Selected Properties of Daclatasvir

<table>
<tr><td>Other names</td><td>Daklinza®, BMS-790052</td></tr>
<tr><td>Manufacturer</td><td>Bristol-Myers Squibb</td></tr>
<tr><td>Pharmacology / Mechanism of Action</td><td>Daclatasvir is a highly potent and selective direct-acting antiviral (DAA) that targets the hepatitis C virus. It interferes with viral replication by inhibiting nonstructural protein 5A (NS5A), leading to suppression of RNA synthesis, virion assembly and secretion.</td></tr>
<tr><td>Activity</td><td>Daclatasvir is active against HCV genotypes 1a, 1b, 2 and 3. It is also expected to be efficacious in patients with genotype 4 infection (based on extrapolations from studies with daclatasvir in combination with peginterferon and ribavirin).
Daclatasvir has not been studied in patients with HCV genotypes 5 and 6. In combination studies using cell-based HCV replicon system, daclatasvir demonstrated synergistic effects with interferon alfa and anti-HCV agents with different pharmacologic targets, including nonstructural protein 3 (NS3) protease inhibitors, nonstructural protein 5B (NS5B) nucleoside and non-nucleoside inhibitors.</td></tr>
<tr><td>Resistance – Genotypic</td><td><u>In cell culture</u>
In HCV replicons, resistance-associated substitutions were observed in genotypes 1 to 4 in the N-terminal 100 amino acid region of NS5A.
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<tr><th>Genotype</th><th>Most Commonly Observed Variants</th><th>Level of Resistance Conferred by Polymorphism</th></tr>
<tr><td>1a</td><td>M28T, L31V/M, Q30E/H/R, Y93C/H/N</td><td>• High level of resistance (EC50 up to 350 nM)</td></tr>
<tr><td>1b</td><td>L31V and Y93H</td><td>• Low (EC50 <1 nM)
• However, relative to genotype 1a substitutions, resistance levels were noted to be higher in genotype 1b (EC50 up to 350 nM)</td></tr>
<tr><td>2</td><td>F28S</td><td>• High (EC50 >300 nM)</td></tr>
<tr><td>3</td><td>Y93H</td><td>• High (EC50 >1,000 nM)</td></tr>
<tr><td>4a</td><td>Residues 30 and 93</td><td>• Low to moderate level of resistance (EC50 0.9-16 nM)
• In general, variants in genotype 4a did not appear to reduce daclatasvir potency (EC50 0.007 to 0.0013 nM)</td></tr>
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<u>In clinical studies</u>
Daclatasvir in combination with sofosbuvir
With the exception of one subject with virologic failure (genotype 3), all participants (in study AI444040) with baseline daclatasvir resistance-associated NS5A variants achieved SVR.

Daclatasvir in combination with peginterferon alfa and ribavirin
The majority of treatment-naïve subjects with baseline daclatasvir resistance-associated NS5A variants achieved SVR. Among treatment-naïve subjects and prior nonresponders who were deem treatment failures (N=210), emergent NS5A resistance-associated variants were seen in genotype 1a (139/153) and 1b (49/57) virus. The most frequently detected polymorphisms at failure included Q30E or Q30R in combination with L31M.

