DACLAWIN ™ 30

COMPOSITION

Each film coated Tablet contains:

Daclatasvir Dihydrochloride

Eq.to Daclatasvir 30 mg

Excipients q.s

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

DACLAWIN ™ 60

COMPOSITION

Each film coated Tablet contains:

Daclatasvir Dihydrochloride

Eq.to Daclatasvir 60 mg

Excipients q.s

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

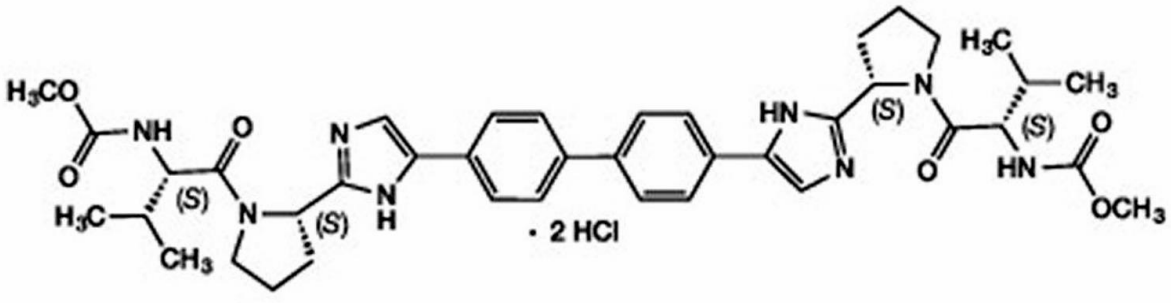
PHARMACEUTICAL FORM

Tablets

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[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). It has a molecular formula of C40H50N8O6●2HCl and a molecular weight of 738.88. The structural formula of daclatasvir dihydrochloride is as follows:



CLINICAL PHARMACOLOGY

Mechanism of action

Daclatasvir is an inhibitor of nonstructural protein 5A (NS5A), a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly.

Pharmacodynamics

Antiviral activity in cell culture

Daclatasvir is an inhibitor of HCV genotypes 1a and 1b replication in cell-based replicon assays with effective concentration (50% reduction, EC50) values of 0.003-0.050 and 0.001-0.009 nM, respectively, depending on the assay method. The daclatasvir EC50 values in the replicon system were 0.003-1.25 nM for genotypes 3a, 4a, 5a and 6a, and 0.034-19 nM for genotype 2a as well as 0.020 nM for infectious genotype 2a (JFH-1) virus.

Daclatasvir showed additive to synergistic interactions with interferon alfa, HCV nonstructural protein 3 (NS3) protease inhibitors, HCV nonstructural protein 5B (NS5B) non-nucleoside inhibitors, and HCV NS5B nucleoside analogues in combination studies using the cell-based HCV replicon system. No antagonism of antiviral activity was observed.

No clinically relevant antiviral activity was observed against a variety of RNA and DNA viruses, including HIV, confirming that daclatasvir, which inhibits a HCV-specific target, is highly elective for HCV.

Resistance in cell culture

HCV genotype 3a replicon variants with reduced susceptibility to daclatasvir were selected in cell culture, and the genotype and phenotype of daclatasvir-resistant variants were characterized. Phenotypic analysis of stable replicon cell lines showed that variant replicons containing A30K, A30T, L31F, S62L, and Y93H substitutions exhibited 56-, 1-, 603-, 1.75-, and 2737-fold reduced susceptibility to daclatasvir, respectively.

Cross-resistance

Based on resistance patterns observed in cell culture replicon studies and HCV genotype 3- 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.

Pharmacokinetics

The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in subjects with chronic HCV. Following multiple oral doses of daclatasvir 60 mg once daily in combination with peginterferon alfa and ribavirin in treatment-naive subjects with genotype 1 chronic HCV, the geometric mean (CV%) daclatasvir Cmax was 1534 (58) ng/ml, AUC0-24h was 14122 (70) ngh/ml, and Cmin was 232 (83) ng/ml.

Absorption

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

Daclatasvir Cmax, AUC, and Cmin 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 vitro and in vivo 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 decreased Daclatasvir Cmax and AUC by 28% and 23%, respectively, compared with administration under fasting conditions. Administration of daclatasvir 60 mg tablet after a light meal resulted in no reduction in daclatasvir exposure.

