DACTOVI
(Daclatasvir)

30mg & 60mg

Tablets

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with DACLATASVIR. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV directacting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate management for HBV infection as clinically indicated

COMPOSITION

Each film-coated tablet contains:
Daclatasvir as dihydrochloride ….30 mg.
(As per Innovator's Specification)

Each film-coated tablet contains:
Daclatasvir as dihydrochloride…... 60 mg.
(As per Innovator's Specification)

THERAPEUTIC INDICATIONS

Daclatasvir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults

DOSAGE AND ADMINISTRATION

The recommended dose of Daclatasvir is 60 mg once daily, to be taken orally with or without meals. Daclatasvir must be administered in combination with other medicinal products. The Summary of Product Characteristics for the other medicinal products in the regimen should also be consulted before initiation of therapy with Daclatasvir

Table:1 Recommended treatment for Daclatasvir interferon-free combination therapy

Patient population*	**Regimen and duration**
HCV GT 1 or 4	
Patients without cirrhosis	Daclatasvir + sofosbuvir for 12 weeks
Patients with cirrhosis CP A or B	Daclatasvir + sofosbuvir + ribavirin for 12 weeks or Daclatasvir + sofosbuvir (without ribavirin) for 24 weeks
CP C	Daclatasvir + sofosbuvir +/- ribavirin for 24 weeks
HCV GT 3	
Patients without cirrhosis	Daclatasvir + sofosbuvir for 12 weeks
Patients with cirrhosis	Daclatasvir + sofosbuvir +/- ribavirin for 24 weeks
Recurrent HCV infection post-liver transplant (GT 1, 3 or 4)	
Patients without cirrhosis	Daclatasvir + sofosbuvir + ribavirin for 12 weeks
Patients with CP A or B cirrhosis GT 1 or 4 GT 3	Daclatasvir + sofosbuvir + ribavirin for 12 weeks Daclatasvir + sofosbuvir +/- ribavirin for 24 weeks
Patients with CP C cirrhosis	Daclatasvir + sofosbuvir +/- ribavirin for 24 weeks

GT: Genotype; CP: Child Pugh * Includes patients co-infected with human immunodeficiency virus (HIV). For dosing recommendations with HIV antiviral agents see other section.

Daclatasvir + peginterferon alfa + ribavirin

This regimen is an alternative recommended regimen for patients with genotype 4 infection, without cirrhosis or with compensated cirrhosis. Daclatasvir is given for 24 weeks, in combination with 24-48 weeks of peginterferon alfa and ribavirin: - If HCV RNA is undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks. - If undetectable HCV RNA is achieved, 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.

Ribavirin Dosing Guidelines

The dose of ribavirin, when combined with Daclatasvir, is weight-based (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively).
For patients with Child-Pugh A, B, or C cirrhosis or recurrence of HCV infection after liver transplantation, the recommended initial dose of ribavirin is 600 mg daily with food. If the starting dose is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (breakpoint 75 kg). If the starting dose is not well-tolerated, the dose should be reduced as clinically indicated, based on haemoglobin and creatinine clearance measurements

Table :2 Ribavirin dosing guidelines for coadministration with Daclatasvir regimen for patients with cirrhosis or post-transplant

Laboratory Value/Clinical Criteria	**Ribavirin Dosing Guideline**
Haemoglobin >12 g/dL > 10 to ≤12 g/dL > 8.5 to ≤10 g/dL ≤8.5 g/dL	 600 mg daily 400 mg daily 200 mg daily Discontinue ribavirin
Creatinine Clearance >50 mL/min >30 to ≤50 mL/min ≤30 mL/min or haemodialysis	 Follow guidelines above for haemoglobin 200 mg every other day Discontinue ribavirin

Treatment discontinuation in patients with inadequate on-treatment virologic response during treatment with Daclatasvir, peginterferon alfa and ribavirin
It is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR); therefore discontinuation of treatment is recommended in these patients. The HCV RNA thresholds that trigger discontinuation of treatment (i.e. treatment stopping rules) are presented in Table 3

Table 3: Treatment stopping rules in patients receiving Daclatasvir in combination with peginterferon alfa and ribavirin with inadequate on-treatment virologic response

HCV RNA	Action
Treatment week 4: >1000 IU/ml	Discontinue Daclatasvir, peginterferon alfa and ribavirin
Treatment week 12: ≥25 IU/ml	Discontinue Daclatasvir, peginterferon alfa and ribavirin
Treatment week 24: ≥25 IU/ml	Discontinue peginterferon alfa and ribavirin (treatment with Daclatasvir is complete at week 24)

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 coadministered with strong inhibitors of CYP3A4.

Moderate inducers of CYP3A4

The dose of Daclatasvir should be increased to 90 mg once daily when coadministered with moderateinducers of CYP3A4.

Missed doses

Patients should be instructed that, if they miss a dose of Daclatasvir, the dose should be taken as soon as possible if remembered within 20 hours of the scheduled dose time. However, if the missed dose is remembered more than 20 hours after the scheduled dose, the dose should be skipped and the next dose taken at the appropriate time.

Special populations

Elderly

No dose adjustment of Daclatasvir is required for patients aged ≥65 year.

Renal impairment

No dose adjustment of Daclatasvir is required for patients with any degree of renal impairment.
Hepatic impairment
No dose adjustment of Daclatasvir is required for patients with mild (Child-Pugh A, score 5-6), moderate(Child-Pugh B, score 7-9) or severe (Child-Pugh C, score ≥10) hepatic impairment.
Paediatric population
The safety and efficacy of Daclatasvir in children and adolescents aged below 18 years have not yet beenestablished. No data are available.