<u>Persistence of resistance mutations</u>
In patients who received 14 day monotherapy treatment with daclatasvir, HCV NS5A resistant polymorphisms were observed for up to 6 months following treatment cessation, suggesting long-term persistence of resistance.[Fridell et al.</td></tr>
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<tr><td></td><td>2011; Wang et al. 2013].</td></tr>
<tr><td>Resistance – Phenotypic</td><td>N/A</td></tr>
<tr><td>Cross-Resistance</td><td>HCV replicons with resistance-associated variants to daclatasvir retained sensitivity to interferon alfa and other DAAs (i.e., NS3 protease and NS5B polymerase nucleoside and non-nucleoside inhibitors).
Daclatasvir-associated resistance mutations confer cross-resistance to other first generation HCV NS5A inhibitors.[Nakamoto et al. 2014]</td></tr>
<tr><td>Oral Bioavailability</td><td>The absolute bioavailability of the daclatasvir oral tablet formulation is 67%.</td></tr>
<tr><td>Effect of Food</td><td>Daclatasvir can be taken without regards to meals. The table below summarizes the effect of food on exposure (relative to fasting state) in healthy subjects following administration of daclatasvir 60 mg tablet.
<table>
<tr><th>Condition</th><th>Effect on Cmax</th><th>Effect on AUC</th></tr>
<tr><td>After high-fat meal</td><td>↓ by 28%</td><td>↓ by 23%</td></tr>
<tr><td>After light meal</td><td>No effect</td><td>No effect</td></tr>
</table></td></tr>
<tr><td>Protein Binding</td><td>In chronic HCV-infected subjects, daclatasvir was 99% protein bound, and binding at steady state was independent of dose over the range of 1 to 100 mg.</td></tr>
<tr><td>Vd</td><td>The estimated Vd at steady state is 47 L.</td></tr>
<tr><td>Tmax</td><td>Following oral administration, the time to peak plasma concentration of daclatasvir was reached in 1 to 2 hours.</td></tr>
<tr><td>Serum T½</td><td>In chronic HCV-infected subjects, the terminal elimination half-life of daclatasvir was 12 to 15 hours.</td></tr>
<tr><td>Drug Concentrations</td><td>The pharmacokinetic properties of daclatasvir were evaluated in healthy and HCV-infected adult subjects. Therapeutic drug concentrations of daclatasvir were achieved after 4 days of once-daily administration. At steady state, exposure to daclatasvir (at the 60 mg dose) was comparable between both groups (as below). Daclatasvir Cmax, AUC, and Cmin increased in a near dose-proportional manner.

Following multiple oral doses of daclatasvir 60 mg once daily in combination with peginterferon alfa and ribavirin:
• Mean Cmax: 1534 +/- 58 ng/mL
• Mean AUC (0 to 24 hours): 14122 +/- 70 ng x hr/mL
• Mean Cmin: 232 +/- 83 ng/mL

Although data from clinical trials on patients greater than 65 years of age are limited, population pharmacokinetic analyses suggest that age had no apparent effect on daclatasvir exposures. Gender and race were identified as statistically significant covariates in these analyses; however, the magnitude of the effect on the pharmacokinetics of daclatasvir was not found to be clinically meaningful.</td></tr>
<tr><td>Minimum target trough concentrations (for wild-type virus)</td><td>
<table>
<tr><th>Genotype</th><th>Effective Concentration (50% reduction, EC50) Values</th></tr>
<tr><td>1a</td><td>0.003-0.050 nM</td></tr>
<tr><td>1b</td><td>0.001-0.009 nM</td></tr>
<tr><td>2a</td><td>0.034-19 nM</td></tr>
<tr><td>3a, 4a, 5a and 6a</td><td>0.003-1.25 nM</td></tr>
</table></td></tr>
<tr><td>CSF (% of serum)</td><td>N/A</td></tr>
<tr><td>Metabolism</td><td>Though it is a CYP3A substrate, daclatasvir primarily undergoes biotransformation by CYP3A4 (with no metabolites circulating at levels greater than 5% of the parent concentration). In vitro and in vivo studies demonstrate that daclatasvir is also a substrate of P-glycoprotein.</td></tr>
<tr><td>Excretion</td><td>Following single-dose oral administration of carbon-labeled daclatasvir in healthy subjects, 88% of the total dose was recovered in feces (53% as unchanged drug) and 6.6% was recovered in the urine (primarily as unchanged drug).</td></tr>
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Dosing – Adult

Indication:
Treatment of chronic hepatitis C virus (HCV) infection in adults in combination with other medicinal products (as below).

Note: The safety and efficacy of daclatasvir have not been established for the following patient populations:

- Patients with HCV/Hepatitis B virus or HCV/HIV co-infection
- Organ transplant (including pre-, peri- or post-live transplant) patients
- Patients with prior exposure to NS5A inhibitor

The usual dose of daclatasvir is 60 mg once daily with or without meals (European Medicines Agency-approved dosing). **Monotherapy with daclatasvir is not recommended.**

