SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Daclavirdin (Daclatasvir 60mg Film Coated Tablet.)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION.
Each film coated tablet contains 65.921mg Daclatasvir Dihydrochloride Eq. to 60mg Daclatasvir.

Excipients with known effect:
Each tablet contains 113 mg of lactose anhydrous.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film coated tablet.
Pale green to green round biconvex film coated tablet plain from both sides

4- Clinical Particulars:
4.1 Therapeutic indications
Chronic hepatitis C virus:
It is indicated with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

4.2 Posology and Method of administration:
Posology
Paediatric population

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

Method of administration

Daclavirdin may be taken with or without food.
Daclavirdin for oral use only.
The recommended dose of Daclavirdin is 60 mg once daily.
Dose recommendation for concomitant medicines
Strong inhibitors of cytochromeP450enzyme3A4(CYP3A4)
The dose of Daclavirdin should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4.

Moderate inducers ofCYP3A4
The dose of Daclavirdin should be increased to 90 mg once daily when co-administered with moderate inducers of CYP3A4.

Missed doses
Patients should be instructed that, if they miss a dose of Daclavirdin, 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 Daclavirdin is required for patients aged ≥65 years.

Renal impairment

No dose adjustment of Daclavirdin is required for patients with any degree of renal impairment.

Hepatic impairment

No dose adjustment of Daclavirdin 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 Daclavirdin in children and adolescents aged below 18 years have not yet been established. No data are available.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Daclavirdin must not be administered as monotherapy. Daclavirdin must be administered in combination with other medicinal products for the treatment of chronic HCV infection.

Severe bradycardia and heartblock

Cases of severe bradycardia and heart block have been observed when Daclavirdin 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 Daclavirdin 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 Daclavirdin 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 Daclavirdin in combination with sofosbuvir.

All patients receiving Daclavirdin 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 Daclavirdin and sofosbuvir are limited.

Data from study ALLY-3 (AI444218) support a 12-week treatment duration of Daclavirdin + 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 Daclavirdin + 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 Daclavirdin and sofosbuvir in patients infected with HCV

genotypes 4 and 6 are limited. There are no clinical data in patients with genotype 5.

PatientswithChild-PughCliverdisease

The safety and efficacy of Daclavirdin in the treatment of HCV infection in patients with Child-Pugh C liver disease have been established in the clinical study ALLY-1 (AI444215, Daclavirdin+ 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 Daclavirdin + 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(hepatitisBvirus)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 Daclavirdin as part of a retreatment regimen in patients with prior exposure to a NS5A inhibitor has not been established.

Pregnancyandcontraception requirements

Daclavirdin 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 Daclavirdin therapy.

When Daclavirdin 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 (see the Summary of Product Characteristics for ribavirin).

4.5 Interactions with other medicinal products and other forms of interaction:

Coadministration of Daclavirdin can alter the concentration of other medicinal products and other medicinal products may alter the concentration of daclatasvir. Refer to section 4.3 for a listing of medicinal products that are contraindicated for use with Daclavirdin due to potential loss of therapeutic effect. Refer to section 4.5 for established and other potentially significant drug-drug interactions.

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, 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

Daclavirdin 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 Daclavirdin

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

Patients on controlled sodium diet

Daclavirdin contains less than 1 mmol sodium (23 mg) per maximum dose of 90 mg, that is to say essentially 'sodium-free'.

Contraindications of concomitant use

Daclavirdin 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 Daclavirdin.

Potential for interaction with other medicinal products

Daclavirdin 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 Daclavirdin 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 Daclavirdin is recommended when co-administered with strong inhibitors of CYP3A4 (see Table 4). 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 Daclavirdin 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.

Refer to the respective Summary of Product Characteristics for drug interaction information for other medicinal products in the regimen.

Patients treated with vitamin K antagonists
As liver function may change during treatment with Daclavirdin, a close monitoring of International Normalized Ratio (INR) values is recommended.

4.6 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.
Daclavirdin 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 Daclavirdin therapy.

Since Daclavirdin is used in combination with other agents, the contraindications and warnings for those medicinal products are applicable.
For detailed recommendations regarding pregnancy and contraception, refer to the Summary of Product Characteristics for ribavirin and peginterferon alfa.

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 Daclavirdin.

