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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:
Each 30-mg film-coated tablet contains 58 mg of lactose (as anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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.

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.

Recommended regimens and treatment duration are provided in Table 1 below (see sections 4.4 and 5.1):

Table 1: Recommended regimens and treatment duration for Daklinza combination therapy

HCV genotype and patient population*	Treatment	Duration
Genotype 1 or 4 without cirrhosis	Daklinza + sofosbuvir	12 weeks Consider prolongation of treatment to 24 weeks for patients with prior treatment including a NS3/4A protease inhibitor (see sections 4.4 and 5.1)
Genotype 1 or 4 with compensated cirrhosis	Daklinza + sofosbuvir	24 weeks Shortening treatment to 12 weeks may be considered for previously untreated patients with cirrhosis and positive prognostic factors such as IL28B CC genotype and/or low baseline viral load. Consider adding ribavirin for patients with very advanced liver disease or with other negative prognostic factors such as prior treatment experience.
Genotype 3 with compensated cirrhosis and/or treatment experienced	Daklinza + sofosbuvir + ribavirin	24 weeks
Genotype 4	Daklinza + peginterferon alfa + ribavirin	24 weeks of Daklinza in combination with 24-48 weeks of peginterferon alfa and ribavirin. If the patient has HCV RNA undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks. If the patient achieves HCV RNA undetectable, 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.

* For the regimen of Daklinza + sofosbuvir, data for 12-week treatment duration are available only for treatment-naïve patients with genotype 1 infection. For Daklinza + sofosbuvir with or without ribavirin, data are available for patients with advanced liver disease (≥F3) without cirrhosis (see sections 4.4 and 5.1). The recommended use of Daklinza + sofosbuvir in genotype 4 is based on extrapolation from genotype 1. For the regimen of Daklinza + peginterferon alfa + ribavirin, data are available for treatment-naïve patients (see section 5.1).

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).

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 2.

Table 2: 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: ≥25 IU/ml	Discontinue Daklinza, peginterferon alfa and ribavirin
Treatment week 24: ≥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 ≥65 years (see sections 4.4 and 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 ≥10) hepatic impairment. Daklinza has not been studied in patients with decompensated cirrhosis (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).

General
The safety and efficacy of the combination of Daklinza and sofosbuvir have been evaluated in one study of limited size that did not include patients with cirrhosis. Further clinical studies with the combination are ongoing.

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.
Due to limited experience using sofosbuvir in combination with Daklinza in patients with genotype 1 infection and compensated cirrhosis, there are uncertainties concerning the most appropriate way to use Daklinza (duration, role of ribavirin) in such patients.
Due to limitations in the pivotal study many uncertainties remain regarding the most effective way to use Daklinza for treatment of genotypes 2 and 3 infection, and how to tailor regimens according to important factors potentially affecting the virological response.
Although not studied in patients with genotype 4 infection, the combination of Daklinza and sofosbuvir is expected to yield similar activity for genotype 4 as observed for genotype 1, based on *in vitro* antiviral activity and available clinical data with Daklinza in combination with peginterferon and ribavirin (see section 5.1).
Daklinza has not been studied in patients with HCV genotypes 5 and 6, and no regimen recommendation can be given.

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

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).

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

HCV/HIV (human immunodeficiency virus) co-infection
The safety and efficacy of Daklinza in the treatment of HCV infection in patients who are co-infected with HIV have not been established.

HCV/HBV (hepatitis B virus) co-infection
The safety and efficacy of Daklinza in the treatment of HCV infection in patients who are co-infected with HBV have not been investigated.

Elderly
Clinical data in patients aged ≥65 years are limited. In clinical studies of Daklinza in combination with sofosbuvir or with peginterferon alfa and ribavirin, no differences in responses were observed between elderly and younger patients.

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 and P-gp. Strong or moderate inducers of CYP3A4 and P-gp may decrease the plasma levels and therapeutic effect of daclatasvir. Coadministration with strong inducers of CYP3A4 and P-gp is contraindicated while dose adjustment of Daklinza is recommended when coadministered with moderate inducers of CYP3A4 and P-gp (see Table 3). Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir. Dose adjustment of Daklinza is recommended when coadministered with strong inhibitors of CYP3A4 (see Table 3). Coadministration of medicines that inhibit P-gp activity is likely to a have limited effect on daclatasvir exposure.

Daclatasvir is an inhibitor of P-gp, organic anion transporting polypeptide (OATP) 1B1, organic cation transporter (OCT)1 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 3).

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.