HCV Genotype	Treatment Regimen	Duration
Genotype 1		
Without cirrhosis	Daclatasvir + sofosbuvir	12 weeks[A]
Compensated cirrhosis[C]		24 weeks[B]
Genotype 3		
With compensated cirrhosis and/or treatment-experienced	Daclatasvir + sofosbuvir	24 weeks
Genotype 4 (use is based on extrapolation from genotype 1 studies, per manufacturer)		
Without cirrhosis	Daclatasvir + sofosbuvir	12 weeks[A]
Compensated cirrhosis[C]		24 weeks[B]
	Daclatasvir + peginterferon + ribavirin (weight-based)	24 weeks of daclatasvir in combination w/ 24-48 weeks of peginterferon alfa and ribavirin[D]

A. In patients with prior treatment (inc. NS3/4A inhibitor), consider treatment duration of 24 weeks
B. In treatment-naïve patients with cirrhosis and positive prognostic factors (i.e., IL28B CC genotype, low baseline viral load), can consider treatment duration of 12 weeks
C. In patients with advanced hepatic disease or negative prognostic factors (i.e., prior treatment experience), consider addition of ribavirin to regimen
D. Per SPC:
    a. If the patient has HCV RNA undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks.
    b. If the patient achieves HCV RNA undetectable, but not at both treatment weeks 4 and 12, daclatasvir should be discontinued at 24 weeks and peginterferon alfa and ribavirin continued for a total duration of 48 weeks.
    c. **Refer to Summary of Product Characteristics regarding virologic treatment stopping rules.**

Dosage Adjustments for Concomitant Agents

- Strong CYP3A4 inhibitors: reduce daclatasvir dose to 30mg daily
- Moderate CYP3A4 inducers: increase daclatasvir dose to 90mg daily
    - Note: co-administration with strong CYP3A4 inducers is **NOT** recommended owing to a potential loss in efficacy

Dosing – Adult (cont'd)	**Dosage Adjustments for Management of Adverse Effects** • Dose reduction to manage adverse reactions is not recommended **Missed Doses** • If the missed dose is remembered LESS than 20 hours after the scheduled dose, the dose should be taken as soon as possible • If the missed dose is remembered MORE than 20 hours after the scheduled dose, the dose should be skipped and the next dose should be taken at the appropriate time
Dosing – Pediatric	No data are currently available on pediatric dosing. Pediatric studies to investigate the safety and efficacy of daclatasvir in children and adolescents aged below 18 years are planned.
Dosage Adjustment in Liver Dysfunction	Relative to unimpaired subjects, non-HCV infected subjects with mild to severe hepatic dysfunction had a lower Cmax and AUC of total daclatasvir following a single 30 mg oral dose. However, there was no clinically significant effect on the free drug concentrations of daclatasvir. Child-Pugh class A (mild impairment), B (moderate), or C (severe): No dosage adjustment is necessary. Decompensated cirrhosis: There are no dosage adjustments provided in manufacturer's labeling. Safety and efficacy have not been established in patients with decompensated liver disease.
Dosage Adjustment in Renal Failure / Dialysis	Relative to those with normal renal function, non-HCV infected subjects with renal dysfunction had higher daclatasvir unbound AUC following a single 60 mg oral dose (18% for CrCl 60 mL/min), 39% for CrCl 30 mL/min, and 51% for CrCl 15 ml/min). In non-HCV infected subjects with ESRD requiring hemodialysis, AUC increased 27%, and unbound AUC increased 20% compared with subjects with normal renal function. No dosage adjustment is necessary with any degree of renal impairment Dialysis: There are no dosage adjustments provided in the manufacturer's labeling. However, owing to its large molecular weight (>exceeding 500g/mole) and high plasma binding, dialysis is unlikely to significantly reduce daclatasvir plasma concentrations.
Toxicity	**Adverse Reactions** Common (incidence ≥10%): • Gastrointestinal: nausea; neurologic: headache; other: fatigue Serious: • Hematologic: anemia, Grade 3 or higher (≥1%); lymphocytopenia, Grade 3 or higher (≥1%), neutropenia, Grade 3 or higher (≥1%) • Note: there were no reports of anemia in subjects receiving ribavirin-sparing treatments. The safety profile of daclatasvir in combination with peginterferon alfa and ribavirin was similar to that seen with peginterferon alfa and ribavirin alone, including among patients with cirrhosis **Laboratory Abnormalities** In a study evaluating daclatasvir in combination with sofosbuvir with or without ribavirin, one patient (who was in the ribavirin treatment group) had a Grade 3 hemoglobin decrease. Laboratory abnormalities among patients treated with daclatasvir, peginterferon alfa and ribavirin were otherwise comparable to those among patients who received placebo, peginterferon and ribavirin.

