, and ALLY-1

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

a In the ALLY-2 trial, Grade 3 and 4 increase in total bilirubin were observed only in subjects receiving concomitant atazanavir

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of Daclatasvir. 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 sofosbuvir in combination with another HCV direct-acting antiviral, including Daclatasvir (*see Warnings and Precautions and Drug Interactions*)

DRUG INTERACTIONS

Potential for Other Drugs to Affect Daclatasvir: Daclatasvir is a substrate of CYP3A. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of Daclatasvir [*see Dosage and Administration, Contraindications,* & Table 10]. Strong inhibitors of CYP3A (eg, clarithromycin, itraconazole, ketoconazole, ritonavir) may increase the plasma levels of Daclatasvir [*see Dosage & Administration* & Table 10]

Potential for Daclatasvir 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 may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B1 or 1B3, or BCRP, which could increase or prolong their therapeutic effect or adverse reactions (see Table 10).

Established and Potentially Significant Drug Interactions: Refer to the prescribing information for other agents in the regimen for drug interaction information. The most conservative recommendation should be followed. Please also refer to (Section Contraindications) and Section (Pharmacokinetics) for complete information on all drug interactions. Table 10 provides clinical recommendations for established or potentially significant drug interactions between Daclatasvir and other drugs [see Contraindications]. Clinically relevant increase in concentration is indicated as "•" and clinically relevant decrease as "•" for drug interaction data [see Clinical Pharmacology]

Table 10: Established and Other Potentially Significant Drug Interactions

| Concomitant Drug Class: Drug Name | Effect on Concentration[a] | Clinical Comment |
|---|---|---|
| *HIV antiviral agents* | | |
| Protease inhibitors:<br>Atazanavir with ritonavir[b], Indinavir, Nelfinavir, Saquinavir | •Daclatasvir | Decrease daclatasvir dose to 30mg once daily |
| Other antiretrovirals:<br>Cobicistat-containing antiretroviral regimens<br>Examples: Atazanavir/cobicistat, elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate | •Daclatasvir | Decrease daclatasvir dose to 30mg once daily except with darunavir combined with cobicistat |
| Non-nucleoside reverse transcriptase inhibitors (NNRTI):<br>Efavirenz[b], Etravirine, Nevirapine | •Daclatasvir | Increase daclatasvir dose to 90mg once daily |
| Strong CYP3A inhibitors (See also HIV antiviral agents) | | |
| Examples: Clarithromycin, itraconazole, ketoconazole,nefazodone, posaconazole,telithromycin,voriconazole | •Daclatasvir | Decrease daclatasvir dose to 30mg once daily when coadministered with strong inhibitors of CYP3A |
| Moderate CYP3A inducers (see also HIV antiviral agents) | | |
| Examples: bosentan, dexamethasone, modafinil, nafcillin, rifapentine | •Daclatasvir | Increase daclatasvir dose to 90mg once daily when coadministered with moderate inducers of CYP3A |
| Anticoagulants | | |
| Dabigatran etexilate mesylate | •Dabigatran | Use of daclatasvir with dabigatran etexilate is not recommended in specific renal impairment groups,depending on the indication. Please see the dabigatran prescribing information for specific recommendations |
| Concomitant Drug Class: Drug Name | Effect on Concentration | Clinical Comment |
| 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. The mechanism of this effects is unkown. If coadministration is required, cardiac monitoring is recommended. [See Warnings and Precautions and Adverse Reaction] |
| Antiarrhythmic: Digoxin[b] | • Digoxin | Patients already receiving daclatasvir initiating digoxin:<br>Initiate treament using the lowest appropiate digoxin dosage. Monitor digoxin concentration; 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% to 30% or by modifying the frequency and cotinue monitoring |
| Lipid-lowering agents | | |
| HMG-CoA reductase inhibitors:<br>Atorvastatin<br>Fluvastatin<br>Pitavastatin<br>Pravastatin [b]<br>Rosuvastatin<br>Simvastatin | • Atorvastatin<br>• Fluvastatin<br>• Pitavastatin<br>• Pravastatin<br>• Rosuvastatin<br>• Simvastatin | Monitor for HMG-CoA reductase Inhibitor associated adverse event such as myopathy |
| Narcotic Analgesic/Treatment of Opioid Dependence | | |
| buprenorphine<br>buprenorphine/naloxone | • buprenorphine<br>• norbuprenorphine | For buprenorphine or buprenorphine/naloxone, no adujstment 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 (*see Clinical Pharmacology* , Tables 2 and 3)

Drugs without Clinically Significant Interactions with Daclatasvir: Please see (Section Pharmacokinetics) for information regarding anticipated interactions that are not clinically relevant. Based on the results of drug interaction trials (see Clinical Pharmacology), no clinically relevant changes in exposure were observed for cyclosporine, darunavir (with ritonavir), dolutegravir, escitalopram, ethinyl estradiol/norgestimate, lopinavir (with ritonavir), methadone, midazolam, tacrolimus, or tenofovir with concomitant use of Daclatasvir. No clinically relevant changes in Daclatasvir exposure were observed with cyclosporine, darunavir (with ritonavir), dolutegravir, escitalopram, famotidine, lopinavir (with ritonavir), omeprazole, sofosbuvir, tacrolimus, or tenofovir. No dosage adjustment for Daclatasvir is necessary with darunavir/cobicistat or moderate CYP3A inhibitors, including atazanavir (unboosted), fosamprenavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, or verapamil

USE IN SPECIFIC POPULATIONS
Pregnancy
*Risk Summary*: No adequate human data are available to determine whether or not Daclatasvir possess 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. 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. 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
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively
If Daclatasvir 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
Lactation
*Risk Summary*: It is not known whether Daclatasvir 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 and any potential adverse effects on the breastfed child from Daclatasvir or from the underlying maternal condition. If Daclatasvir is administered with ribavirin, the nursing mothers' information for ribavirin also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.
Females and Males of Reproductive Potential: If Daclatasvir 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 Use:Safety and effectiveness of Daclatasvir in pediatric patients younger than 18 years of age have not been established
Geriatric Use: Of 1184 subjects treated with the recommended dose of Daclatasvir 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 is required for elderly patients [see Clinical Pharmacology]
Renal Impairment: No dosage adjustment of Daclatasvir is required for patients with any degree of renal impairment [see Clinical Pharmacology]. Refer also to the sofosbuvir and ribavirin prescribing information for information regarding use in patients with renal impairment
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 [see Clinical Pharmacology]

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 the drug

STABILITY:
See expiry on the pack. The medicinal products does not require any special storage conditions

PRESENTATION:
**DEVAZO™** 30mg tablets available in a pack of 28's.
**DEVAZO™** 60mg tablets available in a pack of 28's

INSTRUCTIONS:
As directed by the physician. For oral use only
Keep out of reach of children.
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine

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## (ڈیکلاٹسویر)

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صرف کھانے کے لیے ہے
بچوں کی پہنچ سے دور رکھیں دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
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