Tabulated summary of interactions

Table 3 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 3 were conducted in healthy adult subjects unless otherwise noted. The table is not all-inclusive.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
ANTIVIRALS, HCV		
Nucleotide analogue polymerase inhibitor		
Sofosbuvir 400 mg once daily (daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir* AUC: 0.95 (0.82, 1.10) 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.
Protease inhibitors		
Boceprevir	Interaction not studied. *Expected due to CYP3A4 inhibition by boceprevir:* ↑ Daclatasvir	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with boceprevir or other strong inhibitors of CYP3A4.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
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.
Telaprevir 500 mg q12h (daclatasvir 20 mg once daily) **Telaprevir 750 mg q8h** (daclatasvir 20 mg once daily)	↑ Daclatasvir AUC: 2.32 (2.06, 2.62) C_{max}: 1.46 (1.28, 1.66) ↔ Telaprevir AUC: 0.94 (0.84, 1.04) C_{max}: 1.01 (0.89, 1.14) ↑ Daclatasvir AUC: 2.15 (1.87, 2.48) C_{max}: 1.22 (1.04, 1.44) ↔ Telaprevir AUC: 0.99 (0.95, 1.03) C_{max}: 1.02 (0.95, 1.09) CYP3A4 inhibition by telaprevir	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with telaprevir or other strong inhibitors of CYP3A4.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
Other HCV antivirals		
Peginterferon alfa 180 µg once weekly and ribavirin 1000 mg or 1200 mg/day in two divided doses (daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ Peginterferon alfa C_{min}: ↔* ↔ Ribavirin AUC: 0.94 (0.80, 1.11) C_{max}: 0.94 (0.79, 1.11) C_{min}: 0.98 (0.82, 1.17) *PK parameters for daclatasvir when administered with peginterferon alfa and ribavirin in this study were similar to those observed in a study of HCV-infected subjects administered daclatasvir monotherapy for 14 days. PK trough levels for peginterferon alfa in patients who received peginterferon alfa, ribavirin, and daclatasvir were similar to those in patients who received peginterferon alfa, ribavirin, and placebo.	No dose adjustment of Daklinza, peginterferon alfa, or ribavirin is required.
ANTIVIRALS, HIV or HBV		
Protease inhibitors		
Atazanavir 300 mg/ritonavir 100 mg once daily (daclatasvir 20 mg once daily)	↑ Daclatasvir AUC*: 2.10 (1.95, 2.26) C_{max}*: 1.35 (1.24, 1.47) C_{min}*: 3.65 (3.25, 4.11) CYP3A4 inhibition by ritonavir *results are dose-normalised to 60 mg dose.	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with atazanavir/ritonavir or other strong inhibitors of CYP3A4.
Darunavir/ritonavir **Lopinavir/ritonavir**	Interaction not studied. *Expected due to CYP3A4 inhibition by the protease inhibitor:* ↑ Daclatasvir	Due to the lack of data, coadministration of Daklinza and darunavir or lopinavir is not recommended.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil fumarate 300 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.10 (1.01, 1.21) C_{max}: 1.06 (0.98, 1.15) C_{min}: 1.15 (1.02, 1.30) ↔ Tenofovir AUC: 1.10 (1.05, 1.15) C_{max}: 0.95 (0.89, 1.02) C_{min}: 1.17 (1.10, 1.24)	No dose adjustment of Daklinza or tenofovir is required.
Lamivudine **Zidovudine** **Emtricitabine** **Abacavir** **Didanosine** **Stavudine**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ NRTI	No dose adjustment of Daklinza or the NRTI is required.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (daclatasvir 60 mg once daily/120 mg once daily)	↓ Daclatasvir AUC*: 0.68 (0.60, 0.78) C_{max}*: 0.83 (0.76, 0.92) C_{min}*: 0.41 (0.34, 0.50) Induction of CYP3A4 by efavirenz *results are dose-normalised to 60 mg dose.	The dose of Daklinza should be increased to 90 mg once daily when coadministered with efavirenz.
Etravirine **Nevirapine**	Interaction not studied. *Expected due to CYP3A4 induction by etravirine or nevirapine:* ↓ Daclatasvir	Due to the lack of data, coadministration of Daklinza and etravirine or nevirapine is not recommended.
Rilpivirine	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Rilpivirine	No dose adjustment of Daklinza or rilpivirine is required.
Integrase inhibitors		
Raltegravir **Dolutegravir**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Integrase inhibitor	No dose adjustment of Daklinza or the integrase inhibitor is required.
Fusion inhibitor		
Enfuvirtide	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Enfuvirtide	No dose adjustment of Daklinza or enfuvirtide is required.
CCR5 receptor antagonist		
Maraviroc	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Maraviroc	No dose adjustment of Daklinza or maraviroc is required.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
Pharmacokinetic enhancer		
Cobicistat-containing regimen	Interaction not studied. *Expected due to CYP3A4 inhibition by cobicistat:* ↑ Daclatasvir	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with cobicistat or other strong inhibitors of CYP3A4.
ACID REDUCING AGENTS		
H_2-receptor antagonists		
Famotidine 40 mg single dose (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.82 (0.70, 0.96) C_{max}: 0.56 (0.46, 0.67) C_{min}: 0.89 (0.75, 1.06) Increase in gastric pH	No dose adjustment of Daklinza is required.
Proton pump inhibitors		
Omeprazole 40 mg once daily (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.84 (0.73, 0.96) C_{max}: 0.64 (0.54, 0.77) C_{min}: 0.92 (0.80, 1.05) Increase in gastric pH	No dose adjustment of Daklinza is required.
ANTIBACTERIALS		
Clarithromycin **Telithromycin**	Interaction not studied. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ 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. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ Daclatasvir	Administration of Daklinza with erythromycin may result in increased concentrations of daclatasvir. Caution is advised.
Azithromycin **Ciprofloxacin**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Azithromycin or Ciprofloxacin	No dose adjustment of Daklinza or azithromycin or ciprofloxacin is required.
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied. *Expected due to inhibition of P-gp by daclatasvir:* ↑ Dabigatran etexilate	Safety monitoring is advised when initiating treatment with Daklinza in patients receiving dabigatran etexilate or other intestinal P-gp substrates that have a narrow therapeutic range.
Warfarin	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Warfarin	No dose adjustment of Daklinza or warfarin is required.

Table 3: 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. *Expected due to CYP3A4 induction by the anticonvulsant:* ↓ Daclatasvir	Coadministration of Daklinza with carbamazepine, oxcarbazepine, phenobarbital, phenytoin or other strong inducers of CYP3A4 is contraindicated (see section 4.3).
ANTIDEPRESSANTS		
Selective serotonin reuptake inhibitors		
Escitalopram 10 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.12 (1.01, 1.26) C_{max}: 1.14 (0.98, 1.32) C_{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. *Expected due to CYP3A4 inhibition by the antifungal:* ↑ Daclatasvir	
Fluconazole	Interaction not studied. *Expected due to CYP3A4 inhibition by the antifungal:* ↑ Daclatasvir ↔ Fluconazole	Modest increases in concentrations of daclatasvir are expected, but no dose adjustment of 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. *Expected due to CYP3A4 induction by the antimycobacterial:* ↓ Daclatasvir	

Table 3: Interactions and dose recommendations with other medicinal products

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

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
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. *Expected:* ↔ Daclatasvir ↔ Immunosuppressant	
LIPID LOWERING AGENTS		
HMG-CoA reductase inhibitors		
Rosuvastatin 10 mg single dose (daclatasvir 60 mg once daily)	↑ Rosuvastatin AUC: 1.58 (1.44, 1.74) C_{max}: 2.04 (1.83, 2.26) Inhibition of OATP 1B1 and BCRP by daclatasvir	Caution should be used when Daklinza is coadministered with rosuvastatin or other substrates of OATP 1B1 or BCRP.
Atorvastatin **Fluvastatin** **Simvastatin** **Pitavastatin** **Pravastatin**	Interaction not studied. *Expected due to inhibition of OATP 1B1 and/or BCRP by daclatasvir:* ↑ Concentration of statin	

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
NARCOTIC ANALGESICS		
Buprenorphine/naloxone, 8/2 mg to 24/6 mg once daily individualized dose* (daclatasvir 60 mg once daily) * Evaluated in opioid-dependent adults on stable buprenorphine/naloxone maintenance therapy.	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ Buprenorphine AUC: 1.31 (1.15, 1.48) C_{max}: 1.30 (1.03, 1.64) C_{min}: 1.20 (1.15, 1.48) ↔ Norbuprenorphine AUC: 1.62 (1.33, 1.96) C_{max}: 1.65 (1.38, 1.99) C_{min}: 1.46 (1.16, 1.83) *Compared to historical data.	No dose adjustment of Daklinza or buprenorphine is required.
Methadone, 40-120 mg once daily individualized dose* (daclatasvir 60 mg once daily) * Evaluated in opioid-dependent adults on stable methadone maintenance therapy.	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ R-methadone AUC: 1.08 (0.94, 1.24) C_{max}: 1.07 (0.97, 1.18) C_{min}: 1.08 (0.93, 1.26) *Compared to historical data.	No dose adjustment of Daklinza or methadone is required.
SEDATIVES		
Benzodiazepines		
Midazolam 5 mg single dose (daclatasvir 60 mg once daily)	↔ Midazolam AUC: 0.87 (0.83, 0.92) C_{max}: 0.95 (0.88, 1.04)	No dose adjustment of midazolam, other benzodiazepines or other CYP3A4 substrates is required when coadministered with Daklinza.
Triazolam **Alprazolam**	Interaction not studied. *Expected:* ↔ Triazolam ↔ Alprazolam	

