

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 30 mg film-coated tablets
Daklinza 60 mg film-coated tablets
Daklinza 90 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Daklinza 30 mg film-coated tablets

Each film-coated tablet contains daclatasvir dihydrochloride equivalent to 30 mg daclatasvir.

Daklinza 60 mg film-coated tablets

Each film-coated tablet contains daclatasvir dihydrochloride equivalent to 60 mg daclatasvir.

Daklinza 90 mg film-coated tablets

Each film-coated tablet contains daclatasvir dihydrochloride equivalent to 90 mg daclatasvir.

Excipient(s) with known effect

Each 30-mg film-coated tablet contains 58 mg of lactose (as anhydrous).
Each 60-mg film-coated tablet contains 116 mg of lactose (as anhydrous).
Each 90-mg film-coated tablet contains 173 mg of lactose (as anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Daklinza 30 mg film-coated tablets

Green biconvex pentagonal of dimensions 7.2 mm x 7.0 mm, debossed tablet with "BMS" on one side and "213" on the other side.

Daklinza 60 mg film-coated tablets

Light green biconvex pentagonal of dimensions 9.1 mm x 8.9 mm, debossed tablet with "BMS" on one side and "215" on the other side.

Daklinza 90 mg film-coated tablets

Light green biconvex round of dimension 10.16 mm diameter, embossed tablet with "BMS" on one side and "011" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Daklinza is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults (see sections 4.2, 4.4 and 5.1).

For HCV genotype specific activity, see sections 4.4 and 5.1.

4.2 Posology and method of administration

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

Posology

The recommended dose of Daklinza is 60 mg once daily, to be taken orally with or without meals.

Daklinza 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 Daklinza.

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

Patient population*	Regimen and duration
<i>HCV GT 1 or 4</i>	
Patients without cirrhosis	Daklinza + sofosbuvir for 12 weeks
Patients with cirrhosis <i>CP A or B</i>	Daklinza + sofosbuvir + ribavirin for 12 weeks or Daklinza + sofosbuvir (without ribavirin) for 24 weeks
<i>CP C</i>	Daklinza + sofosbuvir +/- ribavirin for 24 weeks (see sections 4.4 and 5.1)
<i>HCV GT 3</i>	
Patients without cirrhosis	Daklinza + sofosbuvir for 12 weeks
Patients with cirrhosis	Daklinza + sofosbuvir +/- ribavirin for 24 weeks (see section 5.1)
<i>Recurrent HCV infection post-liver transplant (GT 1, 3 or 4)</i>	
Patients without cirrhosis	Daklinza + sofosbuvir + ribavirin for 12 weeks (see section 5.1)
Patients with CP A or B cirrhosis GT 1 or 4 GT 3	Daklinza + sofosbuvir + ribavirin for 12 weeks Daklinza + sofosbuvir +/- ribavirin for 24 weeks
Patients with CP C cirrhosis	Daklinza + sofosbuvir +/- ribavirin for 24 weeks (see sections 4.4 and 5.1)

GT: Genotype; CP: Child Pugh

* Includes patients co-infected with human immunodeficiency virus (HIV). For dosing recommendations with HIV antiviral agents, refer to section 4.5.

Daklinza + peginterferon alfa + ribavirin

This regimen is an alternative recommended regimen for patients with genotype 4 infection, without cirrhosis or with compensated cirrhosis. Daklinza 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, Daklinza 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 Daklinza, is weight-based (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively). Refer to the Summary of Product Characteristics of ribavirin.

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 (see Table 2).

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

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

Dose modification, interruption and discontinuation

Dose modification of Daklinza to manage adverse reactions is not recommended. If treatment interruption of components in the regimen is necessary because of adverse reactions, Daklinza must not be given as monotherapy.

There are no virologic treatment stopping rules that apply to the combination of Daklinza with sofosbuvir.

Treatment discontinuation in patients with inadequate on-treatment virologic response during treatment with Daklinza, 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 Daklinza in combination with peginterferon alfa and ribavirin with inadequate on-treatment virologic response

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

Dose recommendation for concomitant medicines

Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)

The dose of Daklinza should be reduced to 30 mg once daily when coadministered with strong inhibitors of CYP3A4.

Moderate inducers of CYP3A4

The dose of Daklinza should be increased to 90 mg once daily when coadministered with moderate inducers of CYP3A4. See section 4.5.

Missed doses

Patients should be instructed that, if they miss a dose of Daklinza, 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 Daklinza is required for patients aged \geq 65 years (see section 5.2).

Renal impairment

No dose adjustment of Daklinza is required for patients with any degree of renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment of Daklinza 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 \geq 10) hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

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

Method of administration

Daklinza 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 Daklinza. 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 precautions for use

Daklinza must not be administered as monotherapy. Daklinza must be administered in combination with other medicinal products for the treatment of chronic HCV infection (see sections 4.1 and 4.2).

Severe bradycardia and heart block

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

All patients receiving Daklinza 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, see section 4.2. Concerning genotype-specific virological and clinical activity, see section 5.1.

Data to support the treatment of genotype 2 infection with Daklinza and sofosbuvir are limited.

Data from study ALLY-3 (AI444218) support a 12-week treatment duration of Daklinza + sofosbuvir for treatment-naïve and -experienced patients with genotype 3 infection without cirrhosis. Lower rates of SVR were observed for patients with cirrhosis (see section 5.1). Data from compassionate use programmes which included patients with genotype 3 infection and cirrhosis, support the use of Daklinza + sofosbuvir for 24 weeks in these patients. The relevance of adding ribavirin to that regimen is unclear (see section 5.1).

The clinical data to support the use of Daklinza and sofosbuvir in patients infected with HCV genotypes 4 and 6 are limited. There are no clinical data in patients with genotype 5 (see section 5.1).

Patients with Child-Pugh C liver disease

The safety and efficacy of Daklinza in the treatment of HCV infection in patients with Child-Pugh C liver disease have been established in the clinical study ALLY-1 (AI444215, Daklinza + 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 Daklinza + sofosbuvir +/- ribavirin for 24 weeks is proposed for patients with Child-Pugh C (see sections 4.2 and 5.1). 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 Daklinza as part of a retreatment regimen in patients with prior exposure to a NS5A inhibitor has not been established.

Pregnancy and contraception requirements

Daklinza 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 Daklinza therapy (see section 4.6).

When Daklinza 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).

Interactions with medicinal products

Coadministration of Daklinza 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 Daklinza due to potential loss of therapeutic effect. Refer to section 4.5 for established and other potentially significant drug-drug interactions.