Distribution

At steady state, protein binding of daclatasvir in HCV-infected subjects was approximately 99% and independent of dose at the dose range studied (1 mg to 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. In vitro studies indicate that daclatasvir is actively and passively transported into hepatocytes. The active transport is mediated by OCT1 and other unidentified uptake transporters, but not by organic anion transporter (OAT) 2, sodium-taurocholate cotransporting polypeptide (NTCP), or OATPs.

Daclatasvir is an inhibitor of P-gp, OATP 1B1 and BCRP. In vitro daclatasvir is an inhibitor of renal uptake transporters, OAT1 and 3, and OCT2, but is not expected to have a clinical effect on the pharmacokinetics of substrates of these transporters.

Biotransformation

In vitro and in vivo studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 being the major CYP isoform responsible for the metabolism. No metabolites circulated at levels more than 5% of the parent concentration. Daclatasvir in vitro did not inhibit (IC50 >40 µM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6.

Elimination

Following single-dose oral administration of 14C–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 drug). These data indicate that the liver is the major clearance organ for daclatasvir in humans. In vitro studies indicate that daclatasvir is actively and passively transported into hepatocytes. The active transport is mediated by OCT1 and other unidentified uptake transporters. 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 [13C, 15N]-daclatasvir intravenous dose, the total clearance was 4.24 l/h.

THERAPEUTIC INDICATIONS

Daclatasvir is indicated for use with Sofosbuvir for the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection.

Limitations of Use:

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 METHOD OF ADMINISTRATION

Treatment with daclatasvir should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

The recommended dosage of daclatasvir is 60 mg, 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.

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 stopping rules that apply to the combination of daclatasvir with sofosbuvir.

Dose recommendation for concomitant medicines

Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)

The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4.

Moderate inducers of CYP3A4

The dose of daclatasvir should be increased to 90 mg once daily when co-administered with moderate inducers of CYP3A4.

Method of administration

Daclatasvir is to be taken orally with or without food. Patients should be instructed to swallow the whole tablet . The tablet should not be chewed or crushed.

Missed doses

Instruct patients that if they miss a dose of daclatasvir, the dose should be taken as soon as possible if remembered within the same day. However, if the missed dose is not remembered within the same day, the dose should be skipped and the next dose taken at the appropriate time. 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

Patients with hypersensitivity to any of the active or inactive ingredients of this formulation

Co-administration with medicinal products that strongly induce cytochrome P450 3A4 (CYP3A4) 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).

WARNINGS AND PRECAUTIONS

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

Severe bradycardia and heart block

Cases of severe bradycardia and heart block have been observed when daclatasvir is used in combination with sofosbuvir and concomitant amiodarone with or without other drugs that lower heart rate. The mechanism is not established.

The concomitant use of amiodarone was limited through the clinical development of sofosbuvir plus direct-acting antivirals (DAAs). Cases are potentially life threatening, therefore amiodarone should only be used in patients on daclatasvir and sofosbuvir when other alternative antiarrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary it is recommended that patients are closely monitored when initiating daclatasvir in combination with sofosbuvir. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on Daclatasvir in combination with sofosbuvir.

All patients receiving daclatasvir and sofosbuvir in combination with amiodarone with or without other drugs that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Genotype-specific activity

Data from study ALLY-3 (AI444218) support a 12-week treatment duration of daclatasvir + sofosbuvir for treatment-naïve and -experienced patients with genotype 3 infection without cirrhosis. Lower rates of SVR were observed for patients with cirrhosis. Data from ongoing compassionate use programmes which included patients with genotype 3 infection and cirrhosis, support the use of daclatasvir + sofosbuvir for 24 weeks in these patients. The relevance of adding ribavirin to that regimen is unclear.

Decompensated liver disease

The safety and efficacy of daclatasvir in the treatment of HCV infection in patients with decompensated liver disease have not been established.

Retreatment with daclatasvir

The efficacy of daclatasvir as part of a retreatment regimen in patients with prior exposure to a NS5A inhibitor has not been established.

Pregnancy and contraception requirements

Daclatasvir should not be used during pregnancy or in women of childbearing potential not using contraception. Use of highly effective contraception should be continued for 5 weeks after completion of daclatasvir therapy.

When daclatasvir is used in combination with ribavirin, the contraindications and warnings for that medicinal product are applicable. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients.

Organ transplant patients

The safety and efficacy of daclatasvir in the treatment of HCV infection in patients who are pre-, peri-, or post-liver transplant or other organ transplant patients have not been established.

