Daclata®

(Daclatasvir)

Highnoon

COMPOSITION

Daclata 30mg Tablet: Each film-coated tablet contains:
Daclatasvir Dihydrochloride equivalent to Daclatasvir 30mg
Daclata 60mg Tablet: Each film-coated tablet contains:
Daclatasvir Dihydrochloride equivalent to Daclatasvir 60mg

DESCRIPTION

Daclata (Daclatasvir) is an inhibitor of HCV nonstructural protein 5A (NS5A). Daclatasvir is freely soluble in water (>700 mg/mL).

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 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.

PHARMACOKINETICS

Administration of daclatasvir tablets in HCV-infected subjects resulted in approximately dose-proportional increases in Cmax, AUC, and Cmin up to 60 mg once daily. The peak plasma concentrations occurred within 2 hours post dose. High fat meal food effect was observed with Daclatasvir. 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). The terminal elimination half-life of daclatasvir ranged from approximately 12 to 15 hours. Daclatasvir is highly protein bound to plasma proteins and is unlikely to be removed by dialysis.

INDICATIONS AND USAGE

It is indicated for use with sofosbuvir for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1 or genotype 3 infection infection. It's use is limited in: Sustained virologic response (SVR) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving daclatasvir in combination with sofosbuvir for 12 weeks.

DOSAGE AND ADMINISTRATION

The recommended dosage is 60mg, taken orally, once daily in combination with sofosbuvir for 12 weeks. Daclatasvir may be taken with or without food. The optimal duration of Daclatasvir and sofosbuvir for patients with cirrhosis has not been established.
Recommended Treatment Regimen and Duration for Daclatasvir in Patients with Genotype 1 or 3 HCV

	Patient Population	Treatment and
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	

If sofosbuvir is permanently discontinued in a patient receiving daclatasvir with sofosbuvir, then it shtould also be discontinued. All patients should be tested for current or prior HBV infection before initiating HCV treatment with Daclatasvir.

Recommended Daclatasvir Dosage Modification with CYP3A Inhibitors and Inducers

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

CONTRAINDICATIONS

- It 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, Anticonvulsants drugs (phenytoin, carbamazepine, Antimycobacterial agents (rifampin), Herbal products St. John's wort (Hypericum perforatum).

Note: (This is not a comprehensive list of all drugs that strongly induce CYP3A).

ADVERSE REACTIONS

The reported adverse events are: serious symptomatic bradycardia, headache, fatigue, nausea, anemia, rash, insomnia, dizziness, somnolence, alopecia, anxiety, appetite decrease, arthralgia, asthenia, chest pain, chills, concentration impaired, constipation, cough, depression, dry mouth, dyspnea, fever, gastrointestinal discomfort, gastroesophageal reflux disease, influenza like illness, irritability, memory loss, muscle complaints, nasopharyngitis, neutropenia, pain, skin reaction, vision blurred, vomiting, weight decrease and diarrhea. The laboratory abnormalities which include decreased haemoglobin, increased alanine amino transferases, increased aspartate amino transferase, increased total bilirubin and lipase.

DRUG INTERACTIONS

- Daclatasvir is a substrate of CYP3A. Therefore, moderate or strong inducers of CYP3A (bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcillin, rifapentine) may decrease the plasma levels and therapeutic effect of daclatasvir. The strong inhibitors of CYP3A (atazanavir/ritonavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, voriconazoleeg) may increase the plasma levels of daclatasvir. The moderate inhibitors of CYP3A (atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil) may increase the plasma levels of daclatasvir.
- The use of Daclatasvir with anticoagulants (dabigatran etexilate) is not recommended in specific renal impairment groups, depending on the indication.
- The coadministration of antiarrhythmic agents (amiodarone) with Daclatasvir in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If coadministration is required, cardiac monitoring is recommended.
- Patients already receiving daclatasvir initiating digoxin: Initiate treatment using the lowest appropriate digoxin dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. Measure serum digoxin concentrations before initiating daclatasvir, if patient already receiving digoxin prior to initiating daclatasvir.
- Monitor for HMG-CoA reductase inhibitors (Atorvastatin, Fluvastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin) associated adverse events such as myopathy.
- 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.
- 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. 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.
- Cobicistat-containing antiretroviral regimens such as atazanavir / cobicistat, elvitegravir / cobicistat/emtricitabine/ tenofovir disoproxil fumarate increases the daclatasvir concentration.
- Non-nucleoside reverse transcriptase inhibitors (NNRTI): Efavirenzb Etravirine Nevirapine decreases the daclatasvir concentration.
- Narcotic Analgesic/Treatment of Opioid Dependence; For buprenorphine or buprenorphine/naloxone no adjustment is needed, but clinical monitoring for buprenorphine-associated adverse events is recommended.

WARNINGS AND PRECAUTIONS

- The concomitant use of Daclatasvir and other drugs may result in known or potentially significant drug interactions, some of which may lead to
  - 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.
- 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.
- The Serious Symptomatic Bradycardia when coadministered with Sofosbuvir and Amiodarone: The 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.
- 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.
- 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.
- 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 antiHBc 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.
- 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.

USE IN SPECIFIC POPULATIONS

Pregnancy
No data with Daclatasvir in pregnant women are available to inform a drug-associated risk.

Lactation
No information regarding the presence of daclatasvir in human milk, the effects on the breastfed infant, or the effects on milk production is available. Daclatasvir 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 Daclatasvir and any potential adverse effects on the breastfed infant from Daclatasvir or from the underlying maternal condition.

Pediatric Use
Safety and effectiveness of Daclatasvir in pediatric patients younger 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. No dosage adjustment of Daclatasvir is required for elderly patients.

Renal Impairment
No dosage adjustment of Daclatasvir is required for patients with any degree of renal Impairment.

Hepatic Impairment
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. Safety and efficacy of Daclatasvir have not been established in patients with decompensated cirrhosis.

Liver Transplant Patients
The safety and efficacy of Daclatasvir combination therapy have not been established in liver transplant patients.

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.

DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION

Daclata 30mg tablets: Alu.Alu. Blister pack of 4 x 7's.
Daclata 60mg tablets: Alu.Alu. Blister pack of 4 x 7's.

ڈیکلاٹا®

(ڈیکلاٹاسویر)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
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