Paediatric population

Daklinza 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 Daklinza

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

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use (see section 4.3)

Daklinza 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 Daklinza.

Potential for interaction with other medicinal products

Daclatasvir is a substrate of CYP3A4, P-gp and organic cation transporter (OCT) 1. Strong or moderate inducers of CYP3A4 and P-gp may decrease the plasma levels and therapeutic effect of daclatasvir. Co-administration with strong inducers of CYP3A4 and P-gp is contraindicated while dose adjustment of Daklinza is recommended when co-administered with moderate inducers of CYP3A4 and P-gp (see Table 4). Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir. Dose adjustment of Daklinza 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 Daklinza 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.

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 Daklinza, 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		
<i>Nucleotide analogue polymerase inhibitor</i>		
Sofosbuvir 400 mg once daily (daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir* AUC: 0.95 (0.82, 1.10) C _{max} : 0.88 (0.78, 0.99) C _{min} : 0.91 (0.71, 1.16) ↔ GS-331007** AUC: 1.0 (0.95, 1.08) C _{max} : 0.8 (0.77, 0.90) C _{min} : 1.4 (1.35, 1.53) *Comparison for daclatasvir was to a historical reference (data from 3 studies of daclatasvir 60 mg once daily with peginterferon alfa and ribavirin). **GS-331007 is the major circulating metabolite of the prodrug sofosbuvir.	No dose adjustment of Daklinza or sofosbuvir is required.
<i>Protease inhibitors (PIs)</i>		
Boceprevir	Interaction not studied. <i>Expected due to CYP3A4 inhibition by boceprevir:</i> ↑ Daclatasvir	The dose of Daklinza 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) C _{max} : 1.50 (1.39, 1.62) C _{min} : 2.68 (2.42, 2.98) ↑ Simeprevir AUC: 1.44 (1.32, 1.56) C _{max} : 1.39 (1.27, 1.52) C _{min} : 1.49 (1.33, 1.67)	No dose adjustment of Daklinza or simeprevir is required.

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
<p>Telaprevir 500 mg q12h (daclatasvir 20 mg once daily)</p> <p>Telaprevir 750 mg q8h (daclatasvir 20 mg once daily)</p>	<p>↑ Daclatasvir AUC: 2.32 (2.06, 2.62) C_{max}: 1.46 (1.28, 1.66)</p> <p>↔ Telaprevir AUC: 0.94 (0.84, 1.04) C_{max}: 1.01 (0.89, 1.14)</p> <p>↑ Daclatasvir AUC: 2.15 (1.87, 2.48) C_{max}: 1.22 (1.04, 1.44)</p> <p>↔ Telaprevir AUC: 0.99 (0.95, 1.03) C_{max}: 1.02 (0.95, 1.09)</p> <p>CYP3A4 inhibition by telaprevir</p>	<p>The dose of Daklinza should be reduced to 30 mg once daily when coadministered with telaprevir or other strong inhibitors of CYP3A4.</p>
<p><i>Other HCV antivirals</i></p>		
<p>Peginterferon alfa 180 µg once weekly and ribavirin 1000 mg or 1200 mg/day in two divided doses (daclatasvir 60 mg once daily)</p> <p>Study conducted in patients with chronic HCV infection</p>	<p>↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔*</p> <p>↔ Peginterferon alfa C_{min}: ↔*</p> <p>↔ Ribavirin AUC: 0.94 (0.80, 1.11) C_{max}: 0.94 (0.79, 1.11) C_{min}: 0.98 (0.82, 1.17)</p> <p>*PK parameters for daclatasvir when administered with peginterferon alfa and ribavirin in this study were similar to those observed in a study of HCV-infected subjects administered daclatasvir monotherapy for 14 days. PK trough levels for peginterferon alfa in patients who received peginterferon alfa, ribavirin, and daclatasvir were similar to those in patients who received peginterferon alfa, ribavirin, and placebo.</p>	<p>No dose adjustment of Daklinza, peginterferon alfa, or ribavirin is required.</p>

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
ANTIVIRALS, HIV or HBV		
<i>Protease inhibitors (PIs)</i>		
Atazanavir 300 mg/ritonavir 100 mg once daily (daclatasvir 20 mg once daily)	↑ Daclatasvir AUC*: 2.10 (1.95, 2.26) C _{max} *: 1.35 (1.24, 1.47) C _{min} *: 3.65 (3.25, 4.11) CYP3A4 inhibition by ritonavir *results are dose-normalised to 60 mg dose.	The dose of Daklinza 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. <i>Expected due to CYP3A4 inhibition by atazanavir/cobicistat:</i> ↑ Daclatasvir	
Darunavir 800 mg/ritonavir 100 mg once daily (daclatasvir 30 mg once daily)	↔ Daclatasvir AUC: 1.41 (1.32, 1.50) C _{max} : 0.77 (0.70, 0.85) ↔ Darunavir AUC: 0.90 (0.73, 1.11) C _{max} : 0.97 (0.80, 1.17) C _{min} : 0.98 (0.67, 1.44)	No dose adjustment of Daklinza 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. <i>Expected:</i> ↔ Daclatasvir	
Lopinavir 400 mg/ritonavir 100 mg twice daily (daclatasvir 30 mg once daily)	↔ Daclatasvir AUC: 1.15 (1.07, 1.24) C _{max} : 0.67 (0.61, 0.74) ↔ Lopinavir* AUC: 1.15 (0.77, 1.72) C _{max} : 1.22 (1.06, 1.41) C _{min} : 1.54 (0.46, 5.07) * the effect of 60 mg daclatasvir on lopinavir may be higher.	No dose adjustment of Daklinza 60 mg once daily or lopinavir/ritonavir is required.
<i>Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)</i>		
Tenofovir disoproxil fumarate 300 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.10 (1.01, 1.21) C _{max} : 1.06 (0.98, 1.15) C _{min} : 1.15 (1.02, 1.30) ↔ Tenofovir AUC: 1.10 (1.05, 1.15) C _{max} : 0.95 (0.89, 1.02) C _{min} : 1.17 (1.10, 1.24)	No dose adjustment of Daklinza or tenofovir is required.