HCV/HIV (human immunodeficiency virus) co-infection

The safety and efficacy of daclatasvir in the treatment of HCV infection in patients who are co-infected with HIV have not been established.

HCV/HBV (hepatitis B virus) co-infection

The safety and efficacy of daclatasvir in the treatment of HCV infection in patients who are co-infected with HBV have not been investigated.

ADVERSE EVENTS

The overall safety profile of daclatasvir is based on data from patients with chronic HCV infection who received daclatasvir once daily in combination with sofosbuvir.

Daclatasvir in combination with sofosbuvir

The most frequently reported adverse reactions were fatigue, headache, and nausea. No Grade 3 or 4 adverse reactions were reported. Discontinued of patients because of adverse events reported in some cases and which were considered unrelated to study therapy.

Table 1: Adverse Reactions in Clinical Trials

System Organ Class	Adverse Reactions
Blood and lymphatic system disorders	Anaemia
Metabolism and nutrition disorders	Decreased appetite
Psychiatric disorders	Depression, anxiety and insomnia
Nervous system disorders	Headache, dizziness and migraine
Vascular disorders	Hot flush
Respiratory, thoracic and mediastinal disorders	Cough, dyspnoea, dyspnoea exertional and nasal congestion
Gastrointestinal disorders	Nausea, diarrhoea, abdominal pain upper, constipation, flatulence, gastrooesophageal reflux disease, dry mouth and vomiting
Skin and subcutaneous tissue disorders	Pruritus, dry skin, alopecia and rash
Musculoskeletal and connective tissue disorders	Arthralgia and myalgia
General disorders and administration site conditions	Fatigue and irritability

Laboratory abnormalities

Grade 3 hemoglobin decrease is reported for daclatasvir in combination with sofosbuvir with or without ribavirin and it is related to ribavirin treatment group.

Lipase Elevations: Transient, asymptomatic lipase elevations of greater than 3 times the upper limit of normal (ULN) were observed with the combination of daclatasvir and Sofosbuvir.

Post-marketing Experience

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.

DRUG INTERACTIONS

Contraindications of concomitant use

Daclatasvir is contraindicated in combination with medicinal products that strongly induce CYP3A4 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 interaction with other medicinal products

Daclatasvir is a substrate of CYP3A4, P-gp and organic cation transporter (OCT) 1. Strong or moderate inducers of CYP3A4 and P-gp may decrease the plasma levels and therapeutic effect of daclatasvir. Co-administration with strong inducers of CYP3A4 and P-gp is contraindicated while dose adjustment of daclatasvir is recommended when co-administered with moderate inducers of CYP3A4 and P-gp. Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir. Dose adjustment of daclatasvir is recommended when co-administered with strong inhibitors of CYP3A4. Co-

administration of medicines that inhibit P-gp or OCT1 activity is likely to have a limited effect on daclatasvir exposure.

Daclatasvir is an inhibitor of P-gp, organic anion transporting polypeptide (OATP) 1B1, OCT1 and breast cancer resistance protein (BCRP). Administration of daclatasvir may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B1, OCT1 or BCRP, which could increase or prolong their therapeutic effect and adverse reactions. Caution should be used if the medicinal product has a narrow therapeutic range.

Daclatasvir is a very weak inducer of CYP3A4 and caused a 13% decrease in midazolam exposure. However, as this is a limited effect, dose adjustment of concomitantly administered CYP3A4 substrates is not necessary.

The following table provides the information from drug interaction studies with daclatasvir including clinical recommendations for established or potentially significant drug interactions. Clinically relevant increase in concentration is indicated as "↑", clinically relevant decrease as "↓", no clinically relevant change as "↔". If available, ratios of geometric means are shown, with 90% confidence intervals (CI) in parentheses.