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

4.7 Effects on ability to drive and use machines
Dizziness has been reported during treatment with Daclavirdin in combination with sofosbuvir, and dizziness, disturbance in attention, blurred vision and reduced visual acuity have been reported during treatment with Daclavirdin in combination with peginterferon alfa and ribavirin.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of daclatasvir is based on data from 2215 patients with chronic HCV infection who received Daclavirdin 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.

Daclavirdin 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 Daclavirdin regimen for adverse events, only one of which was considered related to study therapy.

Daclavirdin 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.

Laboratory abnormalities

In clinical studies of Daclavirdin in combination with sofosbuvir with or without ribavirin, 2% of patients had Grade 3 haemoglobin decreases; all of these patients received Daclavirdin + sofosbuvir + ribavirin. Grade 3/4 increases in total bilirubin were observed in 5% of patients (all in patients with HIV co- infection 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 Daclavirdin is used in combination with sofosbuvir and concomitant amiodarone and/or other drugs that lower heart rate.

Paediatric population

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

4.9 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.

5 PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {It is a potent inhabitor of non sturctural Protein 5A }, 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 (EC_{50} <1 nM) for genotype 1b, and higher levels of resistance for genotype 1a (EC_{50} up to 350 nM). The most resistant variants with single

amino acid substitution in genotype 2a and genotype 3a were F28S (EC_{50} >300 nM) and Y93H (EC_{50} >1,000 nM), respectively. In genotype 4, amino acid substitutions at 30 and 93 (EC_{50} < 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.

Clinical efficacy and safety

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.

Treatment-naïve patients with HCV genotype 1 who received 12 weeks of treatment had a similar response as those treated for 24 weeks (Table 6).

Table 6: Treatment outcomes, daclatasvir in combination with sofosbuvir,

HCV genotype 1 in Study AI444040

	Treatment-naïve			**Prior telaprevir or boceprevir failures**		
	daclatasvir + sofosbuvir N=70	**daclatasvir + sofosbuvir + ribavirin N=56**	**All N=126**	**daclatasvir + sofosbuvir N=21**	**daclatasvir + sofosbuvir + ribavirin N=20**	**All N=41**
End of treatment HCV RNA undetectable	70 (100%)	56 (100%)	126 (100%)	19 (91%)	19 (95%)	38 (93%)
SVR12 (overall)*	70 (100%)	55 (98%)*	125 (99%)*	21 (100%)	20 (100%)	41 (100%)
12 weeks treatment duration	41/41 (100%)	40/41 (98%)	81/82 (99%)	--	--	--

Table 6: Treatment outcomes, daclatasvir in combination with sofosbuvir, HCV genotype 1 in Study AI444040

	Treatment-naïve			**Prior telaprevir or boceprevir failures**		
	daclatasvir + sofosbuvir N=70	**daclatasvir + sofosbuvir + ribavirin N=56**	**All N=126**	**daclatasvir + sofosbuvir N=21**	**daclatasvir + sofosbuvir + ribavirin N=20**	**All N=41**
24 weeks treatment duration	29/29 (100%)	15/15 (100%)	44/44 (100%)	21 (100%)	20 (100%)	41 (100%)
≥F3 liver fibrosis	--	--	41/41 (100%)	--	--	20/20 (100%)

* Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ. One treatment-naïve patient was missing both post-treatment Weeks 12 and 24 data.

Table 7: Treatment outcomes, daclatasvir in combination with sofosbuvir for 24 weeks, treatment-naïve patients with HCV genotype 2 or 3 in Study AI444040

	Genotype 2			Genotype 3		
	daclatasvir + sofosbuvir N=17	daclatasvir + sofosbuvir + ribavirin N=9	All Genotype 2 N=26	daclatasvir + sofosbuvir N=13	daclatasvir + sofosbuvir + ribavirin N=5	All Genotype 3 N=18
End of treatment HCV RNA undetectable	17 (100%)	9 (100%)	26 (100%)	11 (85%)	5 (100%)	16 (89%)
SVR12*	17 (100%)	8 (89%)*	25 (96%)*	11 (85%)	5 (100%)	16 (89%)
≥ F3 liver fibrosis			8/8 (100%)			5/5 (100%)
Virologic failure						
Virologic breakthrough**	0	0	0	1 (8%)	0	1 (6%)
Relapse**	0	0	0	1/11 (9%)	0	1/16 (6%)

* Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ. One patient with HCV genotype 2 infection was missing both post-treatment Week 12 and 24 data.

** The patient with virologic breakthrough met the original protocol definition of confirmed HCV RNA <LLOQ, detectable at treatment Week 8. Relapse was defined as HCV RNA ≥LLOQ during follow-up after HCV RNA <LLOQ at end of treatment. Relapse includes observations through follow-up Week 24.