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
Lamivudine Zidovudine Emtricitabine Abacavir Didanosine Stavudine	Interaction not studied. <i>Expected:</i> ↔ Daclatasvir ↔ NRTI	No dose adjustment of Daklinza or the NRTI is required.
<i>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</i>		
Efavirenz 600 mg once daily (daclatasvir 60 mg once daily/120 mg once daily)	↓ Daclatasvir AUC*: 0.68 (0.60, 0.78) C _{max} *: 0.83 (0.76, 0.92) C _{min} *: 0.41 (0.34, 0.50) Induction of CYP3A4 by efavirenz *results are dose-normalised to 60 mg dose.	The dose of Daklinza should be increased to 90 mg once daily when coadministered with efavirenz.
Etravirine Nevirapine	Interaction not studied. <i>Expected due to CYP3A4 induction by etravirine or nevirapine:</i> ↓ Daclatasvir	Due to the lack of data, coadministration of Daklinza and etravirine or nevirapine is not recommended.
Rilpivirine	Interaction not studied. <i>Expected:</i> ↔ Daclatasvir ↔ Rilpivirine	No dose adjustment of Daklinza or rilpivirine is required.
<i>Integrase inhibitors</i>		
Dolutegravir 50 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 0.98 (0.83, 1.15) C _{max} : 1.03 (0.84, 1.25) C _{min} : 1.06 (0.88, 1.29) ↑ Dolutegravir AUC: 1.33 (1.11, 1.59) C _{max} : 1.29 (1.07, 1.57) C _{min} : 1.45 (1.25, 1.68) Inhibition of P-gp and BCRP by daclatasvir	No dose adjustment of Daklinza or dolutegravir is required.
Raltegravir	Interaction not studied. <i>Expected:</i> ↔ Daclatasvir ↔ Raltegravir	No dose adjustment of Daklinza or raltegravir is required.
Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	Interaction not studied for this fixed dose combination tablet. <i>Expected due to CYP3A4 inhibition by cobicistat:</i> ↑ Daclatasvir	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with cobicistat or other strong inhibitors of CYP3A4.
<i>Fusion inhibitor</i>		
Enfuvirtide	Interaction not studied. <i>Expected:</i> ↔ Daclatasvir ↔ Enfuvirtide	No dose adjustment of Daklinza or enfuvirtide is required.

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
<i>CCR5 receptor antagonist</i>		
Maraviroc	Interaction not studied. <i>Expected:</i> ↔ Daclatasvir ↔ Maraviroc	No dose adjustment of Daklinza or maraviroc is required.
ACID REDUCING AGENTS		
<i>H₂-receptor antagonists</i>		
Famotidine 40 mg single dose (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.82 (0.70, 0.96) C _{max} : 0.56 (0.46, 0.67) C _{min} : 0.89 (0.75, 1.06) Increase in gastric pH	No dose adjustment of Daklinza is required.
<i>Proton pump inhibitors</i>		
Omeprazole 40 mg once daily (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.84 (0.73, 0.96) C _{max} : 0.64 (0.54, 0.77) C _{min} : 0.92 (0.80, 1.05) Increase in gastric pH	No dose adjustment of Daklinza is required.
ANTIBACTERIALS		
Clarithromycin Telithromycin	Interaction not studied. <i>Expected due to CYP3A4 inhibition by the antibacterial:</i> ↑ Daclatasvir	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with clarithromycin, telithromycin or other strong inhibitors of CYP3A4.
Erythromycin	Interaction not studied. <i>Expected due to CYP3A4 inhibition by the antibacterial:</i> ↑ Daclatasvir	Administration of Daklinza with erythromycin may result in increased concentrations of daclatasvir. Caution is advised.
Azithromycin Ciprofloxacin	Interaction not studied. <i>Expected:</i> ↔ Daclatasvir ↔ Azithromycin or Ciprofloxacin	No dose adjustment of Daklinza or azithromycin or ciprofloxacin is required.
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied. <i>Expected due to inhibition of P-gp by daclatasvir:</i> ↑ Dabigatran etexilate	Safety monitoring is advised when initiating treatment with Daklinza 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. <i>Expected:</i> ↔ Daclatasvir ↔ Warfarin	No dose adjustment of Daklinza 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 Daklinza.

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
ANTICONVULSANTS		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied. <i>Expected due to CYP3A4 induction by the anticonvulsant:</i> ↓ Daclatasvir	Coadministration of Daklinza with carbamazepine, oxcarbazepine, phenobarbital, phenytoin or other strong inducers of CYP3A4 is contraindicated (see section 4.3).
ANTIDEPRESSANTS		
<i>Selective serotonin reuptake inhibitors</i>		
Escitalopram 10 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.12 (1.01, 1.26) C _{max} : 1.14 (0.98, 1.32) C _{min} : 1.23 (1.09, 1.38) ↔ Escitalopram AUC: 1.05 (1.02, 1.08) C _{max} : 1.00 (0.92, 1.08) C _{min} : 1.10 (1.04, 1.16)	No dose adjustment of Daklinza or escitalopram is required.
ANTIFUNGALS		
Ketoconazole 400 mg once daily (daclatasvir 10 mg single dose)	↑ Daclatasvir AUC: 3.00 (2.62, 3.44) C _{max} : 1.57 (1.31, 1.88) CYP3A4 inhibition by ketoconazole	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with ketoconazole or other strong inhibitors of CYP3A4.
Itraconazole Posaconazole Voriconazole	Interaction not studied. <i>Expected due to CYP3A4 inhibition by the antifungal:</i> ↑ Daclatasvir	
Fluconazole	Interaction not studied. <i>Expected due to CYP3A4 inhibition by the antifungal:</i> ↑ Daclatasvir ↔ Fluconazole	Modest increases in concentrations of daclatasvir are expected, but no dose adjustment of Daklinza or fluconazole is required.
ANTIMYCOBACTERIALS		
Rifampicin 600 mg once daily (daclatasvir 60 mg single dose)	↓ Daclatasvir AUC: 0.21 (0.19, 0.23) C _{max} : 0.44 (0.40, 0.48) CYP3A4 induction by rifampicin	Coadministration of Daklinza with rifampicin, rifabutin, rifapentine or other strong inducers of CYP3A4 is contraindicated (see section 4.3).
Rifabutin Rifapentine	Interaction not studied. <i>Expected due to CYP3A4 induction by the antimycobacterial:</i> ↓ Daclatasvir	