Method of administration

Daclatasvir is to be taken orally with or without meals. Patients should be instructed to swallow the tablet whole. The film-coated tablet should not be chewed or crushed due the unpleasant taste of the active substance.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Coadministration 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)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Daclatasvir must not be administered as monotherapy. Daclatasvir must be administered in combination with other medicinal products 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 concomitantly 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

Concerning recommended regimens with different HCV genotypes.
Concerning genotype-specific virological and clinical activity.

Data to support the treatment of genotype 2 infection with Daclatasvir and sofosbuvir are limited. 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 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. The clinical data to support the use of Daclatasvir and sofosbuvir in patients infected with HCV genotypes 4 and 6 are limited. There are no clinical data in patients with genotype 5.

Patients with Child-Pugh C liver disease

The safety and efficacy of Daclatasvir in the treatment of HCV infection in patients with Child-Pugh C liver disease have been established in the clinical study ALLY-1 (AI444215, Daclatasvir + sofosbuvir + ribavirin for 12 weeks); however, SVR rates were lower than in patients with Child-Pugh A and B. Therefore, a conservative treatment regimen of Daclatasvir + sofosbuvir +/- ribavirin for 24 weeks is proposed for patients with Child-Pugh C. Ribavirin may be added based on clinical assessment of an individual patient.

HCV/HBV (hepatitis B virus) co-infection

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

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.

Interactions with medicinal products

Coadministration of Daclatasvir can alter the concentration of other medicinal products and other medicinal products may alter the concentration of daclatasvir.

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycemia, after initiating HCV DAA treatment. Glucose levels of diabetic patients initiating DAA therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when DAA therapy is initiated.

Paediatric population

Daclatasvir is not recommended for use in children and adolescents aged below 18 years because the safety and efficacy have not been established in this population.

Important information about some of the ingredients in Daclatasvir

Daclatasvir contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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. Coadministration with strong inducers of CYP3A4 and P-gp is contraindicated while dose adjustment of Daclatasvir is recommended when coadministered with moderate inducers of CYP3A4and P-gp (see Table 4). Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir. Dose adjustment of Daclatasvir is recommended when coadministered with strong inhibitors of CYP3A4 (see Table 4). Coadministration 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 (see Table 4).

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.

Patients treated with vitamin K antagonists

As liver function may change during treatment with Daclatasvir, a close monitoring of International Normalized Ratio (INR) values is recommended.

Tabulated summary of interactions

Table 4 provides 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. The studies presented in Table 4 were conducted in healthy adult subjects unless otherwise noted. The table is not all-inclusive

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
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) Cmax: 0.88 (0.78, 0.99) Cmin: 0.91 (0.71, 1.16) ↔ GS-331007** AUC: 1.0 (0.95, 1.08) Cmax: 0.8 (0.77, 0.90) Cmin: 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 (PIs)		
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 coadministered 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) Cmax: 1.50 (1.39, 1.62) Cmin: 2.68 (2.42, 2.98) ↑ Simeprevir AUC: 1.44 (1.32, 1.56) Cmax: 1.39 (1.27, 1.52) Cmin: 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) Cmax: 1.46 (1.28, 1.66) ↔ Telaprevir AUC: 0.94 (0.84, 1.04) Cmax: 1.01 (0.89, 1.14) ↑ Daclatasvir AUC: 2.15 (1.87, 2.48) Cmax: 1.22 (1.04, 1.44) ↔ Telaprevir AUC: 0.99 (0.95, 1.03) Cmax: 1.02 (0.95, 1.09) CYP3A4 inhibition by telaprevir	The dose of Daclatasvir should be reduced to 30 mg once daily when coadministered 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: ↔* Cmax: ↔* Cmin: ↔* ↔ Peginterferon alfa Cmin: ↔* ↔ Ribavirin AUC: 0.94 (0.80, 1.11) Cmax: 0.94 (0.79, 1.11) Cmin: 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	No dose adjustment of Daclatasvir, peginterferon alfa, or ribavirin is required.