Table 2: Interactions and Dose Recommendations with Other Medicinal Products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTIVIRALS, HCV		
Nucleotide analogue polymerase inhibitor		
Sofosbuvir 400 mg once daily (daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir* AUC: 0.95 (0.82, 1.10) C_{max}: 0.88 (0.78, 0.99) C_{min}: 0.91 (0.71, 1.16) ↔ GS-331007** AUC: 1.0 (0.95, 1.08) C_{max}: 0.8 (0.77, 0.90) C_{min}: 1.4 (1.35, 1.53) *Comparison for daclatasvir was to a historical reference (data from 3 studies of daclatasvir 60 mg once daily with peginterferon alfa and ribavirin). **GS-331007 is the major circulating metabolite of the prodrug sofosbuvir.	No dose adjustment of daclatasvir or sofosbuvir is required
Protease inhibitors		
Boceprevir	Interaction not studied. Expected due to CYP3A4 inhibition by boceprevir: ↑ Daclatasvir	The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with boceprevir or other strong inhibitors of CYP3A4.
Simeprevir 150 mg once daily (daclatasvir 60 mg once daily)	↑ Daclatasvir AUC: 1.96 (1.84, 2.10) C_{max}: 1.50 (1.39, 1.62) C_{min}: 2.68 (2.42, 2.98) ↑ Simeprevir AUC: 1.44 (1.32, 1.56) C_{max}: 1.39 (1.27, 1.52) C_{min}: 1.49 (1.33, 1.67)	No dose adjustment of daclatasvir or simeprevir is required.
Telaprevir 500 mg q12h (daclatasvir 20 mg once daily) **Telaprevir 750 mg q8h** (daclatasvir 20 mg once daily)	↑ Daclatasvir AUC: 2.32 (2.06, 2.62) C_{max}: 1.46 (1.28, 1.66) ↔ Telaprevir AUC: 0.94 (0.84, 1.04) C_{max}: 1.01 (0.89, 1.14) ↑ Daclatasvir AUC: 2.15 (1.87, 2.48) C_{max}: 1.22 (1.04, 1.44) ↔ Telaprevir AUC: 0.99 (0.95, 1.03) C_{max}: 1.02 (0.95, 1.09) CYP3A4 inhibition by telaprevir	The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with telaprevir or other strong inhibitors of CYP3A4.
Other HCV antivirals		
Peginterferon alfa 180 µg once weekly and ribavirin 1000 mg or 1200 mg/day in two divided doses (daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ Peginterferon alfa C_{min}: ↔* ↔ Ribavirin AUC: 0.94 (0.80, 1.11) C_{max}: 0.94 (0.79, 1.11) C_{min}: 0.98 (0.82, 1.17) *PK parameters for daclatasvir when administered with peginterferon alfa and ribavirin in this study were similar to those observed in a study of HCV-infected subjects administered daclatasvir monotherapy for 14 days. PK trough levels for peginterferon alfa in patients who received peginterferon alfa, ribavirin, and daclatasvir were similar to those in patients who received peginterferon alfa, ribavirin, and placebo.	No dose adjustment of daclatasvir, peginterferon alfa, or ribavirin is required.
ANTIVIRALS, HIV or HBV		
Protease inhibitors		
Atazanavir 300 mg/ritonavir 100 mg once daily (daclatasvir 20 mg once daily)	↑ Daclatasvir AUC*: 2.10 (1.95, 2.26) C_{max}*: 1.35 (1.24, 1.47) C_{min}*: 3.65 (3.25, 4.11) CYP3A4 inhibition by ritonavir *results are dose-normalised to 60 mg dose.	The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with atazanavir/ritonavir or other strong inhibitors of CYP3A4.
Darunavir/ritonavir **Lopinavir/ritonavir**	Interaction not studied. Expected due to CYP3A4 inhibition by the protease inhibitor: ↑ Daclatasvir	Due to the lack of data, co-administration of daclatasvir and darunavir or lopinavir is not recommended.
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil fumarate 300 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.10 (1.01, 1.21) C_{max}: 1.06 (0.98, 1.15) C_{min}: 1.15 (1.02, 1.30) ↔ Tenofovir AUC: 1.10 (1.05, 1.15) C_{max}: 0.95 (0.89, 1.02) C_{min}: 1.17 (1.10, 1.24)	No dose adjustment of daclatasvir or tenofovir is required.
Lamivudine **Zidovudine** **Emtricitabine** **Abacavir** **Didanosine** **Stavudine**	Interaction not studied. Expected: ↔ Daclatasvir ↔ NRTI	No dose adjustment of Daclatasvir or the NRTI is required.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (daclatasvir 60 mg once daily/120 mg once daily)	↓ Daclatasvir AUC*: 0.68 (0.60, 0.78) C_{max}*: 0.83 (0.76, 0.92) C_{min}*: 0.41 (0.34, 0.50) Induction of CYP3A4 by efavirenz *results are dose-normalised to 60 mg dose.	The dose of daclatasvir should be increased to 90 mg once daily when co-administered with efavirenz.
Etravirine **Nevirapine**	Interaction not studied. Expected due to CYP3A4 induction by etravirine or nevirapine: ↓ Daclatasvir	Due to the lack of data, co-administration of daclatasvir and etravirine or nevirapine is not recommended.
Rilpivirine	Interaction not studied. Expected: ↔ Daclatasvir ↔ Rilpivirine	No dose adjustment of daclatasvir or rilpivirine is required.
Integrase inhibitors		
Dolutegravir 50 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 0.98 (0.83, 1.15) C_{max}: 1.03 (0.84, 1.25) C_{tau}: 1.06 (0.88, 1.29) ↑ Dolutegravir AUC: 1.33 (1.11, 1.59) C_{max}: 1.29 (1.07, 1.57) C_{tau}: 1.45 (1.25, 1.68) Inhibition of P-gp and BCRP by daclatasvir	No dose adjustment of daclatasvir or dolutegravir is required.
Raltegravir	Interaction not studied. Expected: ↔ Daclatasvir ↔ Raltegravir	No dose adjustment of daclatasvir or raltegravir is required.
Fusion inhibitor		