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
CARDIOVASCULAR AGENTS		
<i>Antiarrhythmics</i>		
Digoxin 0.125 mg once daily (daclatasvir 60 mg once daily)	<p>↑ Digoxin AUC: 1.27 (1.20, 1.34) C_{max}: 1.65 (1.52, 1.80) C_{min}: 1.18 (1.09, 1.28)</p> <p>P-gp inhibition by daclatasvir</p>	Digoxin should be used with caution when coadministered with Daklinza. 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 Daklinza in combination with sofosbuvir (see sections 4.4 and 4.8).
<i>Calcium channel blockers</i>		
Diltiazem Nifedipine Amlodipine	Interaction not studied. <i>Expected due to CYP3A4 inhibition by the calcium channel blocker:</i> ↑ Daclatasvir	Administration of Daklinza with any of these calcium channel blockers may result in increased concentrations of daclatasvir. Caution is advised.
Verapamil	Interaction not studied. <i>Expected due to CYP3A4 and P-gp inhibition by verapamil:</i> ↑ Daclatasvir	Administration of Daklinza with verapamil may result in increased concentrations of daclatasvir. Caution is advised.
CORTICOSTEROIDS		
Systemic dexamethasone	Interaction not studied. <i>Expected due to CYP3A4 induction by dexamethasone:</i> ↓ Daclatasvir	Coadministration of Daklinza with systemic dexamethasone or other strong inducers of CYP3A4 is contraindicated (see section 4.3).
HERBAL SUPPLEMENTS		
St. John's wort (<i>Hypericum perforatum</i>)	Interaction not studied. <i>Expected due to CYP3A4 induction by St. John's wort:</i> ↓ Daclatasvir	Coadministration of Daklinza with St. John's wort or other strong inducers of CYP3A4 is contraindicated (see section 4.3).

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
HORMONAL CONTRACEPTIVES		
Ethinylestradiol 35 µg once daily for 21 days + norgestimate 0.180/0.215/0.250 mg once daily for 7/7/7 days (daclatasvir 60 mg once daily)	↔ Ethinylestradiol AUC: 1.01 (0.95, 1.07) C _{max} : 1.11 (1.02, 1.20) ↔ Norelgestromin AUC: 1.12 (1.06, 1.17) C _{max} : 1.06 (0.99, 1.14) ↔ Norgestrel AUC: 1.12 (1.02, 1.23) C _{max} : 1.07 (0.99, 1.16)	An oral contraceptive containing ethinylestradiol 35 µg and norgestimate 0.180/0.215/0.250 mg is recommended with Daklinza. Other oral contraceptives have not been studied.
IMMUNOSUPPRESSANTS		
Cyclosporine 400 mg single dose (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.40 (1.29, 1.53) C _{max} : 1.04 (0.94, 1.15) C _{min} : 1.56 (1.41, 1.71) ↔ Cyclosporine AUC: 1.03 (0.97, 1.09) C _{max} : 0.96 (0.91, 1.02)	No dose adjustment of either medicinal product is required when Daklinza 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) C _{max} : 1.07 (1.02, 1.12) C _{min} : 1.10 (1.03, 1.19) ↔ Tacrolimus AUC: 1.00 (0.88, 1.13) C _{max} : 1.05 (0.90, 1.23)	
Sirolimus Mycophenolate mofetil	Interaction not studied. <i>Expected:</i> ↔ Daclatasvir ↔ Immunosuppressant	
LIPID LOWERING AGENTS		
<i>HMG-CoA reductase inhibitors</i>		
Rosuvastatin 10 mg single dose (daclatasvir 60 mg once daily)	↑ Rosuvastatin AUC: 1.58 (1.44, 1.74) C _{max} : 2.04 (1.83, 2.26) Inhibition of OATP 1B1 and BCRP by daclatasvir	Caution should be used when Daklinza is coadministered with rosuvastatin or other substrates of OATP 1B1 or BCRP.
Atorvastatin Fluvastatin Simvastatin Pitavastatin Pravastatin	Interaction not studied. <i>Expected due to inhibition of OATP 1B1 and/or BCRP by daclatasvir:</i> ↑ Concentration of statin	

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
NARCOTIC ANALGESICS		
<p>Buprenorphine/naloxone, 8/2 mg to 24/6 mg once daily individualized dose* (daclatasvir 60 mg once daily)</p> <p>* Evaluated in opioid-dependent adults on stable buprenorphine/naloxone maintenance therapy.</p>	<p>↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔*</p> <p>↑ Buprenorphine AUC: 1.37 (1.24, 1.52) C_{max}: 1.30 (1.03, 1.64) C_{min}: 1.17 (1.03, 1.32)</p> <p>↑ Norbuprenorphine AUC: 1.62 (1.30, 2.02) C_{max}: 1.65 (1.38, 1.99) C_{min}: 1.46 (1.12, 1.89)</p> <p>*Compared to historical data.</p>	<p>No dose adjustment of Daklinza or buprenorphine may be required, but it is recommended that patients should be monitored for signs of opiate toxicity.</p>
<p>Methadone, 40-120 mg once daily individualized dose* (daclatasvir 60 mg once daily)</p> <p>* Evaluated in opioid-dependent adults on stable methadone maintenance therapy.</p>	<p>↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔*</p> <p>↔ R-methadone AUC: 1.08 (0.94, 1.24) C_{max}: 1.07 (0.97, 1.18) C_{min}: 1.08 (0.93, 1.26)</p> <p>*Compared to historical data.</p>	<p>No dose adjustment of Daklinza or methadone is required.</p>
SEDATIVES		
<i>Benzodiazepines</i>		
<p>Midazolam 5 mg single dose (daclatasvir 60 mg once daily)</p>	<p>↔ Midazolam AUC: 0.87 (0.83, 0.92) C_{max}: 0.95 (0.88, 1.04)</p>	<p>No dose adjustment of midazolam, other benzodiazepines or other CYP3A4 substrates is required when coadministered with Daklinza.</p>
<p>Triazolam Alprazolam</p>	<p>Interaction not studied. <i>Expected:</i> ↔ Triazolam ↔ Alprazolam</p>	

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

Interaction studies have only been performed in adults.

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 (see section 5.3).

The potential risk for humans is unknown.

Daklinza should not be used during pregnancy or in women of childbearing potential not using contraception (see section 4.4). Use of highly effective contraception should be continued for 5 weeks after completion of Daklinza therapy (see section 4.5).

Since Daklinza 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 (see section 5.3). A risk to the newborn/infant cannot be excluded. Mothers should be instructed not to breastfeed if they are taking Daklinza.

Fertility

No human data on the effect of daclatasvir on fertility are available.