	HCVinfected 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.	
ANTIVIRALS, HIV or HBV		
Protease inhibitors (Pis)		
Atazanavir 300 mg/ritonavir 100 mg once daily (daclatasvir 20 mg once daily)	↑ Daclatasvir AUC*: 2.10 (1.95, 2.26) Cmax*: 1.35 (1.24, 1.47) Cmin*: 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 coadministered with atazanavir/ritonavir, atazanavir/cobicistat or other strong inhibitors of CYP3A4.
Atazanavir/cobicistat	Interaction not studied. Expected due to CYP3A4 inhibition by atazanavir/cobicistat: ↑ Daclatasvir	
Darunavir 800 mg/ritonavir 100 mg once daily (daclatasvir 30 mg once daily).	↔ Daclatasvir AUC: 1.41 (1.32, 1.50) Cmax: 0.77 (0.70, 0.85) ↔ Darunavir AUC: 0.90 (0.73, 1.11) Cmax: 0.97 (0.80, 1.17) Cmin: 0.98 (0.67, 1.44)	No dose adjustment of Daclatasvir 60 mg once daily, darunavir/ritonavir (800/100 mg once daily or 600/100 mg twice daily) or darunavir/cobicistat is required
Darunavir/cobicistat	Interaction not studied. Expected: ↔ Daclatasvir	
Lopinavir 400 mg/ritonavir 100 mg twice daily (daclatasvir 30 mg once daily)	↔ Daclatasvir AUC: 1.15 (1.07, 1.24) Cmax: 0.67 (0.61, 0.74) ↔ Lopinavir* AUC: 1.15 (0.77, 1.72) Cmax: 1.22 (1.06, 1.41) Cmin: 1.54 (0.46, 5.07) * the effect of 60 mg daclatasvir on lopinavir may be higher.	No dose adjustment of Daclatasvir 60 mg once daily or lopinavir/ritonavir is required.
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)		
Tenofovir disoproxil fumarate 300 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.10 (1.01, 1.21) Cmax: 1.06 (0.98, 1.15) Cmin: 1.15 (1.02, 1.30) ↔ Tenofovir AUC: 1.10 (1.05, 1.15) Cmax: 0.95 (0.89, 1.02) Cmin: 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) Cmax*: 0.83 (0.76, 0.92) Cmin*: 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 coadministered with efavirenz.
Etravirine Nevirapine	Interaction not studied. Expected due to CYP3A4 induction by etravirine or nevirapine: ↓ Daclatasvir	Due to the lack of data, coadministration 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) Interaction not studied for this fixed dose combination tablet.	↔ Daclatasvir AUC: 0.98 (0.83, 1.15) Cmax: 1.03 (0.84, 1.25) Cmin: 1.06 (0.88, 1.29) ↑ Dolutegravir AUC: 1.33 (1.11, 1.59) Cmax: 1.29 (1.07, 1.57) Cmin: 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.
Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	Interaction not studied for this fixed dose combination tablet. Expected due to CYP3A4 inhibition by cobicistat: ↑ Daclatasvir	The dose of Daclatasvir should be reduced to 30 mg once daily when coadministered with cobicistat or other strong inhibitors of CYP3A4.
CCR5 receptor antagonist		
Maraviroc	Interaction not studied. Expected: ↔ Daclatasvir ↔ Maraviroc	No dose adjustment of Daclatasvir or maraviroc is required.
ACID REDUCING AGENTS		
H2-receptor antagonists		
Famotidine 40 mg single dose (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.82 (0.70, 0.96) Cmax: 0.56 (0.46, 0.67) Cmin: 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 AUC: 0.84 (0.73, 0.96) Cmax: 0.64 (0.54, 0.77) Cmin: 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 coadministered 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 or other vitamin K antagonists	Interaction not studied. Expected: ↔ Daclatasvir ↔ Warfarin	No dose adjustment of Daclatasvir or warfarin is required. Close monitoring of INR values is recommended with all vitamin K antagonists. This is due to liver function that may change during treatment with Daclatasvir
ANTICONVULSANTS		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied. Expected due to CYP3A4 induction by the anticonvulsant: ↓ Daclatasvir	Coadministration 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) Cmax: 1.14 (0.98, 1.32) Cmin: 1.23 (1.09, 1.38) ↔Escitalopram AUC: 1.05 (1.02, 1.08) Cmax: 1.00 (0.92, 1.08) Cmin: 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) Cmax: 1.57 (1.31, 1.88) CYP3A4 inhibition by ketoconazole	The dose of Daclatasvir should be reduced to 30 mg once daily

		when coadministered with
Itraconazole Posaconazole Voriconazole	Interaction not studied. Expected due to CYP3A4 inhibition by the antifungal: ↑ Daclatasvir	ketoconazole or other strong inhibitors of CYP3A4.
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) Cmax: 0.44 (0.40, 0.48) CYP3A4 induction by rifampicin	Coadministration 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) Cmax: 1.65 (1.52, 1.80) Cmin: 1.18 (1.09, 1.28) P-gp inhibition by daclatasvir	Digoxin should be used with caution when coadministered 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	Coadministration 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:	Coadministration of Daclatasvir with St. John's wort or other

	↓ Daclatasvir	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) Cmax: 1.11 (1.02, 1.20) ↔ Norelgestromin AUC: 1.12 (1.06, 1.17) Cmax: 1.06 (0.99, 1.14) ↔ Norgestrel AUC: 1.12 (1.02, 1.23) Cmax: 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) Cmax: 1.04 (0.94, 1.15) Cmin: 1.56 (1.41, 1.71) ↔ Cyclosporine AUC: 1.03 (0.97, 1.09) Cmax: 0.96 (0.91, 1.02)	No dose adjustment of either medicinal product is required when Daclatasvir is coadministered 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) Cmax: 1.07 (1.02, 1.12) Cmin: 1.10 (1.03, 1.19) ↔ Tacrolimus AUC: 1.00 (0.88, 1.13) Cmax: 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) Cmax: 2.04 (1.83, 2.26) Inhibition of OATP 1B1 and BCRP by daclatasvir	Caution should be used when Daclatasvir is coadministered 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: Medicinal ↑ 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: ↔* Cmax: ↔* Cmin: ↔* ↑ Buprenorphine AUC: 1.37 (1.24, 1.52) Cmax: 1.30 (1.03, 1.64) Cmin: 1.17 (1.03, 1.32) ↑ Norbuprenorphine AUC: 1.62 (1.30, 2.02) Cmax: 1.65 (1.38, 1.99) Cmin: 1.46 (1.12, 1.89) *Compared to historical data.	No dose adjustment of Daclatasvir or buprenorphine may be required, but it is recommended that patients should be monitored for signs of opiate toxicity.
Methadone, 40-120 mg once daily individualized dose* (daclatasvir 60 mg once daily) * Evaluated in opioid-dependent	↔ Daclatasvir AUC: ↔* Cmax: ↔* Cmin: ↔* ↔ R-methadone AUC: 1.08 (0.94, 1.24)	No dose adjustment of Daclatasvir or methadone is required.

adults on stable methadone maintenance therapy.	Cmax: 1.07 (0.97, 1.18) Cmin: 1.08 (0.93, 1.26) *Compared to historical data.	
SEDATIVES		
Benzodiazepines		
Midazolam 5 mg single dose (daclatasvir 60 mg once daily)	↔ Midazolam AUC: 0.87 (0.83, 0.92) Cmax: 0.95 (0.88, 1.04)	No dose adjustment of midazolam, other benzodiazepines or other CYP3A4 substrates is required when coadministered with Daclatasvir.
Triazolam Alprazolam	Interaction not studied. Expected: ↔ Triazolam ↔ Alprazolam	

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, valsartan), disopyramide, propafenone, flecainide, mexilitine, quinidine or antacids.