No clinically relevant effects on the pharmacokinetics of either medicinal product are expected when daclatasvir is coadministered with any of the following: PDE-5 inhibitors, medicinal products in the ACE inhibitor class (e.g. enalapril), medicinal products in the angiotensin II receptor antagonist class (e.g. losartan, irbesartan, olmesartan, candesartan, valsartan), amiodarone, 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 798 patients with chronic HCV infection who received Daklinza 60 mg once daily either in combination with sofosbuvir with or without ribavirin (n=211) or in combination with peginterferon alfa and ribavirin (n=587, pooled data) from a total of eight clinical trials.

Daklinza in combination with sofosbuvir
The most frequently reported adverse reactions were fatigue, headache, and nausea. No Grade 3 or 4 adverse reactions were reported. Two patients discontinued for adverse events, which were considered unrelated to study therapy.

Daklinza in combination with peginterferon alfa and ribavirin
The most frequently reported adverse reactions were fatigue, headache, pruritus, insomnia, influenza-like illness, dry skin, nausea, decreased appetite, alopecia, rash, asthenia, irritability, myalgia, anaemia, pyrexia, cough, dyspnoea, neutropenia, diarrhoea and arthralgia. The most frequently reported adverse reactions of at least Grade 3 severity (frequency of 1% or greater) were neutropenia, anaemia and lymphopenia. 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 4 by system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very

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

Table 4: Adverse reactions in clinical trials

System Organ Class	**Adverse Reactions**
Frequency	*Daklinza in combination with sofosbuvir ± ribavirin**
Blood and lymphatic system disorders	
common	anaemia*
Metabolism and nutrition disorders	
common	decreased appetite
Psychiatric disorders	
common	depression, anxiety, insomnia
Nervous system disorders	
very common	headache
common	dizziness, migraine
Vascular disorders	
common	hot flush
Respiratory, thoracic and mediastinal disorders	
common	cough, dyspnoea, dyspnoea exertional, nasal congestion
Gastrointestinal disorders	
very common	nausea
common	diarrhoea, abdominal pain upper, constipation, flatulence, gastrooesophageal reflux disease, dry mouth, vomiting
Skin and subcutaneous tissue disorders	
common	pruritus, dry skin, alopecia, rash
Musculoskeletal and connective tissue disorders	
common	arthralgia, myalgia
General disorders and administration site conditions	
very common	fatigue
common	irritability

* Ninety (43%) of the 211 patients received ribavirin in addition to Daklinza and sofosbuvir. There were no reports of anaemia in the ribavirin-free treatment groups of the study.

Laboratory abnormalities
In the clinical trial of Daklinza in combination with sofosbuvir with or without ribavirin, one patient had a Grade 3 hemoglobin decrease; this patient was in a ribavirin treatment group. Laboratory abnormalities among patients treated with Daklinza, peginterferon alfa and ribavirin were similar to those among patients treated with placebo, peginterferon and ribavirin.

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 trials. In phase 1 clinical trials, 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: ATC code: not yet assigned

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, EC_{50}) values of 0.003-0.050 and 0.001-0.009 nM, respectively, depending on the assay method. The daclatasvir EC_{50} values in the replicon system were 0.003-1.25 nM for genotypes 3a, 4a, 5a and 6a, and 0.034-19 nM for genotype 2a as well as 0.020 nM for infectious genotype 2a (JFH-1) virus.
Daclatasvir showed additive to synergistic interactions with interferon alfa, HCV nonstructural protein 3 (NS3) protease inhibitors, HCV nonstructural protein 5B (NS5B) non-nucleoside inhibitors, and HCV NS5B nucleoside analogues in combination studies using the cell-based HCV replicon system. No antagonism of antiviral activity was observed.
No clinically relevant antiviral activity was observed against a variety of RNA and DNA viruses, including HIV, confirming that daclatasvir, which inhibits a HCV-specific target, is highly selective for HCV.

Resistance in cell culture
Substitutions conferring daclatasvir resistance in genotypes 1-4 were observed in the N-terminal 100 amino acid region of NS5A in a cell-based replicon system. L31V and Y93H were frequently observed resistance substitutions in genotype 1b, while M28T, L31V/M, Q30E/H/R, and Y93C/H/N were frequently observed resistance substitutions in genotype 1a. These substitutions conferred low level resistance (EC_{50} <1 nM) for genotype 1b, and higher levels of resistance for genotype 1a (EC_{50} up to 350 nM). The most resistant variants with single amino acid substitution in genotype 2a and genotype 3a were F28S (EC_{50} >300 nM) and Y93H (EC_{50} >1,000 nM), respectively. Polymorphisms observed in genotype 4a did not appear to impact the potency of daclatasvir (EC_{50} 0.007-0.0013 nM); residues 30 and 93 were the most frequently observed variants, and levels of resistance were low to moderate (EC_{50} 0.9-16 nM).

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 Daklinza 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 AI444040 and AI444042 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, with or without ribavirin, in the treatment of infection with chronic HCV genotype 1, 2, or 3 were evaluated in an open-label randomized study (AI444040) in 211 adults without cirrhosis. Among the 167 patients with HCV genotype 1 infection, 126 were treatment-naïve and 41 had failed prior therapy with a protease inhibitor (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 5 and 6). 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 5).

Table 5: Treatment outcomes, daclatasvir in combination with sofosbuvir, HCV genotype 1

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

	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.

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.

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 7. 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 7. 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 7: 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/RBV N=42**	**daclatasvir + pegIFN/RBV N=12**	**pegIFN/RBV 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.

[‡] On-treatment virologic failure includes virologic breakthrough (confirmed increased in viral load >1 $\log_{10}$ from nadir or any confirmed HCV RNA ≥LLOQ after confirmed undetectable while on treatment), patients who met the protocol-defined treatment futility criteria, and patients with missing or detectable HCV RNA at end of treatment. Relapse was defined as confirmed detectable HCV RNA ≥LLOQ during follow-up among patients with HCV undetectable at end of treatment.

