Daclavir

Daclatasvir

COMPOSITION
Daclavir Tablet: Each film coated tablet contains Daclatasvir Dihydrochloride INN equivalent to Daclatasvir 60 mg.

PHARMACOLOGICAL INFORMATION
Therapeutic class: Antiviral agent.

PHARMACOLOGICAL ACTION
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 does 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 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.

Absorption and Bioavailability: 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 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 60 mg 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 60 mg 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.

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 [13C 15N]-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 25 mg 14C-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 mg14C- 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 1 mg to 100 mg 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 [13C 15N]-Daclatasvir intravenous dose, the total clearance was 4.2 L/h.

Specific Populations:
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 of Daclatasvir was estimated to be 26%, 60% and 80% higher in subjects with creatinine clearance (Cl_{cr}) values of 60, 30, and 15 mL/min, respectively, relative to subjects with normal renal function (Cl_{cr} of 90 mL/min, defined using the Cockcroft-Gault Cl_{cr} formula) and Daclatasvir unbound AUC (0-inf) was predicted to be18%, 39% and 51% higher for subjects with Cl_{cr} 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-inf) compared to subjects with normal renal function as defined using the Cockcroft-Gault Cl_{cr} formula. (0-inf) 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 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 to a corresponding matched control group. The C_{max} and AUC 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} (0-inf) and AUC 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.

Geriatric: 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.

Pediatric and Adolescent: The pharmacokinetics of Daclatasvir in pediatric patients has not been evaluated.

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.

Therapeutic Indications
Daclatasvir is a hepatitis C virus (HCV) nucleotide analog NS5A polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.

Dosage
Recommended Dosage: The recommended dosage of Daclavir is 60 mg, taken orally, once daily in combination with Sofosbuvir for 12 weeks. Daclavir may be taken with or without food. The optimal duration of Daclavir and Sofosbuvir for patients with cirrhosis has not been established.

Dosage Modification Due to Drug Interactions: Refer to the drug interactions and contraindication sections for other drugs before co-administration with Daclavir.

Strong inhibitors of Cytochrome P450 enzyme 3A (CYP3A): Reduce the dosage of Daclavir to 30 mg once daily when co-administered with strong CYP3A inhibitors using the 30 mg tablet.

Moderate CYP3A inducers: Increase the dosage of Daclavir to 90 mg once daily using an appropriate combination of tablets (three 30 mg tablets or one 60 mg and one 30 mg. tablet) when co-administered with moderate CYP3A inducers.

Strong CYP3A inducers: Daclavir is contraindicated in combination with strong CYP3A inducers.

Dosage reduction of Daclavir for adverse reactions is not recommended.

Side Effects
The following serious adverse reactions are described below Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone.

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. One subject experienced a serious adverse event that was considered unrelated to Daclatasvir, and 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 are presented in the following table

Adverse Reaction n (%) n=152	
Headache	14 % (21)
Fatigue	14 % (21)
Nausea	8% (12) 8% (12)
Diarrhea	5% (7)

Table: Adverse Reactions Reported at 5% Frequency, Daclatasvir + Sofosbuvir for 12 Weeks

Contraindications
Daclatasvir is contraindicated in combination with drugs that strongly induce CYP3A and thus, may lead to lower exposure and loss of efficacy of Daclatasvir.

Drug interactions
Potential for Other Drugs to Affect Daclavir: Daclatasvir is a substrate of CYP3A. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of Daclatasvir.

Strong inhibitors of CYP3A (e.g., Clarithromycin, Itraconazole, Ketoconazole, Ritonavir) may increase the plasma levels of Daclatasvir.

Potential for Daclavir 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 Daclavir may increase systemic exposure to medicinal products thatare substrates of P-gp, OATP 1B1 or 1B3 or BCRP, which could increase or prolong theirtherapeutic effect or adverse reactions.

Established and Potentially Significant Drug Interactions: Refer to the prescribing information for Sofosbuvir for drug interaction information. The most conservative recommendation should be followed.

Precautions
Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions: The concomitant use of Daclavir and other drugs may result in known or potentially significant drug interactions, some of which may lead to

- Loss of therapeutic effect of Daclavir and possible development of resistance
- Dosage adjustments of concomitant medications or Daclavir
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs or Daclavir

Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone: Post marketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when Amiodarone is co-administered with Sofosbuvirin combination with another HCV direct-acting antiviral, including Daclavir. 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 Daclavir in combination with Sofosbuvir is not recommended.

For patients taking Amiodarone who have no alternative treatment options and who will be co-administered Daclavir and Sofosbuvir:

- 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 Daclavir 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 Daclavir 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.

Pregnancy
No data with Daclatasvir in pregnant women are available to inform a drug-associated risk. In animal reproduction studies in rats and rabbits, no evidence of fetal harm was observed with oral administration of Daclavir during organogenesis at doses that produced exposures up to 6 and 22 times, respectively, the recommended human dose (RHD) of 60 mg. 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. Consider the benefits and risks of Daclavir when prescribing Daclavir to a pregnant woman

Nursing Mothers
No information regarding the presence of Daclatasvir in human milk, the effects on the breastfed infant or the effects on milk production is available. Daclavir is present in the milk of lactating rats. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Daclavir and any potential adverse effects on the breastfed infant from Daclavir or from the underlying maternal condition.

Pediatric Use
Safety and effectiveness of Daclavir in children less than 18 years of age have not been established.

Geriatric Use
Safety was similar across older and younger subjects and there were no safety findings unique to subjects 65 years and older. Sustained virologic response (SVR) rates were comparable among older and younger subjects. No dosage adjustment of Daclavir is required for elderly patients.

Patients with Impaired Renal Function: No dosage adjustment of Daclavir is required for patients with any degree of renal impairment.

Hepatic Impairment: No dosage adjustment of Daclavir is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment. Safety and efficacy of Daclavir have not been established in patients with decompensated cirrhosis.

Overdosage
There is no known antidote for overdose of Daclavir. Treatment of overdose with Daclavir 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.

PHARMACEUTICAL INFORMATION
Storage Conditions:
Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging
Daclavir Tablet: Each commercial box contains 1x10's Tablets in Alu-Alu blister pack.

BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

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