Paediatric population

Medicinal Interaction studies have only been performed in adults.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no data from the use of daclatasvir in pregnant women. Studies of daclatasvir in animals have shown embryotoxic and teratogenic effects. The potential risk for humans is unknown.

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. Since Daclatasvir is used in combination with other agents, the contraindications and warnings for those medicinal products are applicable.

Breast-feeding

It is not known whether daclatasvir is excreted in human milk. Available pharmacokinetic and toxicological data in animals have shown excretion of daclatasvir and metabolites in milk. A risk to the newborn/infant cannot be excluded. Mothers should be instructed not to breastfeed if they are taking Daclatasvir.

Fertility

No human data on the effect of daclatasvir on fertility are available. In rats, no effect on mating or fertility was seen.

Dizziness has been reported during treatment with Daclatasvir in combination with sofosbuvir, anddizziness, disturbance in attention, blurred vision and reduced visual acuity have been reported during treatment with Daclatasvir in combination with peginterferon alfa and ribavirin

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness has been reported during treatment with Daclatasvir in combination with sofosbuvir, and dizziness, disturbance in attention, blurred vision and reduced visual acuity have been reported during treatment with Daclatasvir in combination with peginterferon alfa and ribavirin

ADVERSE DRUG REACTIONS

Summary of the safety profile

The overall safety profile of daclatasvir is based on data from 2215 patients with chronic HCV infection who received Daclatasvir once daily either in combination with sofosbuvir with or without ribavirin (n=679, pooled data) or in combination with peginterferon alfa and ribavirin (n=1536, pooled data) from a total of 14 clinical studies.

Daclatasvir in combination with sofosbuvir The most frequently reported adverse reactions were fatigue, headache, and nausea. Grade 3 adverse reactions were reported in less than 1% of patients, and no patients had a Grade 4 adverse reaction. Four patients discontinued the Daclatasvir regimen for adverse events, only one of which was considered related to study therapy.

Daclatasvir in combination with peginterferon alfa and ribavirin The most frequently reported adverse reactions were fatigue, headache, pruritus, anaemia, influenza like illness, nausea, insomnia, neutropenia, asthenia, rash, decreased appetite, dry skin, alopecia, pyrexia, myalgia, irritability, cough, diarrhoea, dyspnoea and arthralgia. The most frequently reported adverse reactions of at least Grade 3 severity (frequency of 1% or greater) were neutropenia, anaemia, lymphopenia and thrombocytopenia. 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.

Tabulated list of adverse reactions

Adverse reactions are listed in Table 5 by regimen, system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Adverse Reactions	
Frequency	Daclatasvir +sofosbuvir + Ribavirin N=203	Daclatasvir +sofosbuvir N=476
Blood and lymphatic system disorders		
very common	anaemia	
Metabolism and nutrition disorders		
common	decreased appetite	
Psychiatric disorders		
common	insomnia	irritability insomnia

Nervous system disorders		
very common	headache	headache
common	dizziness, migraine	dizziness, migraine
Vascular disorders		
common	hot flush	
Respiratory, thoracic and mediastinal disorders		
common	dyspnoea, dyspnoea exertional, cough, nasal congestion	
Gastrointestinal disorders		
very common	nausea	
common	diarrhoea, vomiting, abdominal pain, gastrooesophageal reflux disease, constipation, dry mouth, flatulence	nausea, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders		
common	rash, alopecia, pruritus, dry skin	
Musculoskeletal and connective tissue disorders		
common	arthralgia, myalgia	arthralgia, myalgia
General disorders and administration site conditions		
very common	fatigue	fatigue

Laboratory abnormalities

In clinical studies of Daclatasvir in combination with sofosbuvir with or without ribavirin, 2% of patients had Grade 3 haemoglobin decreases; all of these patients received Daclatasvir + sofosbuvir + ribavirin. Grade 3/4 increases in total bilirubin were observed in 5% of patients (all in patients with HIV coinfection who were receiving concomitant atazanavir, with Child-Pugh A, B, or C cirrhosis, or who were post-liver transplant).

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when Daclatasvir is used in combination with sofosbuvir and concomitant amiodarone and/or other drugs that lower heart rate.

Paediatric population

The safety and efficacy of Daclatasvir in children and adolescents aged <18 years have not yet been established. No data are available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com.

OVERDOSE

There is limited experience of accidental overdose of daclatasvir in clinical studies. In phase 1 clinical studies, healthy subjects who received up to 100 mg once daily for up to 14 days or single doses up to 200 mg had no unexpected adverse reactions. 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%) and has a molecular weight >500, dialysis is unlikely to significantly reduce plasma concentrations of daclatasvir.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: J05AP07

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 inhibits both viral RNA replication and virion assembly.

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) PIs, 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 selective for HCV.