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.

Patients demographics and main disease characteristics are summarised in Table 8.

Table 8: Demographics and main disease characteristics in Study ALLY-1

	Cirrhotic cohort N = 60	Post-Liver Transplant N = 53
Age (years): median (range)	58 (19-75)	59 (22-82)
Race: White	57 (95%)	51 (96%)

Table 8: Demographics and main disease characteristics in Study ALLY-1

	Cirrhotic cohort N = 60	Post-Liver Transplant N = 53
Black/African American	3 (5%)	1 (2%)
Other	0	1 (2%)
HCV genotype:		
1a	34 (57%)	31 (58%)
1b	11 (18%)	10 (19%)
2	5 (8%)	0
3	6 (10%)	11 (21%)
4	4 (7%)	0
6	0	1 (2%)
Fibrosis stage		
F0	0	6 (11%)
F1	1 (2%)	10 (19%)
F2	3 (5%)	7 (13%)
F3	8 (13%)	13 (25%)
F4	48 (80%)	16 (30%)
Not reported	0	1 (2%)
CP classes		ND
CP A	12 (20%)	
CP B	32 (53%)	
CP C	16 (27%)	
MELD score		ND
mean	13.3	
median	13.0	
Q1, Q3	10, 16	
Min, Max	8, 27	

ND: Not determined

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

Table 9: Treatment outcomes, daclatasvir in combination with sofosbuvir and ribavirin for 12 weeks, patients with cirrhosis or HCV recurrence after liver transplantation, Study ALLY-1

	Cirrhotic cohort N=60		Post-LiverTransplant N=53	
End of treatment HCV RNA undetectable	58/60 (97%)		53/53 (100%)	
	SVR12	**Relapse**	**SVR12**	**Relapse**
All patients	50/60 (83%)	9/58* (16%)	50/53 (94%)	3/53 (6%)
Cirrhosis			ND	ND
CP A	11/12 (92%)	1/12 (8%)		

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.

Table 9: Treatment outcomes, daclatasvir in combination with sofosbuvir and ribavirin for 12 weeks, patients with cirrhosis or HCV recurrence after liver transplantation, Study ALLY-1

	Cirrhotic cohort N=60		Post-Liver Transplant N=53	
CP B	30/32 (94%)	2/32 (6%)		
CP C	9/16 (56%)	6/14 (43%)		
Genotype 1	37/45 (82%)	7/45 (16%)	39/41 (95%)	2/41 (5%)
1a	26/34 (77%)	7/33 (21%)	30/31 (97%)	1/31 (3%)
1b	11/11 (100%)	0%	9/10 (90%)	1/10 (10%)
Genotype 2	4/5 (80%)	1/5 (20%)	--	--
Genotype 3	5/6 (83%)	1/6 (17%)	10/11 (91%)	1/11 (9%)
Genotype 4	4/4 (100%)	0%	--	--
Genotype 6	--	--	1/1 (100%)	0%

ND: Not determined

* 2 patients had detectable HCV RNA at the end of treatment; 1 of these patients achieved SVR.

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 infections were eligible to enroll, including patients with compensated cirrhosis (Child-Pugh A). The dose of daclatasvir was adjusted for concomitant antiretroviral use. Patient demographics and baseline disease characteristics are summarized in Table 10.

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 compensated cirrhosis (Child-Pugh A). The dose of daclatasvir was adjusted for concomitant antiretroviral use. Patient demographics and baseline disease characteristics are summarized in Table 10.

Table 10: Demographics and baseline characteristics in Study ALLY-2

Patient disposition	daclatasvir + sofosbuvir 12 weeks N = 153
Age (years): median (range)	53 (24-71)
Race:	
White	97 (63%)
Black/African American	50 (33%)
Other	6 (4%)
HCV genotype:	
1a	104 (68%)
1b	23 (15%)
2	13 (8%)
3	10 (7%)
4	3 (2%)
Compensated cirrhosis	24 (16%)
Concomitant HIV therapy:	
PI-based	70 (46%)
NNRTI-based	40 (26%)
Other	41 (27%)
None	2 (1%)

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.

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

as summarized in Table 11.