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

Daclatasvir in combination with sofosbuvir

In study AI444040, baseline NS5A polymorphisms known to reduce susceptibility to inhibition by daclatasvir *in vitro* were detected in 16% (33/203) of subjects (9/130 genotype 1a, 4/32 genotype 1b, 14/23 genotype 2, and 6/18 genotype 3). These NS5A resistance-associated polymorphisms (RAPs) included M28T, Q30E/H/R, L31M, and Y93C/H/N in genotype 1a subjects; L31M and Y93H in genotype 1b subjects; L31M in genotype 2 subjects; and A30K/S, L31M, and Y93H in genotype 3 subjects.

Except for a single patient infected with genotype 3 who experienced viral relapse after treatment with daclatasvir and sofosbuvir without ribavirin, all patients with pre-existing daclatasvir resistant variants achieved SVR. Resistance analysis of the one genotype 3-infected patient who relapsed revealed no other resistance-associated changes at relapse other than the pre-existing NS5A-A30K-S62I/V polymorphisms.

Daclatasvir in combination with peginterferon alfa and ribavirin
Pretreatment NS5A polymorphisms known to confer loss of daclatasvir susceptibility *in vitro* (genotype 1a: M28T, Q30H/R, L31M/V, Y93H/N; genotype 1b: L31M, Y93C/H; genotype 4: L28M, L30R, M31V) were observed in 9/125 (7%) genotype 1a, 8/50 (16%) genotype 1b, and 57/94 (61%) genotype 4 treatment-naïve patients. The majority of patients (5/9 [56%] genotype 1a, 6/8 [75%] genotype 1b and 52/57 [91%] genotype 4 patients) with these pretreatment NS5A RAPs achieved SVR.
In 210 (153 genotype 1a and 57 genotype 1b) treatment-naïve patients and prior nonresponders who experienced treatment failure, NS5A resistance-associated variants generally emerged (139/153 genotype 1a and 49/57 genotype 1b). The most frequently detected NS5A variants 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%]). These NS5A variants were detected together in 36/49 (74%) of patients at failure and either emerged together (25/36 [69%] of patients with L31M/V-Y93H) or if one emerged, the other pre-existed (11/36 [31%] patients).
In 133 (103 genotype 1a and 30 genotype 1b) treatment-naïve patients and prior nonresponders who did not achieve SVR24 and were monitored at 48 weeks post-treatment, signature genotype 1a and genotype 1b NS5A resistance-associated variants generally persisted; replacement by wild-type sequence was detected in 2/133 (2%; 2/103 genotype 1a and 0/30 genotype 1b patients) of virologic failures.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Daklinza 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 subjects with chronic HCV. Following multiple oral doses of daclatasvir 60 mg once daily in combination with peginterferon alfa and ribavirin in treatment-naïve subjects 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 and HCV-infected subjects.
In vitro and *in vivo* studies showed that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.

Effect of food on oral absorption
In healthy subjects, administration of daclatasvir 60 mg tablet after a high-fat meal decreased daclatasvir 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 subjects was approximately 99% and independent of dose at the dose range studied (1 mg to 100 mg). In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [^{13}C,^{15}N]-daclatasvir intravenous dose, estimated volume of distribution at steady state was 47 l.

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

Biotransformation
In vitro and *in vivo* studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 being the major CYP isoform responsible for the metabolism. No metabolites circulated at levels more than 5% of the parent concentration. Daclatasvir *in vitro* did not inhibit (IC_{50} >40 μM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6.

Elimination
Following single-dose oral administration of ^{14}C–daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% as unchanged drug) and 6.6% was excreted in the urine (primarily as unchanged drug). Following multiple-dose administration of daclatasvir in HCV-infected subjects, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 μg [^{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 (CLcr) values of 60, 30 and 15 ml/min, respectively, relative to subjects with normal renal function. Subjects with end-stage renal disease requiring hemodialysis had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to subjects with normal renal function (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 trials indicated that age had no apparent effect on the pharmacokinetics of daclatasvir. Data on patients ≥65 years are limited (see section 4.4).

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 trials identified race (categories “other” [subjects who are not white, black or Asian] and “black”) as a statistically significant covariate on daclatasvir apparent oral clearance (CL/F) and apparent volume of distribution (Vc/F) resulting in slightly higher exposures compared to white subjects, 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

30 months

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

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.

▼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 60 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:
Each 60-mg film-coated tablet contains 116 mg of lactose (as anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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.

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.

Recommended regimens and treatment duration are provided in Table 1 below (see sections 4.4 and 5.1):

Table 1: Recommended regimens and treatment duration for Daklinza combination therapy

HCV genotype and patient population*	Treatment	Duration
Genotype 1 or 4 without cirrhosis	Daklinza + sofosbuvir	12 weeks Consider prolongation of treatment to 24 weeks for patients with prior treatment including a NS3/4A protease inhibitor (see sections 4.4 and 5.1)
Genotype 1 or 4 with compensated cirrhosis	Daklinza + sofosbuvir	24 weeks Shortening treatment to 12 weeks may be considered for previously untreated patients with cirrhosis and positive prognostic factors such as IL28B CC genotype and/or low baseline viral load. Consider adding ribavirin for patients with very advanced liver disease or with other negative prognostic factors such as prior treatment experience.
Genotype 3 with compensated cirrhosis and/or treatment experienced	Daklinza + sofosbuvir + ribavirin	24 weeks
Genotype 4	Daklinza + peginterferon alfa + ribavirin	24 weeks of Daklinza in combination with 24-48 weeks of peginterferon alfa and ribavirin. If the patient has HCV RNA undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks. If the patient achieves HCV RNA undetectable, 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.

* For the regimen of Daklinza + sofosbuvir, data for 12-week treatment duration are available only for treatment-naïve patients with genotype 1 infection. For Daklinza + sofosbuvir with or without ribavirin, data are available for patients with advanced liver disease (≥F3) without cirrhosis (see sections 4.4 and 5.1). The recommended use of Daklinza + sofosbuvir in genotype 4 is based on extrapolation from genotype 1. For the regimen of Daklinza + peginterferon alfa + ribavirin, data are available for treatment-naïve patients (see section 5.1).

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).

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 2.

Table 2: 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: ≥25 IU/ml	Discontinue Daklinza, peginterferon alfa and ribavirin
Treatment week 24: ≥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 ≥65 years (see sections 4.4 and 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 ≥10) hepatic impairment. Daklinza has not been studied in patients with decompensated cirrhosis (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).

General
The safety and efficacy of the combination of Daklinza and sofosbuvir have been evaluated in one study of limited size that did not include patients with cirrhosis. Further clinical studies with the combination are ongoing.