Pregnancy and Lactation	**Pregnancy** Studies of daclatasvir use during human pregnancy have not been conducted and it is unknown if daclatasvir crosses the placenta. However, developmental toxicities (embryotoxic and teratogenic effects) and maternal toxicity were observed in animal studies with daclatasvir. Therefore, daclatasvir is not recommended for use in pregnant women, or in women of childbearing potential not using highly effective contraception. In addition, use of a reliable form of contraception should continue for 5 weeks following completion of daclatasvir treatment. **Lactation** Based on currently available evidence, the potential for toxicity in a newborn/infant cannot be excluded. Reports describing the use of ledipasvir/sofosbuvir during human lactation are unavailable. Data from animal studies, however, indicate that daclatasvir was detectable in the milk of lactating rats at concentrations 1.7-fold and 2-fold the maternal plasma levels. As infant risk from drug exposure cannot be ruled out, breastfeeding is not recommended during therapy with daclatasvir.
Drug Interactions	**Effect of Daclatasvir on Other Drugs' Pharmacokinetics** Daclatasvir is a weak CYP3A4 inducer. In general, dose adjustment of concomitantly administered CYP3A4 substrates is not necessary. Daclatasvir does not inhibit (IC50 >40 µM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6. Daclatasvir is an inhibitor of P-gp, organic anion transporting polypeptide (OATP) 1B1, organic cation transporter (OCT)1 and breast cancer resistance protein (BCRP). Co-administration of daclatasvir with substrates of P-gp, OATP 1B1, OCT1 or BCRP may produce an increase in their systemic exposure, potentially prolonging their therapeutic effect and risk of adverse reactions. Therefore, caution and regular monitoring for toxicity is recommended when daclatasvir is coadministered with the following agents with a narrow therapeutic range: • Dabigatran • Digoxin In vitro studies suggest that daclatasvir also inhibits renal uptake transporters, organic anion transporters (OAT) 1 and 3, but the inhibitory effects are not expected to be clinically relevant. **Effect of Other Drugs on Daclatasvir's Pharmacokinetics** Strong CYP3A4 and P-gp inducers may lead to lower exposures of daclatasvir. Therefore, coadministration with the following agents is contraindicated. • Phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, rifapentine, systemic dexamethasone, and the herbal product St John's wort (Hypericum perforatum) Moderate CYP3A4 and P-gp inducers may decrease the plasma levels and therapeutic effect of daclatasvir. Strong CYP3A4 inhibitors may increase plasma levels of daclatasvir. Therefore, dose adjustment of daclatasvir (i.e., **decrease to 30mg daily)** is recommended when coadministered with the following agents: • HCV protease inhibitors: boceprevir; telaprevir • Antibacterials: clarithromycin; telithromycin • Antifungals: ketoconazole (systemic) P-gp inhibitors are likely to a have limited effect on daclatasvir exposure. No dose adjustment is recommended.

Baseline Assessment	Determination of hepatitis C genotype prior to initiation of therapy
Routine Labs	HCV RNA levels at Week 4, 12 and 24, or at end of treatment
Dosage Forms	30 mg film-coated tablets 60 mg film-coated tablets
Storage	No special storage conditions

References:

Fridell RA, Wang C, Sun JH, et al. Genotypic and phenotypic analysis of variants resistant to hepatitis C virus nonstructural protein 5A replication complex inhibitor BMS-790052 in humans: in vitro and in vivo correlations. Hepatology 2011; 54: 1924-1935.

Nakamoto S, Kanda T, Wu S, et al. Hepatitis C virus NS5A inhibitors and drug resistance mutations. World J Gastroenterol 2014;20:2902-12.

Product Information: Daklinza oral film-coated tablets, daclatasvir oral film-coated tablets. Bristol-Myers Squibb Pharma EEIG (per EMA), Uxbridge, United Kingdom, 2014.

Wang C, Sun JH, O'Boyle DR, et al. Persistence of resistant variants in hepatitis C virus-infected patients treated with the NS5A replication complex inhibitor daclatasvir. Antimicrob Agents Chemother 2013; 57: 2054-2065.