Table 11: Treatment outcomes, daclatasvir in combination with sofosbuvir in patients with HCV/HIV co-infection in Study ALLY-2

	8 weeks therapy	12 weeks therapy	
	HCV Treatment-naïve N=50	HCV Treatment-naïve N=101	HCV Treatment-experienced* N=52
End of treatment HCV RNA undetectable	50/50 (100%)	100/101 (99%)	52/52 (100%)
SVR12	38/50 (76%)	98/101 (97%)	51/52 (98%)
No cirrhosis**	34/44 (77%)	88/90 (98%)	34/34 (100%)
With cirrhosis**	3/5 (60%)	8/9 (89%)	14/15 (93%)
Genotype 1	31/41 (76%)	80/83 (96%)	43/44 (98%)
1a	28/35 (80%)	68/71 (96%)	32/33 (97%)
1b	3/6 (50%)	12/12 (100%)	11/11 (100%)
Genotype 2	5/6 (83%)	11/11 (100%)	2/2 (100%)
Genotype 3	2/3 (67%)	6/6 (100%)	4/4 (100%)
Genotype 4	0	1/1 (100%)	2/2 (100%)
Virologic failure			
Detectable HCV RNA at end of treatment	0	1/101 (1%)	0
Relapse	10/50 (20%)	1/100 (1%)	1/52 (2%)
Missing post-treatment data	2/50 (4%)	1/101 (1%)	0

* Mainly interferon-based therapy +/-NS3/4 PI.

** Cirrhosis was determined by liver biopsy, FibroScan >14.6 kPa, or FibroTest score ≥0.75 and aspartate aminotransferase (AST) platelet ratio index (APRI) >2. For 5 patients, cirrhosis status was indeterminate.

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 $\log_{10}$ 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 (see

Table 12).

Table 12: Treatment outcomes, daclatasvir in combination with sofosbuvir for 12 weeks, patients with HCV genotype 3 in Study ALLY-3

	Treatment-naïve N=101	Treatment-experienced* N=51	Total N=152
End of treatment HCV RNA undetectable	100 (99%)	51 (100%)	151 (99%)
SVR12	91 (90%)	44 (86%)	135 (89%)
No cirrhosis**	73/75 (97%)	32/34 (94%)	105/109 (96%)
With cirrhosis**	11/19 (58%)	9/13 (69%)	20/32 (63%)
Virologic failure			
Virologic breakthrough	0	0	0
Detectable HCV RNA at end of treatment	1 (1%)	0	1 (0.7%)
Relapse	9/100 (9%)	7/51 (14%)	16/151 (11%)

* Mainly interferon-based therapy, but 7 patients received sofosbuvir + ribavirin and 2 patients received a cyclophilin inhibitor.

** Cirrhosis was determined by liver biopsy (METAVIR F4) for 14 patients, FibroScan >14.6 kPa for 11 patients or FibroTest score ≥0.75 and aspartate aminotransferase (AST): platelet ratio index (APRI) >2 for 7 patients. For 11 patients, cirrhosis status was missing or inconclusive (FibroTest score >0.48 to <0.75 or APRI >1 to ≤2).

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 (see Table 13). SVR12 rates were consistently high across most subgroups including gender, age, race, baseline HCV RNA, and IL28B genotype. All 3 HCV/HIV co- infected patients achieved SVR12.

Table 13: Treatment outcomes, daclatasvir in combination with sofosbuvir and ribavirin for 24 weeks, HCV genotype 3 patients with cirrhosis in Study ALLY-3C

	Treatment-naïve N=54	Treatment-experienced N=24	Total N=78
End of treatment HCV RNA undetectable	54/54 (100.0%)	21/24 (87.5%)	75/78 (96.2%)
Responder (SVR12)	50/54 (92.6%)	19/24 (79.2%)	69/78 (88.5%)*
Non-responder (non-SVR12)	4/54 (7.4%)	5/24 (20.8%)	9/78 (11.5%)
Virologic failure			
Virologic breakthrough	0	0	0

Table 13: Treatment outcomes, daclatasvir in combination with sofosbuvir and ribavirin for 24 weeks, HCV genotype 3 patients with cirrhosis in Study ALLY-3C

	Treatment-naïve N=54	Treatment-experienced N=24	Total N=78
Detectable HCV RNA at end of treatment	0	2/24 (8.3%)	2/78 (2.6%)
Relapse	0	2/21 (9.5%)	2/75 (2.7%)
Non-virologic failure			
Other non-responder**	4/54 (7.4%)	0	4/78 (5.1%)
No HCV RNA on treatment	0	1/24 (4.2%)	1/78 (1.3%)

* One treatment-experienced patient achieved SVR12 per local HCV RNA results.