Resistance in cell culture

Substitutions conferring daclatasvir resistance in genotypes 1-4 were observed in the N-terminal 100 amino acid region of NS5A in a cell-based replicon system. L31V and Y93H were frequently observed resistance substitutions in genotype 1b, while M28T, L31V/M, Q30E/H/R, and Y93C/H/N were frequently observed resistance substitutions in genotype 1a. These substitutions conferred low level resistance (EC50 <1 nM) for genotype 1b, and higher levels of resistance for genotype 1a (EC50 up to 350 nM). The most resistant variants with single amino acid substitution in genotype 2a and genotype 3a were F28S (EC50 >300 nM) and Y93H (EC50 >1,000 nM), respectively. In genotype 4, amino acid substitutions at 30 and 93 (EC50 < 16 nM) were frequently selected.

Cross-resistance

HCV replicons expressing daclatasvir-associated resistance substitutions remained fully sensitive to interferon alfa and other anti-HCV agents with different mechanisms of action, such as NS3 protease and NS5B polymerase (nucleoside and non-nucleoside) inhibitors

Pharmacokinetic properties

The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in patients with chronic HCV. Following multiple oral doses of daclatasvir 60 mg once daily in combination with peginterferon alfa and ribavirin in treatment-naïve patients with genotype 1 chronic HCV, the geometric mean (CV%) daclatasvir Cmax was 1534 (58) ng/ml, AUC0-24h was 14122 (70) ng•h/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 subjects and HCV-infected patients. 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 patients was approximately 99% and independent of dose at the dose range studied (1 mg to 100 mg). In patients 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 co-transporting 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 patients, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours. In patients who received daclatasvir 60 mg tablet orally followed by 100 µg [13C,15N]-daclatasvir intravenous dose, the total clearance was 4.24 l/h.

Special populations

Renal impairment

The pharmacokinetics of daclatasvir following a single 60 mg oral dose were studied in non-HCV infected subjects with renal impairment. Daclatasvir unbound AUC was estimated to be 18%, 39% and 51% higher for subjects with creatinine clearance (CLcr) values of 60, 30 and 15 ml/min, respectively, relative to subjects with normal renal function. Subjects with end-stage renal disease requiring hemodialysis had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to subjects with normal renal function.

Hepatic impairment

The pharmacokinetics of daclatasvir following a single 30 mg oral dose were studied in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with unimpaired subjects. The Cmax and AUC of total daclatasvir (free and protein-bound drug) were lower in subjects with hepatic impairment; however, hepatic impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir.

Elderly

Population pharmacokinetic analysis of data from clinical studies indicated that age had no apparent effect on the pharmacokinetics of daclatasvir.

Paediatric population

The pharmacokinetics of daclatasvir in pediatric patients have not been evaluated.

Gender

Population pharmacokinetic analysis identified gender as a statistically significant covariate on daclatasvir apparent oral clearance (CL/F) with female subjects having slightly lower CL/F, but the magnitude of the effect on daclatasvir exposure is not clinically important.

Race

Population pharmacokinetic analysis of data from clinical studies identified race (categories “other” [patients who are not white, black or Asian] and “black”) as a statistically significant covariate on daclatasvir apparent oral clearance (CL/F) and apparent volume of distribution (Vc/F) resulting in slightly higher exposures compared to white patients, but the magnitude of the effect on daclatasvir exposure is not clinically important.

Summary of clinical studies

In the majority of clinical studies of daclatasvir in combination with sofosbuvir or with peginterferon alfa and ribavirin, plasma HCV RNA values were measured using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System, with a lower limit of quantification (LLOQ) of 25 IU/ ml. HCV RNA values in the ALLY-3C (AI444379) study were measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test (version 2.0), with an LLOQ of 15 IU/mL.

SVR was the primary endpoint to determine the HCV cure rate, which was defined as HCV RNA less than LLOQ at 12 weeks after the end of treatment (SVR12) for studies AI444040, ALLY-1 (AI444215), ALLY-2 (AI444216), ALLY-3 (AI444218), ALLY-3C (AI444379), AI444042 and AI444043 and as HCV RNA undetectable at 24 weeks after the end of treatment (SVR24) for study AI444010.

Daclatasvir in combination with sofosbuvir

The efficacy and safety of daclatasvir 60 mg once daily in combination with sofosbuvir 400 mg once daily in the treatment of patients with chronic HCV

infection were evaluated in five open-label studies (AI444040, ALLY-1, ALLY-2, ALLY-3, and ALLY-3C).

In study AI444040, 211 adults with HCV genotype 1, 2, or 3 infection and without cirrhosis received daclatasvir and sofosbuvir, with or without ribavirin. Among the 167 patients with HCV genotype 1 infection, 126 were treatment-naïve and 41 had failed prior therapy with a PI regimen (boceprevir or telaprevir). All 44 patients with HCV genotype 2 (n=26) or 3 (n=18) infection were treatment-naïve. Treatment duration was 12 weeks for 82 treatment-naïve HCV genotype 1 patients, and 24 weeks for all other patients in the study. The 211 patients had a median age of 54 years (range: 20 to 70); 83% were white; 12% were black/African-American; 2% were Asian; 20% were Hispanic or Latino. The mean score on the FibroTest (a validated non-invasive diagnostic assay) was 0.460 (range: 0.03 to 0.89). Conversion of the FibroTest score to the corresponding METAVIR score suggests that 35% of all patients (49% of patients with prior PI failure, 30% of patients with genotype 2 or 3) had ≥F3 liver fibrosis. Most patients (71%, including 98% of prior PI failures) had IL-28B rs12979860 non-CC genotypes.