In rats, no effect on mating or fertility was seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Dizziness has been reported during treatment with Daklinza in combination with sofosbuvir, and dizziness, disturbance in attention, blurred vision and reduced visual acuity have been reported during treatment with Daklinza 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 Daklinza 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.

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

Daklinza 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$)

and very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions in clinical studies

System Organ Class	Adverse Reactions	
Frequency	<i>Daklinza +sofosbuvir + ribavirin</i> N=203	<i>Daklinza +sofosbuvir</i> 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 Daklinza in combination with sofosbuvir with or without ribavirin, 2% of patients had Grade 3 haemoglobin decreases; all of these patients received Daklinza + 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 Daklinza is used in combination with sofosbuvir and concomitant amiodarone and/or other drugs that lower heart rate (see sections 4.4 and 4.5).

Paediatric population

The safety and efficacy of Daklinza 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 via the national reporting system listed in Appendix V.

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: Direct-acting antiviral, ATC code: J05AX14

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.

Clinical efficacy and safety

In 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. 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), 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 four open-label studies (AI444040, ALLY-1, ALLY-2 and ALLY-3).

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%)	--	--	--
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%)
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%)

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

	Cirrhotic cohort N = 60	Post-Liver Transplant N = 53
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 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	
	SVR12	Relapse	SVR12	Relapse
End of treatment				
HCV RNA undetectable	58/60 (97%)		53/53 (100%)	
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%)		
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 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 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 summarised 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%)

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
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 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 (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%)

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
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).

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 13. 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.

Treatment outcomes in study AI444010 for patients with HCV genotype 4 are presented in Table 13. 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 13: 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 N=82	pegIFN/RB V N=42	daclatasvir + pegIFN/RBV N=12	pegIFN/RB V 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

Limited data are available from an ongoing follow-up study to assess durability of response up to 3 years after treatment with daclatasvir. Among patients who achieved SVR12 with daclatasvir and sofosbuvir (± ribavirin) with a median duration of post-SVR12 follow-up of 15 months, no relapses have occurred. Among patients who achieved SVR12 with daclatasvir + pegIFN/RBV with a median duration of post-SVR12 follow-up of 22 months, 1% 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 14.

Table 14: 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	Genotype 1b	Genotype 2	Genotype 3
	N=301	N=79	N=44	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.

No data are available on the persistence of daclatasvir resistance-associated substitutions beyond 6 months post-treatment in patients treated with daclatasvir and sofosbuvir with/without ribavirin. Emergent daclatasvir resistance-associated substitutions have been shown to persist for 2 years post-treatment and beyond for patients treated with other 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-naïve 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).

5.2 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 [¹³C,¹⁵N]-daclatasvir intravenous dose, estimated volume of distribution at steady state was 47 l. *In vitro* studies indicate that daclatasvir is actively and passively transported into hepatocytes. The active transport is mediated by OCT1 and other unidentified uptake transporters, but not by organic anion transporter (OAT) 2, sodium-taurocholate cotransporting polypeptide (NTCP), or OATPs.

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

Biotransformation

In vitro and *in vivo* studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 being the major CYP isoform responsible for the metabolism. No metabolites circulated at levels more than 5% of the parent concentration. Daclatasvir *in vitro* did not inhibit ($IC_{50} > 40 \mu M$) 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.

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 (CL_{cr}) 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 (see section 4.2).

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 (V_c/F) resulting in slightly higher exposures compared to white patients, but the magnitude of the effect on daclatasvir exposure is not clinically important.

5.3 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 embryofoetal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Anhydrous lactose
Microcrystalline cellulose
Croscarmellose sodium
Silicon dioxide (E551)
Magnesium stearate

Tablet film-coat
Hypromellose
Titanium dioxide (E171)
Macrogol 400
Indigo carmine aluminum lake (E132)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Daklinza 30 mg and 60 mg film-coated tablets
30 months

Daklinza 90 mg film-coated tablets
2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinyl Chloride/poly-chloro-tri-fluoro-ethylene (PVC/PCTFE) clear blister/aluminum foil lidding.
Pack size of 28 film-coated tablets in perforated unit dose blisters.
Pack size of 28 film-coated tablets in non-perforated calendar blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/939/001
EU/1/14/939/002
EU/1/14/939/003
EU/1/14/939/004
EU/1/14/939/005
EU/1/14/939/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2014

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Bristol-Myers Squibb S.r.l.
Loc. Fontana del Ceraso
03012 Anagni (FR)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to evaluate the recurrence of hepatocellular carcinoma associated with Daklinza, the MAH shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	Q2 2021

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 30 mg film-coated tablets
daclatasvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 30 mg of daclatasvir (as dihydrochloride).

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
28 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/939/001 28 tablets (calendar pack)
EU/1/14/939/002 28 x 1 tablet

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daklinza 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER (PERFORATED) TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 30 mg tablets
daclatasvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BMS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTER (NON-PERFORATED) TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 30 mg tablets
daclatasvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 60 mg film-coated tablets
daclatasvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 60 mg of daclatasvir (as dihydrochloride).

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
28 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/939/003 28 tablets (calendar pack)
EU/1/14/939/004 28 x 1 tablet

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daklinza 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER (PERFORATED) TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 60 mg tablets
daclatasvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BMS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTER (NON-PERFORATED) TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 60 mg tablets
daclatasvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 90 mg film-coated tablets
daclatasvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 90 mg of daclatasvir (as dihydrochloride).

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
28 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/939/005 28 tablets (calendar pack)
EU/1/14/939/006 28 x 1 tablet

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daklinza 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER (PERFORATED) TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 90 mg tablets
daclatasvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BMS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTER (NON-PERFORATED) TEXT

1. NAME OF THE MEDICINAL PRODUCT

Daklinza 90 mg tablets
daclatasvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Daklinza 30 mg film-coated tablets
Daklinza 60 mg film-coated tablets
Daklinza 90 mg film-coated tablets
daclatasvir

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Daklinza is and what it is used for
2. What you need to know before you take Daklinza
3. How to take Daklinza
4. Possible side effects
5. How to store Daklinza
6. Contents of the pack and other information

1. What Daklinza is and what it is used for

Daklinza contains the active ingredient daclatasvir. It is used to treat adults with hepatitis C, an infectious disease that affects the liver, caused by the hepatitis C virus.

This medicine works by stopping the hepatitis C virus from multiplying and infecting new cells. This lowers the amount of hepatitis C virus in your body and removes the virus from your blood over a period of time.

Daklinza must always be used together with other medicines against hepatitis C infection and must never be used by itself.