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.
Due to limited experience using sofosbuvir in combination with Daklinza in patients with genotype 1 infection and compensated cirrhosis, there are uncertainties concerning the most appropriate way to use Daklinza (duration, role of ribavirin) in such patients.
Due to limitations in the pivotal study many uncertainties remain regarding the most effective way to use Daklinza for treatment of genotypes 2 and 3 infection, and how to tailor regimens according to important factors potentially affecting the virological response.
Although not studied in patients with genotype 4 infection, the combination of Daklinza and sofosbuvir is expected to yield similar activity for genotype 4 as observed for genotype 1, based on *in vitro* antiviral activity and available clinical data with Daklinza in combination with peginterferon and ribavirin (see section 5.1).
Daklinza has not been studied in patients with HCV genotypes 5 and 6, and no regimen recommendation can be given.

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

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).

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

HCV/HIV (human immunodeficiency virus) co-infection
The safety and efficacy of Daklinza in the treatment of HCV infection in patients who are co-infected with HIV have not been established.

HCV/HBV (hepatitis B virus) co-infection
The safety and efficacy of Daklinza in the treatment of HCV infection in patients who are co-infected with HBV have not been investigated.

Elderly
Clinical data in patients aged ≥65 years are limited. In clinical studies of Daklinza in combination with sofosbuvir or with peginterferon alfa and ribavirin, no differences in responses were observed between elderly and younger patients.

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 and P-gp. Strong or moderate inducers of CYP3A4 and P-gp may decrease the plasma levels and therapeutic effect of daclatasvir. Coadministration with strong inducers of CYP3A4 and P-gp is contraindicated while dose adjustment of Daklinza is recommended when coadministered with moderate inducers of CYP3A4 and P-gp (see Table 3). Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir. Dose adjustment of Daklinza is recommended when coadministered with strong inhibitors of CYP3A4 (see Table 3). Coadministration of medicines that inhibit P-gp activity is likely to a have limited effect on daclatasvir exposure.

Daclatasvir is an inhibitor of P-gp, organic anion transporting polypeptide (OATP) 1B1, organic cation transporter (OCT)1 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 3).

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.

Tabulated summary of interactions

Table 3 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 3 were conducted in healthy adult subjects unless otherwise noted. The table is not all-inclusive.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
ANTIVIRALS, HCV		
Nucleotide analogue polymerase inhibitor		
Sofosbuvir 400 mg once daily (daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir* AUC: 0.95 (0.82, 1.10) 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.
Protease inhibitors		
Boceprevir	Interaction not studied. *Expected due to CYP3A4 inhibition by boceprevir:* ↑ Daclatasvir	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with boceprevir or other strong inhibitors of CYP3A4.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
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.
Telaprevir 500 mg q12h (daclatasvir 20 mg once daily) **Telaprevir 750 mg q8h** (daclatasvir 20 mg once daily)	↑ Daclatasvir AUC: 2.32 (2.06, 2.62) C_{max}: 1.46 (1.28, 1.66) ↔ Telaprevir AUC: 0.94 (0.84, 1.04) C_{max}: 1.01 (0.89, 1.14) ↑ Daclatasvir AUC: 2.15 (1.87, 2.48) C_{max}: 1.22 (1.04, 1.44) ↔ Telaprevir AUC: 0.99 (0.95, 1.03) C_{max}: 1.02 (0.95, 1.09) CYP3A4 inhibition by telaprevir	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with telaprevir or other strong inhibitors of CYP3A4.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
Other HCV antivirals		
Peginterferon alfa 180 µg once weekly and ribavirin 1000 mg or 1200 mg/day in two divided doses (daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ Peginterferon alfa C_{min}: ↔* ↔ Ribavirin AUC: 0.94 (0.80, 1.11) C_{max}: 0.94 (0.79, 1.11) C_{min}: 0.98 (0.82, 1.17) *PK parameters for daclatasvir when administered with peginterferon alfa and ribavirin in this study were similar to those observed in a study of HCV-infected subjects administered daclatasvir monotherapy for 14 days. PK trough levels for peginterferon alfa in patients who received peginterferon alfa, ribavirin, and daclatasvir were similar to those in patients who received peginterferon alfa, ribavirin, and placebo.	No dose adjustment of Daklinza, peginterferon alfa, or ribavirin is required.
ANTIVIRALS, HIV or HBV		
Protease inhibitors		
Atazanavir 300 mg/ritonavir 100 mg once daily (daclatasvir 20 mg once daily)	↑ Daclatasvir AUC*: 2.10 (1.95, 2.26) C_{max}*: 1.35 (1.24, 1.47) C_{min}*: 3.65 (3.25, 4.11) CYP3A4 inhibition by ritonavir *results are dose-normalised to 60 mg dose.	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with atazanavir/ritonavir or other strong inhibitors of CYP3A4.
Darunavir/ritonavir **Lopinavir/ritonavir**	Interaction not studied. *Expected due to CYP3A4 inhibition by the protease inhibitor:* ↑ Daclatasvir	Due to the lack of data, coadministration of Daklinza and darunavir or lopinavir is not recommended.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil fumarate 300 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.10 (1.01, 1.21) C_{max}: 1.06 (0.98, 1.15) C_{min}: 1.15 (1.02, 1.30) ↔ Tenofovir AUC: 1.10 (1.05, 1.15) C_{max}: 0.95 (0.89, 1.02) C_{min}: 1.17 (1.10, 1.24)	No dose adjustment of Daklinza or tenofovir is required.
Lamivudine **Zidovudine** **Emtricitabine** **Abacavir** **Didanosine** **Stavudine**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ NRTI	No dose adjustment of Daklinza or the NRTI is required.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (daclatasvir 60 mg once daily/120 mg once daily)	↓ Daclatasvir AUC*: 0.68 (0.60, 0.78) C_{max}*: 0.83 (0.76, 0.92) C_{min}*: 0.41 (0.34, 0.50) Induction of CYP3A4 by efavirenz *results are dose-normalised to 60 mg dose.	The dose of Daklinza should be increased to 90 mg once daily when coadministered with efavirenz.
Etravirine **Nevirapine**	Interaction not studied. *Expected due to CYP3A4 induction by etravirine or nevirapine:* ↓ Daclatasvir	Due to the lack of data, coadministration of Daklinza and etravirine or nevirapine is not recommended.
Rilpivirine	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Rilpivirine	No dose adjustment of Daklinza or rilpivirine is required.
Integrase inhibitors		
Raltegravir **Dolutegravir**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Integrase inhibitor	No dose adjustment of Daklinza or the integrase inhibitor is required.
Fusion inhibitor		
Enfuvirtide	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Enfuvirtide	No dose adjustment of Daklinza or enfuvirtide is required.
CCR5 receptor antagonist		
Maraviroc	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Maraviroc	No dose adjustment of Daklinza or maraviroc is required.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
Pharmacokinetic enhancer		
Cobicistat-containing regimen	Interaction not studied. *Expected due to CYP3A4 inhibition by cobicistat:* ↑ Daclatasvir	The dose of Daklinza should be reduced to 30 mg once daily when coadministered with cobicistat or other strong inhibitors of CYP3A4.
ACID REDUCING AGENTS		
H_2-receptor antagonists		
Famotidine 40 mg single dose (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.82 (0.70, 0.96) C_{max}: 0.56 (0.46, 0.67) C_{min}: 0.89 (0.75, 1.06) Increase in gastric pH	No dose adjustment of Daklinza is required.
Proton pump inhibitors		
Omeprazole 40 mg once daily (daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.84 (0.73, 0.96) C_{max}: 0.64 (0.54, 0.77) C_{min}: 0.92 (0.80, 1.05) Increase in gastric pH	No dose adjustment of Daklinza is required.
ANTIBACTERIALS		
Clarithromycin **Telithromycin**	Interaction not studied. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ 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. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ Daclatasvir	Administration of Daklinza with erythromycin may result in increased concentrations of daclatasvir. Caution is advised.
Azithromycin **Ciprofloxacin**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Azithromycin or Ciprofloxacin	No dose adjustment of Daklinza or azithromycin or ciprofloxacin is required.
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied. *Expected due to inhibition of P-gp by daclatasvir:* ↑ Dabigatran etexilate	Safety monitoring is advised when initiating treatment with Daklinza in patients receiving dabigatran etexilate or other intestinal P-gp substrates that have a narrow therapeutic range.
Warfarin	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Warfarin	No dose adjustment of Daklinza or warfarin is required.