SVR12 was achieved by 99% patients with HCV genotype 1, 96% of those with genotype 2 and 89% of those with genotype 3 (see Tables 6 and 7). Response was rapid (viral load at Week 4 showed that more than 97% of patients responded to therapy), and was not influenced by HCV subtype (1a/1b), IL28B genotype, or use of ribavirin. Among treatment-naïve patients with HCV RNA results at both follow-up Weeks 12 and 24, concordance between SVR12 and SVR24 was 99.5% independent of treatment duration.

Advanced cirrhosis and post-liver transplant (ALLY-1)

In study ALLY-1, the regimen of daclatasvir, sofosbuvir, and ribavirin administered for 12 weeks was evaluated in 113 adults with chronic hepatitis C and Child-Pugh A, B or C cirrhosis (n=60) or HCV recurrence after liver transplantation (n=53). Patients with HCV genotype 1, 2, 3, 4, 5 or 6 infection were eligible to enroll. Patients received daclatasvir 60 mg once daily, sofosbuvir 400 mg once daily, and ribavirin (600 mg starting dose) for 12 weeks and were monitored for 24 weeks post treatment.

SVR12 was achieved by 83% (50/60) of patients in the cirrhosis cohort, with a marked difference between patients with Child-Pugh A or B (92-94%) as compared to those with Child-Pugh C and 94% of patients in the post-liver transplant cohort (Table 9). SVR rates were comparable regardless of age, race, gender, IL28B allele status, or baseline HCV RNA level. In the cirrhosis cohort, 4 patients with hepatocellular carcinoma underwent liver transplantation after 1–71 days of treatment; 3 of the 4 patients received 12 weeks of post-liver transplant treatment extension and 1 patient, treated for 23 days before transplantation, did not receive treatment extension. All 4 patients achieved SVR12.

HCV/HIV co-infection (ALLY-2)

In study ALLY-2, the combination of daclatasvir and sofosbuvir administered for 12 weeks was evaluated in 153 adults with chronic hepatitis C and HIV co-infection; 101 patients were HCV treatment-naïve and 52 patients had failed prior HCV therapy. Patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection were eligible to enroll, including patients with compenstated cirrhosis (ChildPugh A). The dose of daclatasvir was adjusted for concomitant antiretroviral use

Overall, SVR12 was achieved by 97% (149/153) of patients administered daclatasvir and sofosbuvir for 12 weeks in ALLY-2. SVR rates were >94% across combination antiretroviral therapy (cART) regimens, including boosted-PI-, NNRTI-, and integrase inhibitor (INSTI)-based therapies. 24 SVR rates were comparable regardless of HIV regimen, age, race, gender, IL28B allele status, or baseline HCV RNA level. Outcomes by prior treatment experience are presented in Table 11. A third treatment group in study ALLY-2 included 50 HCV treatment-naïve HIV co-infected patients who received daclatasvir and sofosbuvir for 8 weeks. Demographic and baseline characteristics of these 50 patients were generally comparable to those for patients who received 12 weeks of study treatment. The SVR rate for patients treated for 8 weeks was lower with this treatment duration.

HCV Genotype 3 (ALLY-3)

In study ALLY-3, the combination of daclatasvir and sofosbuvir administered for 12 weeks was evaluated in 152 adults infected with HCV genotype 3; 101 patients were treatment-naïve and 51 patients had failed prior antiviral therapy. Median age was 55 years (range: 24 to 73); 90% of patients were white; 4% were black/African-American; 5% were Asian; 16% were Hispanic or Latino. The median viral load was 6.42 log10 IU/ml, and 21% of patients had compensated cirrhosis. Most patients (61%) had IL-28B rs12979860 non-CC genotypes. SVR12 was achieved in 90% of treatment-naïve patients and 86% of treatment-experienced patients. Response was rapid (viral load at Week 4 showed that more than 95% of patients responded to therapy) and was not influenced by IL28B genotype. SVR12 rates were lower among patients with cirrhosis

HCV Genotype 3 with compensated cirrhosis (ALLY-3C)

In study ALLY-3C, the combination of daclatasvir, sofosbuvir and ribavirin administered for 24 weeks was evaluated in 78 adults infected with HCV genotype 3 with compensated cirrhosis; the majority of patients were male (57 [73.1%]); median age was 55 years (range 33 to 70); 88.5% were white; 9.0% were Asian; and 2.6% were American Indian or Alaska native; 54 (69.2%) patients were treatment-naïve and 24 (30.8%) patients were treatment-experienced. The overall median HCV RNA was 6.38 log10 IU/mL; the majority of patients (59%) had IL-28B rs12979860 non-CC genotypes. Seventy-seven (77 [98.7%]) of treated patients in this study were infected with HCV GT-3a, and 1 patient (1.3%) was infected with HCV GT-3b. The SVR12 rates were achieved by 88.5% of patients, including 92.6% of treatment-naïve and 79.2% of treatment-experienced patients. SVR12 rates were consistently high across most subgroups including gender, age, race, baseline HCV RNA, and IL28B genotype. All 3 HCV/HIV coinfected patients achieved SVR12.

Compassionate Use

Patients with HCV infection (across genotypes) at high risk of decompensation or death within 12 months if left untreated were treated under compassionate use programmes. Patients with genotype 3 infection were treated with daclatasvir + sofosbuvir +/- ribavirin for 12 or 24 weeks, where the longer treatment duration was associated with a lower risk for relapse (around 5%) in a preliminary analysis. The relevance of including ribavirin as part of the 24-week regimen is unclear. In one cohort the majority of patients were treated with daclatasvir + sofosbuvir + ribavirin for 12 weeks. The relapse rate was around 15%, and similar for patients with Child-Pugh A, B and C. The programmes do not allow for a direct comparison of efficacy between the 12- and 24-week regimens.