It is very important that you also read the package leaflets for the other medicines that you will be taking with Daklinza. If you have any questions about your medicines, please ask your doctor or pharmacist.

2. What you need to know before you take Daklinza

Do not take Daklinza

- if you are allergic to daclatasvir or any of the other ingredients of this medicine (listed in section 6 of this leaflet)
- if you are taking (by mouth or other ways that affect the whole body) any of the following medicines
 - phenytoin, carbamazepine, oxcarbazepine or phenobarbital, used to treat epileptic seizures
 - rifampicin, rifabutin or rifapentine, antibiotics used to treat tuberculosis
 - dexamethasone, a steroid used to treat allergic and inflammatory diseases
 - medicines containing St. John's wort (*Hypericum perforatum*, a herbal preparation).

These medicines lower the effect of Daklinza and may result in your treatment not working. If you take any of these medicines, tell your doctor immediately.

Since Daklinza must always be used in combination with other medicines against hepatitis C infection, please make sure that you read the "Do not take" section of the package leaflets for these medicines. If you are unsure of any information in the package leaflets, please contact your doctor or pharmacist.

Warnings and precautions

Talk to your doctor or pharmacist before taking Daklinza.

Tell your doctor if any of the following applies:

- you currently take, or have taken in the last few months, the medicine amiodarone to treat irregular heartbeats (your doctor may consider alternative treatments if you have taken this medicine)
- you have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely
- your liver is damaged and not functioning properly (decompensated liver disease)

Tell your doctor immediately if you are taking any medicines for heart problems and during treatment you experience:

- Shortness of breath
- Light-headedness
- Palpitations
- Fainting

Children and adolescents

Daklinza is not recommended for patients below 18 years of age. Daklinza has not yet been studied in children and adolescents.

Other medicines and Daklinza

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Daklinza may affect the way some medicines work. In addition some medicines may affect the way Daklinza works. Your doctor may need to adjust the dose of Daklinza or you may not be able to take Daklinza with certain medicines.

Do not take Daklinza if you are taking any of the following medicines:

- phenytoin, carbamazepine, oxcarbazepine or phenobarbital, used to treat epileptic seizures
- rifampicin, rifabutin or rifapentine, antibiotics used to treat tuberculosis
- dexamethasone, a steroid used to treat allergic and inflammatory diseases
- medicines containing St. John's wort (*Hypericum perforatum*, a herbal preparation).

These medicines lower the effect of Daklinza so your treatment will not work. If you take any of these medicines, tell your doctor immediately.

Tell your doctor or pharmacist if you take any of the following medicines:

- amiodarone or digoxin, used to treat irregular heart beats
- atazanavir/ritonavir, atazanavir/cobicistat, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate combination tablet, etravirine, nevirapine or efavirenz, used to treat HIV infection
- boceprevir or telaprevir, used to treat hepatitis C infection
- clarithromycin, telithromycin or erythromycin, used to treat bacterial infections
- warfarin and other similar medicines called vitamin K antagonists used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.
- dabigatran etexilate, used to prevent blood clots
- ketoconazole, itraconazole, posaconazole or voriconazole, used to treat fungal infections
- verapamil, diltiazem, nifedipine or amlodipine, used to decrease blood pressure

- rosuvastatin, atorvastatin, fluvastatin, simvastatin, pitavastatin or pravastatin, used to lower blood cholesterol
- oral contraceptives

With some of these medicines, your doctor may need to adjust your dose of Daklinza.

Pregnancy and contraception

Tell your doctor if you are pregnant, think you may be pregnant or are planning to become pregnant. If you become pregnant, stop taking Daklinza and tell your doctor immediately.

If you are pregnant you must not take Daklinza.

If you can become pregnant, use effective contraception during and for 5 weeks after your treatment with Daklinza.

Daklinza is sometimes used together with ribavirin. Ribavirin can harm your unborn baby. It is therefore very important that you (or your partner) do not become pregnant during this treatment.

Breast-feeding

It is not known whether Daklinza passes into human breast milk. You should not breastfeed during treatment with Daklinza.

Driving and using machines

Some patients have reported dizziness, difficulty concentrating, and vision problems while taking Daklinza with other medicines for their hepatitis C infection. If you have any of these side effects, do not drive or use any tools or machines.

Daklinza contains lactose

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), talk to your doctor before taking Daklinza.

3. How to take Daklinza

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose

The recommended dose of Daklinza is **60 mg once a day**. Swallow the tablet whole. Do not chew or crush the tablet as it has a very unpleasant taste. Daklinza can be taken with or without a meal.

Some other medicines can interact with Daklinza, affecting the levels of Daklinza in your body. If you are taking any of these medicines, your doctor may decide to change your daily dose of Daklinza to ensure that the treatment is safe and effective for you.

Since Daklinza must always be used with other medicines against hepatitis C infection, please read the package leaflets for these medicines. If you have any questions, ask your doctor or pharmacist.

How long to take Daklinza

Make sure you take Daklinza for as long as your doctor has told you to take it.

The duration of your treatment with Daklinza will be either 12 or 24 weeks. The duration of your treatment will depend on whether you have previously received treatment for your hepatitis C infection, the condition of your liver, and what other medicines you will take with Daklinza. You may have to take your other medicines for different lengths of time.

If you take more Daklinza than you should

If you accidentally take more Daklinza tablets than your doctor recommended, contact your doctor at once or contact the nearest hospital for advice. Keep the tablet blister with you so that you can easily describe what you have taken.

If you forget to take Daklinza

It is important not to miss a dose of this medicine.

If you do miss a dose:

- and you notice within 20 hours of the time you usually take Daklinza, you must take the tablet as soon as possible. Then take the next dose at your usual time.
- and you notice 20 hours or more after the time you usually take Daklinza, wait and take the next dose at your usual time. Do not take a double dose (two doses close together).

If you stop taking Daklinza

It is important that you continue to take Daklinza during the whole treatment period. Otherwise the medicine may not work against the hepatitis C virus. **Do not stop taking Daklinza unless your doctor told you to stop.**

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When Daklinza is used together with sofosbuvir (without ribavirin), the following side effects have been reported.

Very common (may affect more than 1 in 10 people):

- headache, fatigue

Common (may affect up to 1 in 10 people):

- difficulty sleeping
- dizziness
- migraine
- nausea (feeling sick), diarrhoea, abdominal pain
- joint pain, aching or tender muscles, not caused by exercise

When Daklinza is used together with sofosbuvir and ribavirin, the following side effects have been reported.