Table 3: 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. *Expected due to CYP3A4 induction by the anticonvulsant:* ↓ Daclatasvir	Coadministration of Daklinza with carbamazepine, oxcarbazepine, phenobarbital, phenytoin or other strong inducers of CYP3A4 is contraindicated (see section 4.3).
ANTIDEPRESSANTS		
Selective serotonin reuptake inhibitors		
Escitalopram 10 mg once daily (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.12 (1.01, 1.26) C_{max}: 1.14 (0.98, 1.32) C_{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. *Expected due to CYP3A4 inhibition by the antifungal:* ↑ Daclatasvir	
Fluconazole	Interaction not studied. *Expected due to CYP3A4 inhibition by the antifungal:* ↑ Daclatasvir ↔ Fluconazole	Modest increases in concentrations of daclatasvir are expected, but no dose adjustment of 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. *Expected due to CYP3A4 induction by the antimycobacterial:* ↓ Daclatasvir	

Table 3: Interactions and dose recommendations with other medicinal products

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

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
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. *Expected:* ↔ Daclatasvir ↔ Immunosuppressant	
LIPID LOWERING AGENTS		
HMG-CoA reductase inhibitors		
Rosuvastatin 10 mg single dose (daclatasvir 60 mg once daily)	↑ Rosuvastatin AUC: 1.58 (1.44, 1.74) C_{max}: 2.04 (1.83, 2.26) Inhibition of OATP 1B1 and BCRP by daclatasvir	Caution should be used when Daklinza is coadministered with rosuvastatin or other substrates of OATP 1B1 or BCRP.
Atorvastatin **Fluvastatin** **Simvastatin** **Pitavastatin** **Pravastatin**	Interaction not studied. *Expected due to inhibition of OATP 1B1 and/or BCRP by daclatasvir:* ↑ Concentration of statin	

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
NARCOTIC ANALGESICS		
Buprenorphine/naloxone, 8/2 mg to 24/6 mg once daily individualized dose* (daclatasvir 60 mg once daily) * Evaluated in opioid-dependent adults on stable buprenorphine/naloxone maintenance therapy.	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ Buprenorphine AUC: 1.31 (1.15, 1.48) C_{max}: 1.30 (1.03, 1.64) C_{min}: 1.20 (1.15, 1.48) ↔ Norbuprenorphine AUC: 1.62 (1.33, 1.96) C_{max}: 1.65 (1.38, 1.99) C_{min}: 1.46 (1.16, 1.83) *Compared to historical data.	No dose adjustment of Daklinza or buprenorphine is required.
Methadone, 40-120 mg once daily individualized dose* (daclatasvir 60 mg once daily) * Evaluated in opioid-dependent adults on stable methadone maintenance therapy.	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ R-methadone AUC: 1.08 (0.94, 1.24) C_{max}: 1.07 (0.97, 1.18) C_{min}: 1.08 (0.93, 1.26) *Compared to historical data.	No dose adjustment of Daklinza or methadone is required.
SEDATIVES		
Benzodiazepines		
Midazolam 5 mg single dose (daclatasvir 60 mg once daily)	↔ Midazolam AUC: 0.87 (0.83, 0.92) C_{max}: 0.95 (0.88, 1.04)	No dose adjustment of midazolam, other benzodiazepines or other CYP3A4 substrates is required when coadministered with Daklinza.
Triazolam **Alprazolam**	Interaction not studied. *Expected:* ↔ Triazolam ↔ Alprazolam	

No clinically relevant effects on the pharmacokinetics of either medicinal product are expected when daclatasvir is coadministered with any of the following: PDE-5 inhibitors, medicinal products in the ACE inhibitor class (e.g. enalapril), medicinal products in the angiotensin II receptor antagonist class (e.g. losartan, irbesartan, olmesartan, candesartan, valsartan), amiodarone, 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 798 patients with chronic HCV infection who received Daklinza 60 mg once daily either in combination with sofosbuvir with or without ribavirin (n=211) or in combination with peginterferon alfa and ribavirin (n=587, pooled data) from a total of eight clinical trials.

Daklinza in combination with sofosbuvir
The most frequently reported adverse reactions were fatigue, headache, and nausea. No Grade 3 or 4 adverse reactions were reported. Two patients discontinued for adverse events, which were considered unrelated to study therapy.