Enfuvirtide	Interaction not studied. Expected: ↔ Daclatasvir ↔ Enfuvirtide	No dose adjustment of daclatasvir or enfuvirtide is required.
CCR5 receptor antagonist		
Maraviroc	Interaction not studied. Expected: ↔ Daclatasvir ↔ Maraviroc	No dose adjustment of Daclatasvir or maraviroc is required.
Pharmacokinetic enhancer		
Cobicistat-containing regimen	Interaction not studied. Expected due to CYP3A4 inhibition by cobicistat: ↑ Daclatasvir	The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with cobicistat or other strong inhibitors of CYP3A4.
ACID REDUCING AGENTS		
H_2-receptor antagonists		
Famotidine 40 mg single dose (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.82 (0.70, 0.96) C_{max}: 0.56 (0.46, 0.67) C_{tau}: 0.89 (0.75, 1.06) Increase in gastric pH	No dose adjustment of daclatasvir is required.
Proton pump inhibitors		
Omeprazole 40 mg once daily (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.84 (0.73, 0.96) C_{max}: 0.64 (0.54, 0.77) C_{tau}: 0.92 (0.80, 1.05) Increase in gastric pH	No dose adjustment of daclatasvir is required.
ANTIBACTERIALS		
Clarithromycin **Telithromycin**	Interaction not studied. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ Daclatasvir	The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with clarithromycin, telithromycin or other strong inhibitors of CYP3A4.
Erythromycin	Interaction not studied. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ Daclatasvir	Administration of daclatasvir with erythromycin may result in increased concentrations of Daclatasvir. Caution is advised.
Azithromycin **Ciprofloxacin**	Interaction not studied. Expected: ↔ Daclatasvir ↔ Azithromycin or Ciprofloxacin	No dose adjustment of daclatasvir or azithromycin or ciprofloxacin is required.
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied. *Expected due to inhibition of P-gp by daclatasvir:* ↑ Dabigatran etexilate	Safety monitoring is advised when initiating treatment with daclatasvir in patients receiving dabigatran etexilate or other intestinal P-gp substrates that have a narrow therapeutic range
Warfarin	Interaction not studied. Expected: ↔ Daclatasvir ↔ Warfarin	No dose adjustment of daclatasvir or warfarin is required.
ANTICONVULSANTS		
Carbamazepine **Oxcarbazepine** **Phenobarbital** **Phenytoin**	Interaction not studied. *Expected due to CYP3A4 induction by the anticonvulsant:* ↓ Daclatasvir	Co-administration of daclatasvir with carbamazepine, oxcarbazepine, phenobarbital, phenytoin or other strong inducers of CYP3A4 is contraindicated.
ANTIDEPRESSANTS		
Selective serotonin reuptake inhibitors		
Escitalopram 10 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.12 (1.01, 1.26) C_{max}: 1.14 (0.98, 1.32) C_{tau}: 1.23 (1.09, 1.38) ↔Escitalopram AUC: 1.05 (1.02, 1.08) C_{max}: 1.00 (0.92, 1.08) C_{tau}: 1.10 (1.04, 1.16)	No dose adjustment of daclatasvir or escitalopram is required.
ANTIFUNGALS		
Ketoconazole 400 mg once daily (daclatasvir 10 mg single dose)	↑ Daclatasvir AUC: 3.00 (2.62, 3.44) C_{max}: 1.57 (1.31, 1.88) CYP3A4 inhibition by ketoconazole	The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with ketoconazole or other strong inhibitors of CYP3A4.
Itraconazole **Posaconazole** **Voriconazole**	Interaction not studied. *Expected due to CYP3A4 inhibition by the antifungal:* ↑ Daclatasvir	
Fluconazole	Interaction not studied. *Expected due to CYP3A4 inhibition by the antifungal:* ↑ Daclatasvir ↔ Fluconazole	Modest increases in concentrations of daclatasvir are expected, but no dose adjustment of daclatasvir or fluconazole is required.
ANTIMYCOBACTERIALS		
Rifampicin 600 mg once daily (daclatasvir 60 mg single dose)	↓ Daclatasvir AUC: 0.21 (0.19, 0.23) C_{max}: 0.44 (0.40, 0.48) CYP3A4 induction by rifampicin	Co-administration of daclatasvir with rifampicin, rifabutin, rifapentine or other strong inducers of CYP3A4 is contraindicated.
Rifabutin **Rifapentine**	Interaction not studied. *Expected due to CYP3A4 induction by the antimycobacterial:* ↓ Daclatasvir	
CARDIOVASCULAR AGENTS		
Antiarrhythmics		
Digoxin 0.125 mg once daily (daclatasvir 60 mg once daily)	↑ Digoxin AUC: 1.27 (1.20, 1.34) C_{max}: 1.65 (1.52, 1.80) C_{tau}: 1.18 (1.09, 1.28) P-gp inhibition by daclatasvir	Digoxin should be used with caution when co-administered with daclatasvir. The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Amiodarone	Interaction not studied.	Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with daclatasvir in combination with sofosbuvir
Calcium channel blockers		
Diltiazem **Nifedipine** **Amlodipine**	Interaction not studied. *Expected due to CYP3A4 inhibition by the calcium channel blocker:* ↑ Daclatasvir	Administration of daclatasvir with any of these calcium channel blockers may result in increased concentrations of daclatasvir. Caution is advised.
Verapamil	Interaction not studied. *Expected due to CYP3A4 and P-gp inhibition by verapamil:* ↑ Daclatasvir	Administration of daclatasvir with verapamil may result in increased concentrations of daclatasvir. Caution is advised.