** Other non-responders included 4 patients with HCV RNA < LLOQ target not detected (TND) at end of treatment, but who were lost to follow-up at post-treatment Week 12 and subsequent time points, and 1 patient who had no on-treatment HCV RNA results due to early discontinuation.

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/RBVto 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.

Treatment outcomes in study AI444010 for patients with HCV genotype 4 are presented in Table 14. 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 daclatasvir- treated 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.

Table 14: Treatment outcomes, daclatasvir in combination with

peginterferon alfa and ribavirin (pegIFN/RBV), treatment-naïve patients with HCV genotype 4

	Study AI444042		Study AI444010	
	daclatasvir + pegIFN/RBV	pegIFN/RBV	daclatasvir + pegIFN/RBV	pegIFN/RBV
	N=82	N=42	N=12	N=6
End of treatment HCV RNA undetectable	74 (90%)	27 (64%)	12 (100%)	4 (67%)
SVR12*	67 (82%)	18 (43%)	12 (100%)	3 (50%)
No cirrhosis	56/69 (81%)**	17/38 (45%)	12/12 (100%)	3/6 (50%)
With cirrhosis	7/9 (78%)**	1/4 (25%)	0	0
Virologic failure				
On-treatment virologic failure	8 (10%)	15 (36%)	0	0
Relapse	2/74 (3%)	8/27 (30%)	0	1/4 (25%)

* Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ.

** Cirrhosis status was not reported for four patients in the daclatasvir + pegIFN/RBV group.

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 (see section 4.5). 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.

Observed emergent NS5A resistance-associated variants are reported in Table 15.

Table 15: Summary of noted newly emergent HCV NS5A substitutions on treatment or during follow-up in treated non-SVR12 subjects infected with HCV genotypes 1 through 3

Category/ Substitution, n (%)	Genotype 1a N=301	Genotype 1b N=79	Genotype 2 N=44	Genotype 3 N=197
Non-responders (non-SVR12)	14*	1	2*	21**
with baseline and post-baseline sequence	12	1	1	20
with emergent NS5A RAVs***	10 (83%)	1 (100%)	0	16 (80%)
M28: T	2 (17%)	--	--	0
Q30: H, K, R	9 (75%)	--	--	--
L31: I, M, V	2 (17%)	0	0	1 (5%)
P32-deletion	0	1 (100%)	0	0
H58: D, P	2 (17%)	--	--	--
S62: L	--	--	--	2 (10%)
Y93: C, H, N	2 (17%)	0	0	11 (55%)

* Patient(s) lost to follow-up
** One patient considered a protocol failure (non-SVR) achieved SVR
*** NS5A RAVs monitored at amino acid positions are 28, 29, 30, 31, 32, 58, 62, 92, and 93

The 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 post- treatment 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 1a and 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with daclatasvir in one or more subsets of the paediatric population in the treatment of chronic hepatitis C (see section 4.2 for information on paediatric use).

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 C_{max} was 1534 (58) ng/ml, AUC_{0-24h} was 14122 (70) ng•h/ml, and C_{min} 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 C_{max}, AUC, and C_{min} 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 C_{max} 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 [^{13}C,^{15}N]-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 (IC_{50} >40 μM) CYP enzymes 1A2,2B6,2C8, 2C9, 2C19, or 2D6.

Elimination

Following single-dose oral administration of ^{14}C–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 [^{13}C,^{15}N]-daclatasvir intravenous dose, the total clearance was 4.24 l/h.

Specialpopulations

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 haemodialysis had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to subjects with normal renal function (see section 4.2).

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 C_{max} 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 paediatric 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous (SuperTab AN 22)
Microcrystalline cellulose (PH 101)
Croscarmellose sodium
Collidal silicon dioxide (Aerosil 200)
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep at a temperature not exceeding 30 °C, in a dry place. Keep out of reach of children.

6.5 Nature and contents of container

Carton box containing (Al/Al) strip of 7 film coated tablets+insert leaflet.

6.6 Instructions for use and handling and disposal

No special requirements.

7 MARKET AUTHORIZATION HOLDER

Eva Pharma for Pharmaceuticals & Medical Appliances

8 MARKETING AUTHORISATION NUMBER(S)

06505/08048/REN/2021

9-DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 05-October-2017
Date of latest renewal: 26-08-2021

10-DATE OF REVISION OF THE TEXT

24-October-2023

11. Reference