Daklinza in combination with peginterferon alfa and ribavirin
The most frequently reported adverse reactions were fatigue, headache, pruritus, insomnia, influenza-like illness, dry skin, nausea, decreased appetite, alopecia, rash, asthenia, irritability, myalgia, anaemia, pyrexia, cough, dyspnoea, neutropenia, diarrhoea and arthralgia. The most frequently reported adverse reactions of at least Grade 3 severity (frequency of 1% or greater) were neutropenia, anaemia and lymphopenia. 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 4 by system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very

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

Table 4: Adverse reactions in clinical trials

System Organ Class	**Adverse Reactions**
Frequency	*Daklinza in combination with sofosbuvir ± ribavirin**
Blood and lymphatic system disorders	
common	anaemia*
Metabolism and nutrition disorders	
common	decreased appetite
Psychiatric disorders	
common	depression, anxiety, insomnia
Nervous system disorders	
very common	headache
common	dizziness, migraine
Vascular disorders	
common	hot flush
Respiratory, thoracic and mediastinal disorders	
common	cough, dyspnoea, dyspnoea exertional, nasal congestion
Gastrointestinal disorders	
very common	nausea
common	diarrhoea, abdominal pain upper, constipation, flatulence, gastrooesophageal reflux disease, dry mouth, vomiting
Skin and subcutaneous tissue disorders	
common	pruritus, dry skin, alopecia, rash
Musculoskeletal and connective tissue disorders	
common	arthralgia, myalgia
General disorders and administration site conditions	
very common	fatigue
common	irritability

* Ninety (43%) of the 211 patients received ribavirin in addition to Daklinza and sofosbuvir. There were no reports of anaemia in the ribavirin-free treatment groups of the study.

Laboratory abnormalities
In the clinical trial of Daklinza in combination with sofosbuvir with or without ribavirin, one patient had a Grade 3 hemoglobin decrease; this patient was in a ribavirin treatment group. Laboratory abnormalities among patients treated with Daklinza, peginterferon alfa and ribavirin were similar to those among patients treated with placebo, peginterferon and ribavirin.

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 trials. In phase 1 clinical trials, 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: ATC code: not yet assigned

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, EC_{50}) values of 0.003-0.050 and 0.001-0.009 nM, respectively, depending on the assay method. The daclatasvir EC_{50} values in the replicon system were 0.003-1.25 nM for genotypes 3a, 4a, 5a and 6a, and 0.034-19 nM for genotype 2a as well as 0.020 nM for infectious genotype 2a (JFH-1) virus.
Daclatasvir showed additive to synergistic interactions with interferon alfa, HCV nonstructural protein 3 (NS3) protease inhibitors, HCV nonstructural protein 5B (NS5B) non-nucleoside inhibitors, and HCV NS5B nucleoside analogues in combination studies using the cell-based HCV replicon system. No antagonism of antiviral activity was observed.
No clinically relevant antiviral activity was observed against a variety of RNA and DNA viruses, including HIV, confirming that daclatasvir, which inhibits a HCV-specific target, is highly selective for HCV.

Resistance in cell culture
Substitutions conferring daclatasvir resistance in genotypes 1-4 were observed in the N-terminal 100 amino acid region of NS5A in a cell-based replicon system. L31V and Y93H were frequently observed resistance substitutions in genotype 1b, while M28T, L31V/M, Q30E/H/R, and Y93C/H/N were frequently observed resistance substitutions in genotype 1a. These substitutions conferred low level resistance (EC_{50} <1 nM) for genotype 1b, and higher levels of resistance for genotype 1a (EC_{50} up to 350 nM). The most resistant variants with single amino acid substitution in genotype 2a and genotype 3a were F28S (EC_{50} >300 nM) and Y93H (EC_{50} >1,000 nM), respectively. Polymorphisms observed in genotype 4a did not appear to impact the potency of daclatasvir (EC_{50} 0.007-0.0013 nM); residues 30 and 93 were the most frequently observed variants, and levels of resistance were low to moderate (EC_{50} 0.9-16 nM).

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 Daklinza 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 AI444040 and AI444042 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, with or without ribavirin, in the treatment of infection with chronic HCV genotype 1, 2, or 3 were evaluated in an open-label randomized study (AI444040) in 211 adults without cirrhosis. Among the 167 patients with HCV genotype 1 infection, 126 were treatment-naïve and 41 had failed prior therapy with a protease inhibitor (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 5 and 6). 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 5).

Table 5: Treatment outcomes, daclatasvir in combination with sofosbuvir, HCV genotype 1

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

	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.

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.

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 7. 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 7. 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 7: 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/RBV N=42**	**daclatasvir + pegIFN/RBV N=12**	**pegIFN/RBV 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.

[‡] On-treatment virologic failure includes virologic breakthrough (confirmed increased in viral load >1 $\log_{10}$ from nadir or any confirmed HCV RNA ≥LLOQ after confirmed undetectable while on treatment), patients who met the protocol-defined treatment futility criteria, and patients with missing or detectable HCV RNA at end of treatment. Relapse was defined as confirmed detectable HCV RNA ≥LLOQ during follow-up among patients with HCV undetectable at end of treatment.

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

Daclatasvir in combination with sofosbuvir

In study AI444040, baseline NS5A polymorphisms known to reduce susceptibility to inhibition by daclatasvir *in vitro* were detected in 16% (33/203) of subjects (9/130 genotype 1a, 4/32 genotype 1b, 14/23 genotype 2, and 6/18 genotype 3). These NS5A resistance-associated polymorphisms (RAPs) included M28T, Q30E/H/R, L31M, and Y93C/H/N in genotype 1a subjects; L31M and Y93H in genotype 1b subjects; L31M in genotype 2 subjects; and A30K/S, L31M, and Y93H in genotype 3 subjects.

Except for a single patient infected with genotype 3 who experienced viral relapse after treatment with daclatasvir and sofosbuvir without ribavirin, all patients with pre-existing daclatasvir resistant variants achieved SVR. Resistance analysis of the one genotype 3-infected patient who relapsed revealed no other resistance-associated changes at relapse other than the pre-existing NS5A-A30K-S62I/V polymorphisms.

Daclatasvir in combination with peginterferon alfa and ribavirin
Pretreatment NS5A polymorphisms known to confer loss of daclatasvir susceptibility *in vitro* (genotype 1a: M28T, Q30H/R, L31M/V, Y93H/N; genotype 1b: L31M, Y93C/H; genotype 4: L28M, L30R, M31V) were observed in 9/125 (7%) genotype 1a, 8/50 (16%) genotype 1b, and 57/94 (61%) genotype 4 treatment-naïve patients. The majority of patients (5/9 [56%] genotype 1a, 6/8 [75%] genotype 1b and 52/57 [91%] genotype 4 patients) with these pretreatment NS5A RAPs achieved SVR.
In 210 (153 genotype 1a and 57 genotype 1b) treatment-naïve patients and prior nonresponders who experienced treatment failure, NS5A resistance-associated variants generally emerged (139/153 genotype 1a and 49/57 genotype 1b). The most frequently detected NS5A variants 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%]). These NS5A variants were detected together in 36/49 (74%) of patients at failure and either emerged together (25/36 [69%] of patients with L31M/V-Y93H) or if one emerged, the other pre-existed (11/36 [31%] patients).
In 133 (103 genotype 1a and 30 genotype 1b) treatment-naïve patients and prior nonresponders who did not achieve SVR24 and were monitored at 48 weeks post-treatment, signature genotype 1a and genotype 1b NS5A resistance-associated variants generally persisted; replacement by wild-type sequence was detected in 2/133 (2%; 2/103 genotype 1a and 0/30 genotype 1b patients) of virologic failures.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Daklinza 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 subjects with chronic HCV. Following multiple oral doses of daclatasvir 60 mg once daily in combination with peginterferon alfa and ribavirin in treatment-naïve subjects 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 and HCV-infected subjects.
In vitro and *in vivo* studies showed that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.