CORTICOSTEROIDS		
Systemic dexamethasone	Interaction not studied. *Expected due to CYP3A4 induction by dexamethasone:* ↓ Daclatasvir	Co-administration of daclatasvir with systemic dexamethasone or other strong inducers of CYP3A4 is contraindicated.
HERBAL SUPPLEMENTS		
St. John's wort *(Hypericum perforatum)*	Interaction not studied. *Expected due to CYP3A4 induction by St. John's wort:* ↓ Daclatasvir	Co-administration of daclatasvir with St. John's wort or other strong inducers of CYP3A4 is contraindicated.
HORMONAL CONTRACEPTIVES		
Ethinylestradiol 35 µg once daily for 21 days + norgestimate 0.180/0.215/0.250 mg once daily for 7/7/7 days (daclatasvir 60 mg once daily)	↔ Ethinylestradiol AUC: 1.01 (0.95, 1.07) C_{max}: 1.11 (1.02, 1.20) ↔ Norelgestromin AUC: 1.12 (1.06, 1.17) C_{max}: 1.06 (0.99, 1.14) ↔ Norgestrel AUC: 1.12 (1.02, 1.23) C_{max}: 1.07 (0.99, 1.16)	An oral contraceptive containing ethinylestradiol 35 µg and norgestimate 0.180/0.215/0.250 mg is recommended with daclatasvir. Other oral contraceptives have not been studied.
IMMUNOSUPPRESSANTS		
Cyclosporine 400 mg single dose (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.40 (1.29, 1.53) C_{max}: 1.04 (0.94, 1.15) C_{min}: 1.56 (1.41, 1.71) ↔ Cyclosporine AUC: 1.03 (0.97, 1.09) C_{max}: 0.96 (0.91, 1.02)	No dose adjustment of either medicinal product is required when daclatasvir is co-administered with cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil.
Tacrolimus 5 mg single dose (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.05 (1.03, 1.07) C_{max}: 1.07 (1.02, 1.12) C_{min}: 1.10 (1.03, 1.19) ↔ Tacrolimus AUC: 1.00 (0.88, 1.13) C_{max}: 1.05 (0.90, 1.23)	
Sirolimus **Mycophenolate mofetil**	Interaction not studied. Expected: ↔ Daclatasvir ↔ Immunosuppressant	
LIPID LOWERING AGENTS		
HMG-CoA reductase inhibitors		
Rosuvastatin 10 mg single dose (daclatasvir 60 mg once daily)	↑ Rosuvastatin AUC: 1.58 (1.44, 1.74) C_{max}: 2.04 (1.83, 2.26) Inhibition of OATP 1B1 and BCRP by daclatasvir	Caution should be used when daclatasvir is co-administered with rosuvastatin or other substrates of OATP 1B1 or BCRP.
Atorvastatin **Fluvastatin** **Simvastatin** **Pitavastatin** **Pravastatin**	Interaction not studied. *Expected due to inhibition of OATP 1B1 and/or BCRP by daclatasvir:* ↑ Concentration of statin	
NARCOTIC ANALGESICS		
Buprenorphine/naloxone, 8/2 mg to 24/6 mg once daily individualized dose* (daclatasvir 60 mg once daily) *** Evaluated in opioid-dependent adults on stable buprenorphine/naloxone maintenance therapy.**	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ Buprenorphine AUC: 1.31 (1.15, 1.48) C_{max}: 1.30 (1.03, 1.64) C_{min}: 1.20 (1.15, 1.48) ↔ Norbuprenorphine AUC: 1.62 (1.33, 1.96) C_{max}: 1.65 (1.38, 1.99) C_{min}: 1.46 (1.16, 1.83) *Compared to historical data	No dose adjustment of daclatasvir or buprenorphine is required.
Methadone, 40-120 mg once daily individualized dose* (daclatasvir 60 mg once daily) * Evaluated in opioid-dependent adults on stable methadone maintenance therapy.	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ R-methadone AUC: 1.08 (0.94, 1.24) C_{max}: 1.07 (0.97, 1.18) C_{min}: 1.08 (0.93, 1.26) *Compared to historical data.	No dose adjustment of daclatasvir or methadone is required.
SEDATIVES		
Benzodiazepines		
Midazolam 5 mg single dose (daclatasvir 60 mg once daily)	↔ Midazolam AUC: 0.87 (0.83, 0.92) C_{max}: 0.95 (0.88, 1.04)	No dose adjustment of midazolam, other benzodiazepines or other CYP3A4 substrates is required when co-administered with daclatasvir.
Triazolam **Alprazolam**	Interaction not studied. Expected: ↔ Triazolam ↔ Alprazolam	

USAGE IN SPECIAL POPULATIONS

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 daclatasvir during organogenesis at doses that produced exposures up to 6 and 22 times, respectively, the recommended human dose (RHD) of 60 mg. However, embryo fetal 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. Benefits and risk assessment should be considered when prescribing daclatasvir 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. 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. Sustained virologic response (SVR) rates were comparable among older and younger subjects. 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.

No clinically relevant effects on the pharmacokinetics of either medicinal product are expected when daclatasvir is coadministered with any of the following: PDE-5 inhibitors, medicinal products in the ACE inhibitor class (e.g. enalapril), medicinal products in the angiotensin II receptor antagonist class (e.g. losartan, irbesartan, olmesartan, candesartan, and valsartan), disopyramide, propafenone, flecainide, mexilitine, quinidine or antacids.

Paediatric population

Interaction studies have only been performed in adults.

OVER DOSAGE

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.

INCOMPATIBILITIES

Not applicable

STORAGE CONDITIONS

Store protected from moisture at a temperature not exceeding 30°C.

KEEP OUT OF REACH OF CHILDREN

Keep the container tightly closed

Dispense in original container

SHELF-LIFE

24 months

PACKAGING INFORMATION

Daclawin™ Tablets 30 mg: 28 tablets packed in HDPE container with silica gel and purified cotton closed with child resistant closure.

Daclawin™ Tablets 60 mg: 28 tablets packed in HDPE container with silica gel and purified cotton closed with child resistant closure.

For sale in India only.

Daclawin ™ 30 and Daclawin TM 60 are sold under a license from BMS and MPP.

Manufactured by:

Hetero Labs Limited (Unit II)

Kalyanpur (Village), Chakkan Road,

Baddi (Tehsil), Solan (Distt),

Himachal Pradesh – 173 205.

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