Daclatasvir in combination with peginterferon alfa and ribavirin

AI444042 and AI444010 were randomised, double-blind studies that evaluated the efficacy and safety of daclatasvir in combination with peginterferon alfa and ribavirin (pegIFN/RBV) in the treatment of chronic HCV infection in treatment-naïve adults with compensated liver disease (including cirrhosis).

AI444042 enrolled patients with HCV genotype 4 infection and AI444010 enrolled patients with either genotype 1 or 4. AI444043 was an open-label, single-arm study of daclatasvir with pegIFN/RBV in treatment-naïve adults with chronic HCV genotype 1 infection who were co-infected with HIV.

AI444042: Patients received daclatasvir 60 mg once daily (n=82) or placebo (n=42) plus pegIFN/RBV for 24 weeks. Patients in the daclatasvir treatment group who did not have HCV RNA undetectable at both Weeks 4 and 12 and all placebo-treated patients continued pegIFN/RBV for another 24 weeks. Treated patients had a median age of 49 years (range: 20 to 71); 77% of patients were white; 19% were black/African-American; 4% were Hispanic or Latino. Ten percent of patients had compensated cirrhosis, and 75% of patients had IL-28B rs12979860 non-CC genotypes. Treatment outcomes in study AI444042 are presented in Table 14. Response was rapid (at Week 4 91% of daclatasvir-treated patients had HCV RNA <LLOQ). SVR12 rates were higher for patients with the IL-28B CC genotype than for those with non-CC genotypes and for patients with baseline HCV RNA less than 800,000 IU/ml but consistently higher in the daclatasvir-treated patients than for placebo-treated patients in all subgroups.

AI444010: Patients received daclatasvir 60 mg once daily (n=158) or placebo (n=78) plus pegIFN/RBV through Week 12. Patients assigned to daclatasvir 60 mg once-daily treatment group who had HCV RNA <LLOQ at Week 4 and undetectable at Week 10 were then randomised to receive another 12 weeks of daclatasvir 60 mg + pegIFN/RBV or placebo + pegIFN/RBV for a total treatment duration of 24 weeks. Patients originally assigned to placebo and those in the daclatasvir group who did not achieve

HCV RNA <LLOQ at Week 4 and undetectable at Week 10 continued pegIFN/RBV to complete 48 weeks of treatment. Treated patients had a median age of 50 years (range: 18 to 67); 79% of patients were white; 13% were black/African-American; 1% were Asian; 9% were Hispanic or Latino. Seven percent of patients had compensated cirrhosis; 92% had HCV genotype 1 (72% 1a and 20% 1b) and 8% had HCV genotype 4; 65% of patients had IL-28B rs12979860 non-CC genotypes.

For HCV genotype 1, SVR12 rates were 64% (54% for 1a; 84% for 1b) for patients treated with daclatasvir + pegIFN/RBV and 36% for patients treated with placebo + pegIFN/RBV. For daclatasvirtreated patients with HCV RNA results at both follow-up Weeks 12 and 24, concordance of SVR12 and SVR24 was 97% for HCV genotype 1 and 100% for HCV genotype 4

AI444043: 301 treatment-naïve patients with HCV genotype 1 infection and HIV co-infection (10% with compensated cirrhosis) were treated with daclatasvir in combination with pegIFN/RBV. The dose of daclatasvir was 60 mg once daily, with dose adjustments for concomitant antiretroviral use. Patients achieving virologic response [HCV RNA undetectable at weeks 4 and 12] completed therapy after 24 weeks while those who did not achieve virologic response received an additional 24 weeks of treatment with pegIFN/RBV, to complete a total of 48 weeks of study therapy. SVR12 was achieved by 74% of patients in this study (genotype 1a: 70%, genotype 1b: 79%).

Long term efficacy data

Data are available from a completed follow-up study to assess durability of response for approximately 3 years after treatment with daclatasvir. Among 258 patients who achieved SVR12 with daclatasvir and sofosbuvir (± ribavirin) with a median duration of post-SVR12 follow-up of 38 months, no relapses occurred (with relapses defined as confirmed or last available HCV RNA ≥ LLOQ). Among 302 patients who achieved SVR12 with daclatasvir + pegIFN/RBV with a median duration of post-SVR12 follow-up of 44 months, 2% (n=6) of patients relapsed.

Resistance in clinical studies

Frequency of baseline NS5A resistance-associated variants (RAVs) Baseline NS5A RAVs were frequently observed in clinical studies of daclatasvir. In 9 phase 2/3 studies with daclatasvir in combination with peginterferon alfa + ribavirin or in combination with sofosbuvir +/- ribavirin, the following frequencies of such RAVs were seen at baseline: 7% in genotype 1a infection (M28T, Q30, L31, and/or Y93), 11% in genotype 1b infection (L31 and/or Y93H), 51% in genotype 2 infection (L31M), 8% in genotype 3 infection (Y93H) and 64% in genotype 4 infection (L28 and/or L30)

Daclatasvir in combination with sofosbuvir

Impact of baseline

NS5A RAVs on cure rates The baseline NS5A RAVs described above had no major impact on cure rates in patients treated with sofosbuvir + daclatasvir +/- ribavirin, with the exception of the Y93H RAV in genotype 3 infection (seen in 16/192 [8%] of patients). The SVR12 rate in genotype-3 infected patients with this RAV is reduced (in practice as relapse after end of treatment response), especially in patients with cirrhosis. The overall cure rate for genotype-3 infected patients who were treated for 12 weeks with sofosbuvir + daclatasvir (without ribavirin) in the presence and absence of the Y93H RAV was 7/13 (54%) and 134/145 (92%), respectively. There was no Y93H RAV present at baseline for genotype-3 infected patients treated for 12-weeks with sofosbuvir + daclatasvir + ribavirin, and thus SVR outcomes cannot be assessed.