Effect of food on oral absorption
In healthy subjects, administration of daclatasvir 60 mg tablet after a high-fat meal decreased daclatasvir 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 subjects was approximately 99% and independent of dose at the dose range studied (1 mg to 100 mg). In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [^{13}C,^{15}N]-daclatasvir intravenous dose, estimated volume of distribution at steady state was 47 l.

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

Biotransformation
In vitro and *in vivo* studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 being the major CYP isoform responsible for the metabolism. No metabolites circulated at levels more than 5% of the parent concentration. Daclatasvir *in vitro* did not inhibit (IC_{50} >40 μM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6.

Elimination
Following single-dose oral administration of ^{14}C–daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% as unchanged drug) and 6.6% was excreted in the urine (primarily as unchanged drug). Following multiple-dose administration of daclatasvir in HCV-infected subjects, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 μg [^{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 (CLcr) values of 60, 30 and 15 ml/min, respectively, relative to subjects with normal renal function. Subjects with end-stage renal disease requiring hemodialysis had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to subjects with normal renal function (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 trials indicated that age had no apparent effect on the pharmacokinetics of daclatasvir. Data on patients ≥65 years are limited (see section 4.4).

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 trials identified race (categories “other” [subjects who are not white, black or Asian] and “black”) as a statistically significant covariate on daclatasvir apparent oral clearance (CL/F) and apparent volume of distribution (Vc/F) resulting in slightly higher exposures compared to white subjects, 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

30 months

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/1/14/939/003
EU/1/14/939/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daklinza 30 mg

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daklinza 60 mg

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

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Daklinza 30 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

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 have an infection with the human immunodeficiency virus (HIV) or a hepatitis B infection
- you have had, or are waiting to have a liver or another organ transplant
- your liver is damaged and not functioning properly (decompensated liver disease)

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 if you take any of the following medicines:
- atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir, etravirine, nevirapine, efavirenz or any medicine combined with cobicistat, used to treat HIV infection
- boceprevir or telaprevir, used to treat hepatitis C infection
- clarithromycin, telithromycin or erythromycin, used to treat bacterial infections
- dabigatran etexilate, used to to prevent blood clots
- ketoconazole, itraconazole, posaconazole or voriconazole, used to treat fungal infections
- digoxin, used to treat irregular heart beats
- 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 is **one tablet once a day** of Daklinza 60 mg. 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 (with or without ribavirin), the following side effects have been reported.

Very common (may affect more than 1 in 10 people):
- headache, nausea (feeling sick), fatigue

Common (may affect up to 1 in 10 people):
- decreased appetite
- difficulty sleeping
- dizziness
- migraine
- shortness of breath
- hot flush
- itching, dry skin, unusual hair loss or thinning, rash
- diarrhoea, upper abdominal pain, constipation, excessive gas in the stomach or bowel, heartburn, vomiting
- cough, nasal congestion (blocked nose), dry mouth
- joint pain, aching or tender muscles, not caused by exercise
- depression, anxiety, irritability
- reduction in red blood cells (anaemia)

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 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 30 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:

Belgique/België/Belgien
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11

Lietuva
Bristol-Myers Squibb Gyógyszerkereskedelmi Kft.
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Eesti
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Tél: + 33 (0)810 410 500

Hrvatska
Bristol-Myers Squibb spol. s r.o.
TEL: +385 (1) 6311-833

Ireland
Bristol-Myers Squibb Pharmaceuticals Ltd
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Bristol-Myers Squibb Gyógyszerkereskedelmi Kft.
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Bristol-Myers Squibb B.V.
Tel: + 31 (0)30 300 2222

Norge
Bristol-Myers Squibb Norway Ltd
Tlf: + 47 67 55 53 50

Österreich
Bristol-Myers Squibb GesmbH
Tel: + 43 1 60 14 30

Polska
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

Portugal
Bristol-Myers Squibb Farmacêutica Portuguesa, S.A.
Tel: + 351 21 440 70 00

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Bristol-Myers Squibb Gyógyszerkereskedelmi Kft.
Tel: + 40 (0)21 272 16 00

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Bristol-Myers Squibb spol. s r.o.
Tel: + 386 1 236 47 00

Slovenská republika
Bristol-Myers Squibb spol. s r.o.
Tel: + 421 2 59298411

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Oy Bristol-Myers Squibb (Finland) Ab
Puh/Tel: + 358 9 251 21 230

Sverige
Bristol-Myers Squibb AB
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United Kingdom
Bristol-Myers Squibb Pharmaceuticals Ltd
Tel: + 44 (0800) 731 1736

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.

Package leaflet: Information for the patient

Daklinza 60 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.

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- 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.

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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 have an infection with the human immunodeficiency virus (HIV) or a hepatitis B infection
- you have had, or are waiting to have a liver or another organ transplant
- your liver is damaged and not functioning properly (decompensated liver disease)

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 if you take any of the following medicines:
- atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir, etravirine, nevirapine, efavirenz or any medicine combined with cobicistat, used to treat HIV infection
- boceprevir or telaprevir, used to treat hepatitis C infection
- clarithromycin, telithromycin or erythromycin, used to treat bacterial infections
- dabigatran etexilate, used to to prevent blood clots
- ketoconazole, itraconazole, posaconazole or voriconazole, used to treat fungal infections
- digoxin, used to treat irregular heart beats
- 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 is **one tablet once a day** of Daklinza 60 mg. 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 (with or without ribavirin), the following side effects have been reported.

Very common (may affect more than 1 in 10 people):
- headache, nausea (feeling sick), fatigue

Common (may affect up to 1 in 10 people):
- decreased appetite
- difficulty sleeping
- dizziness
- migraine
- shortness of breath
- hot flush
- itching, dry skin, unusual hair loss or thinning, rash
- diarrhoea, upper abdominal pain, constipation, excessive gas in the stomach or bowel, heartburn, vomiting
- cough, nasal congestion (blocked nose), dry mouth
- joint pain, aching or tender muscles, not caused by exercise
- depression, anxiety, irritability
- reduction in red blood cells (anaemia)

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 60 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 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 60 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.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.