Very common (may affect more than 1 in 10 people):

- headache, nausea (feeling sick), fatigue
- reduction in red blood cells (anaemia)

Common (may affect up to 1 in 10 people):

- decreased appetite
- difficulty sleeping, irritability
- dizziness
- migraine
- shortness of breath, cough, nasal congestion (blocked nose)
- hot flush
- dry skin, unusual hair loss or thinning, rash, itching
- diarrhoea, vomiting, abdominal pain, constipation, heartburn, excessive gas in the stomach or bowel
- dry mouth
- joint pain, aching or tender muscles, not caused by exercise

When Daklinza is used together with peginterferon alfa and ribavirin the reported side effects are the same as those listed in the package leaflets for these medicines. The most common of these side effects are listed below.

Very common (may affect more than 1 in 10 people):

- decreased appetite
- difficulty sleeping
- headache
- shortness of breath
- nausea
- fatigue
- flu-like illness, fever
- itching, dry skin, unusual hair loss or thinning, rash
- diarrhoea
- cough
- joint pain, aching or tender muscles, not caused by exercise, unusual weakness
- irritability
- reduction in red blood cells (anaemia), reduction in white blood cells

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly [via the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Daklinza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Daklinza contains

- The active substance is daclatasvir. Each film-coated tablet contains 30 mg, 60 mg or 90 mg daclatasvir (as dihydrochloride)
- The other ingredients are
 - *Tablet core*: anhydrous lactose (see section 2), microcrystalline cellulose, croscarmellose sodium, silicon dioxide (E551) and magnesium stearate
 - *Film-coating*: hypromellose, titanium dioxide (E171), macrogol 400, indigo carmine aluminum lake (E132), yellow iron oxide (E172)

What Daklinza looks like and contents of the pack

Daklinza 30 mg: the film-coated tablet is green, biconvex, pentagonal shape with "BMS" debossed on one side and "213" on the other side.

Daklinza 60 mg: the film-coated tablet is light green, biconvex, pentagonal shape with "BMS" debossed on one side and "215" on the other side.

Daklinza 90 mg: the film-coated tablet is light green, biconvex, round shape with "BMS" embossed on one side and "011" on the other side

Daklinza 30 mg, 60 mg and 90 mg film-coated tablets are available in packs of 28 tablets in non-perforated calendar blisters and perforated unit dose blisters.

Not all packages may be marketed in your country.

Marketing Authorisation Holder

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

Manufacturer

Bristol-Myers Squibb S.r.l.
Loc. Fontana del Ceraso
03012 Anagni (FR)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Lietuva

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България

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Norge

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Polska

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Κύπρος

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România

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Slovenija

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Slovenská republika

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Suomi/Finland

Oy Bristol-Myers Squibb (Finland) Ab
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This leaflet was last revised in <{MM/YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

ANNEX IV
SCIENTIFIC CONCLUSIONS

Scientific conclusions

Hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection is not uncommon due to overlapping transmission modes. HCV infection is known to cause suppression of HBV replication in co-infected patients. The virological and immunological aspects of HBV/HCV co-infection are not fully comprehended. Although liver disease activity and progression are generally more severe in the presence of double infection, HBV replication is often suppressed in the presence of HCV coinfection. The European Association for the Study of the Liver (EASL) recommendations on treatment of hepatitis C makes reference to the potential risk of HBV reactivation during or after HCV clearance.

Direct-acting antiviral agents (DAAs) target specific non-structural proteins of the hepatitis C virus and result in disruption of viral replication and infection. Given their increased potency against HCV and lack of anti-HBV activity, the risk of HBV reactivation may be greater with newer HCV treatment regimens than with the previously approved interferon-based HCV treatments. Literature cases (Balagopal et al., 2015; Collins et al., 2015; Ende et al., 2015) described HCV viral load in patients treated with direct acting antivirals (DAA) in interferon-free regimens, and further cases have been identified in EudraVigilance. Some of the cases identified with DAAs had serious outcomes, with worsening of hepatic status and at least one case where the patient required liver transplantation.

HBV replication after starting treatment with DAAs for HCV infection is not currently described in the product information of currently authorised products and in view of the seriousness of the events described, the need for intervention on HBV replication and the biological plausibility of the replication it was considered that further investigation was warranted. The current referral procedure was triggered by the European Commission (EC) to allow further investigation of the risk of hepatitis B virus replication after starting treatment with DAAs and recommend any appropriate measure to minimise the risk.

Following the initiation of this review, results from a study (Reig et al. 2016) performed between October 2014 and December 2015 in Hepatology Units of four University Spanish hospitals in patients with chronic hepatitis C and a history of hepatocellular carcinoma (HCC) treated with DAAs suggested unexpected early HCC recurrence.

It was considered that in addition to the hepatitis B virus reactivation, the risk of hepatocellular carcinoma should also be further investigated and that consideration should be given for adequate measures to optimise the safe and effective use of these medicinal products. The European Commission therefore extended the scope of the procedure in April 2016 to allow consideration of other data to assess the risk of hepatocellular carcinoma and its impact on the benefit-risk balance for all DAAs in the treatment of chronic hepatitis C.

As both requests for the triggered procedure result from the evaluation of data resulting from pharmacovigilance activities, the EC requested the opinion to be adopted by the Committee for Medicinal Products for Human Use (CHMP) on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC).

Overall summary of the scientific evaluation by the PRAC

In its assessment, the PRAC considered all the data submitted by the MAHs, as well as literature and additional information from a scientific advisory group in relation to the risk of hepatitis B reactivation and to the recurrence and occurrence of hepatocellular carcinoma.

Hepatitis B virus reactivation

With regards to the risk of hepatitis B reactivation, since chronic hepatitis B infection (HbsAg+) was generally considered an exclusion criterion and the collection of data regarding HBV serology and

DNA was not mandatory in the development programme of DAAs agents, there is limited information on hepatitis B reactivation obtainable from the completed clinical trials. Therefore data on HBV reactivation with DAAs mostly arose post-marketing.

The available data provide evidence that the reactivation of HBV replication may occur in the context of the treatment of chronic HCV active infection with any form of effective treatment in patients co-infected with HBV and HCV. The reactivation may occur mostly in subjects with detectable HBsAg and active HBV replication of any level, as evaluated by measurable levels of HBV-DNA, but may also occur in subjects without detectable HBsAg though with detectable anti-HBc antibody, of which a small percentage may also present with variable levels of active HBV replication.