Emerging resistance

In a pooled analysis of 629 patients who received daclatasvir and sofosbuvir with or without ribavirin in Phase 2 and 3 studies for 12 or 24 weeks, 34 patients qualified for resistance analysis due to virologic failure or early study discontinuation and having HCV RNA greater than 1,000 IU/ml.

sofosbuvir resistance-associated substitution S282T emerged in only 1 non-SVR12 patient infected with genotype 3. Emergent daclatasvir resistance-associated substitutions have been shown to persist for 3 years posttreatment and beyond for patients treated with daclatasvir-based regimens.

Daclatasvir in combination with peginterferon alfa and ribavirin

Baseline NS5A RAVs (at M28T, Q30, L31, and Y93 for genotype 1a; at L31 and Y93 for genotype 1b) increase the risk for non-response in treatment-naive patients infected with genotype 1aand genotype 1b infection. The impact of baseline NS5A RAVs on cure rates of genotype 4 infection is not apparent. In case of non-response to therapy with daclatasvir + peginterferon alfa + ribavirin, NS5A RAVs generally emerged at failure (139/153 genotype 1a and 49/57 genotype 1b). The most frequently detected NS5A RAVs included Q30E or Q30R in combination with L31M. The majority of genotype 1a failures had emergent NS5A variants detected at Q30 (127/139 [91%]), and the majority of genotype 1b failures had emergent NS5A variants detected at L31 (37/49 [76%]) and/or Y93H (34/49 [69%]). In limited numbers of genotype 4-infected patients with non-response, substitutions L28M and L30H/S were detected at failure.

PRECLINICAL SAFETY DATA

Toxicology

In repeat-dose toxicology studies in animals, hepatic effects (Kupffer-cell hypertrophy/ hyperplasia, mononuclear cell infiltrates and bile duct hyperplasia) and adrenal gland effects (changes in cytoplasmic vacuolation and adrenal cortical hypertrophy/hyperplasia) were observed at exposures similar or slightly higher than the clinical AUC exposure. In dogs, bone marrow hypocellularity with correlating clinical pathology changes were observed at exposures 9-fold the clinical AUC exposure. None of these effects have been observed in humans.

Carcinogenesis and mutagenesis

Daclatasvir was not carcinogenic in mice or in rats at exposures 8-fold or 4-fold, respectively, the clinical AUC exposure. No evidence of mutagenic or clastogenic activity was observed in in vitro mutagenesis (Ames) tests, mammalian mutation assays in Chinese hamster ovary cells, or in an in vivo oral micronucleus study in rats.

Fertility

Daclatasvir had no effects on fertility in female rats at any dose tested. The highest AUC value in unaffected females was 18-fold the clinical AUC exposure. In male rats, effects on reproductive endpoints were limited to reduced prostate/seminal vesicle weights, and minimally increased dysmorphic sperm at 200 mg/kg/day; however, neither finding adversely affected fertility or the number of viable conceptuses sired. The AUC associated with this dose in males is 19-fold the clinical AUC exposure.

Embryo-foetal development

Daclatasvir is embryotoxic and teratogenic in rats and rabbits at exposures at or above 4-fold (rat) and 16-fold (rabbit) the clinical AUC exposure. Developmental toxicity consisted of increased embryofetal lethality, reduced foetal body weights and increased incidence of foetal malformations and variations. In rats, malformations mainly affected the brain, skull, eyes, ears, nose, lip, palate or limbs and in rabbits, the ribs and cardiovascular area. Maternal toxicity including mortality, abortions, adverse clinical signs, decreases in body weight and food consumption was noted in both species at exposures 25-fold (rat) and 72-fold (rabbit) the clinical AUC exposure. In a study of pre- and postnatal development in rats, there was neither maternal nor developmental toxicity at doses up to 50 mg/kg/day, associated with AUC values 2-fold the clinical AUC exposure. At the highest dose (100 mg/kg/day), maternal toxicity included mortality and dystocia; developmental toxicity included slight reductions in offspring viability in the peri- and neonatal periods; and reductions in birth weight that persisted into adulthood. The AUC value associated with this dose is 4-fold the clinical AUC exposure.

Excretion into milk

Daclatasvir was excreted into the milk of lactating rats with concentrations 1.7- to 2-fold maternal plasma levels.

PRESENTATION

Dactovi 30mg: 28's tablets are available in alu alu bliser packaging.

Dactovi 60mg: 28's tablets are available in alu alu bliser packaging**.**

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.

- Protect from sunlight, moisture and heat.

- Store below 30°C.

- Keep all medicines out of sight & reach of children.

REGISTRATION NUMBER

Dactovi 30mg: 084779

Dactovi 60mg: 084780

Manufacturing License Number: 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

SEARLE

Manufactured by:

The Searle Company Limited.

F-319, S.I.T.E., Karachi-Pakistan.

Marketed by:

Searle Biosciences (Pvt.) Limited,

First Floor, N.I.C.L. Building, Abbasi Shaheed Road, Karachi - Pakistan.

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