Although severe and even fatal cases of HBV reactivation have been described in the literature, the available data indicate that reactivation of HBV replication may mostly be mild and without clinical consequences. The impact of chronic HCV infection characteristics, such as HCV genotype, viral load and histopathologic staging, on the risk of occurrence of HBV reactivation could not be clarified from the available data. It may be assumed however that patients with more advanced liver disease may have a higher risk of severe clinical complications should HBV reactivation occur. Generally, the reactivation occurred shortly after the initiation of treatment in a pattern that implies a correlation with the rapid decrease in HCV viral load which characterises the viral load dynamics with DAAs.

Overall, the PRAC was of the view that evidence exists of a risk of HBV reactivation in HBV/HCV co-infected patients treated with DAAs and therefore HBV reactivation in co-infected patients should be considered as an important identified risk which should be closely monitored through routine risk minimisation activities.

In order to minimise the risk of HBV reactivation, the PRAC recommended that all patients should be screened for HBV infection before initiation of treatment with DAAs and that patients presenting a co-infection HBV/HCV should be monitored and managed according to current clinical guidelines. The product information should reflect these recommendations and inform healthcare professionals about this risk. In addition, patients should be advised to contact their doctor if they have ever been infected with HBV as close monitoring is required.

Hepatocellular carcinoma

With regards to the review of HCC with DAAs, MAHs were requested to perform a comprehensive review of all available data from clinical trials, observational studies, spontaneous reports and published literature on HCC in patients with chronic hepatitis C after treatment with DAAs.

A study from Reig et al. (2016) showed a signal of HCC recurrence in patients treated with DAAs; similar results were obtained by Conti et al. (2016). Other published data from larger cohorts did not support the findings (Pol et al, 2016). However, these cohorts were either not designed for assessing HCC recurrence, as is the case of the ANRS CO22 HEPATHER cohort, or included a limited number of patients with a previous HCC reaching complete radiological response and subsequently treated with DAAs as in the ANRS CO12 CirVir cohort.

Overall, the PRAC considered that further studies were warranted to further characterise the risk of HCC recurrence associated with DAAs, in order to address remaining uncertainties about this potential risk and conclude on the need for any additional advice on clinical management. Taking all available data into account, the PRAC was of the view that MAHs should conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol setting out criteria for entry and follow-up of patients in terms of timing and method for screening. The protocol of this study shall be submitted to the PRAC by 15 June 2017 and the final study results by Q4 2019.

Based on the findings of Reig et al, concerns on the development of *de novo* HCC in cirrhotic HCV patients treated with DAA were also raised, as these patients may harbour not yet diagnosed HCC.

Clinical trial data on incidence of new on-set HCC show higher point estimates for HCC after reaching SVR with IFN-free regimens compared to IFN-containing regimens, also when stratifying by presence of cirrhosis. However, the difficulty of fully controlling confounding in this non-randomised comparison was recognised. Still, it was considered that the impact of DAAs therapies on the incidence and type of de novo HCC should be further investigated by the MAHs through a prospective cohort study to be conducted in HCV infected patients with compensated cirrhosis (CPT-A) without history of HCC and treated with DAAs. The research should capture prospectively the known risk factors for HCC and the periodic image testing for HCC diagnosis, according to current European clinical guidelines (EASL). A feasibility assessment of the use of existing data sources for this purpose should be submitted for PRAC assessment by 15 June 2017. Should the use of existing data sources not show feasible, a proposal for a prospective collection of data should be provided.

The PRAC was also of the view that ‘emergence of hepatocellular carcinoma’ and ‘recurrence of hepatocellular carcinoma’ should be considered as important potential risks. In addition, ‘patients with previous HCC’ should be considered as missing information, since this population was excluded from available clinical trials. The RMP of the relevant medicinal products will be updated accordingly.

In conclusion, the PRAC considered that the benefit-risk balance of DAAs-containing products remained favourable subject to the amendments of the terms of the marketing authorisations.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for direct-acting antiviral agents (DAAs) indicated in the treatment chronic hepatitis C.
- The PRAC reviewed the totality of the data submitted in writing and during the oral explanations by the marketing authorisation holders in relation to the risk of hepatitis B reactivation and to the concerns raised following reports of hepatocellular carcinoma in patients using DAAs, as well as the outcome of the meeting of the scientific advisory group on HIV/Viral diseases.
- Concerning HBV reactivation, the PRAC concluded that available data provide evidence of a risk of HBV reactivation in patients co-infected with HBV/HCV treated for chronic hepatitis C with DAAs. The PRAC was of the view that all patients should be screened for hepatitis B virus infection before initiation of treatment with DAAs. Patients with HBV/HCV co-infection should be monitored during and after treatment according to current clinical guidelines. The product information will include a warning to inform about the risk of hepatitis B reactivation and reflect these recommendations.
- Concerning the risk of recurrence of HCC in patients using DAAs, the PRAC considered that further data are required on the impact of DAAs treatment on the incidence of HCC recurrence. All MAHs of DAAs shall conduct a prospective safety study in a well-defined group of patients based on an agreed protocol setting out criteria for entry and follow-up. A joint study is encouraged.
- The PRAC was also of the opinion that the impact of DAAs treatment on the incidence and type of de novo hepatocellular carcinoma should be further investigated through a prospective cohort study in HCV infected patients with cirrhosis. A joint study is encouraged.

In view of the above, the PRAC considers that the benefit-risk balance of direct-acting antivirals remains favourable subject to the amendments to the terms of the marketing authorisations.

The PRAC, as a consequence, recommends the variation to the terms of the marketing authorisations for Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax.

CHMP opinion and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CHMP agreed with the overall scientific conclusions and grounds for recommendation.

In accordance with the PRAC recommendation, in order to evaluate the recurrence of hepatocellular carcinoma associated with direct-acting antivirals, the MAHs shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol setting out criteria for entry and follow-up of patients in terms of timing and method for screening.

After further consideration of the timelines proposed for the submission of the final study report and taking into account that the protocol is due to be submitted by 15 June 2017, the CHMP was of the opinion that the date for the submission of the final study report should be postponed to Q2 2021 in order to allow sufficient time for agreement on a joint protocol and for collection of sufficient data to adequately respond to the scientific question.

The wording of the condition to the marketing authorisation has been amended accordingly.

In addition, interim results should be submitted for PRAC assessment by Q4 2019.

The RMP should be updated accordingly within 3 months of this CHMP opinion.

Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax.