1. NAME OF THE MEDICINAL PRODUCT

MyDekla 60

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 mg daclatasvir (as dihydrochloride).

Each tablet also contains 116 mg anhydrous lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Green, film-coated, capsule-shaped, biconvex, beveled edge tablet, debossed with 'D' on the left side and 'T' on the right side of the score line on one side and '6' on the left side and '0' on the right side of the score line on the other side of the tablet.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MyDekla 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).

Consideration should be given to official treatment guidelines for HCV infection (e.g. those of the WHO).

4.2 Posology and method of administration

Posology

Treatment with MyDekla should be initiated and monitored by a health care provider experienced in the management of chronic hepatitis C.

The recommended dose of daclatasvir is 60 mg (1 tablet) once daily.

MyDekla must be administered in combination with other medicinal products.

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

Patient population*	**Regimen and duration**
All genotypes	
Patients without cirrhosis	Daclatasvir + sofosbuvir for 12 weeks
Patients with cirrhosis (CP A, B or C)	Daclatasvir + sofosbuvir for 24 weeks

CP: Child Pugh

* Includes patients co-infected with human immunodeficiency virus (HIV).

Dose recommendation for concomitant medicines

Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)

The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4. This product should not be used in combination with strong inhibitors of CYP3A4 since appropriate dose adjustments cannot be made. For these patients daclatasvir 30 mg tablets should be used. See section 4.5.

Moderate inducers of CYP3A4

The dose of daclatasvir should be increased to 90 mg once daily when co-administered with moderate inducers of CYP3A4. This dose adjustment cannot be achieved with this product. Daclatasvir 30 mg tablets should be used. See section 4.5.

Missed doses

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

Renal impairment

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

Hepatic impairment

No dose adjustment of MyDekla is required for patients with any degree of hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

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

Method of administration

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

4.3 Contraindications

MyDekla should not be given to patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

MyDekla should not be co-administered with medicinal products that strongly induce cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein transporter (P-gp) as these substances may lead to lower exposure and loss of efficacy of MyDekla. 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

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

Severe bradycardia and heart block

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

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

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

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

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

HCV/HBV (hepatitis B virus) co-infection

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

Retreatment with daclatasvir

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

Pregnancy and contraception requirements

MyDekla 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 MyDekla therapy (see section 4.6).

Interactions with medicinal products

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

Use in diabetic patients

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

Paediatric population

MyDekla 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.

Excipients

Patients with rare hereditary, problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

It is important to consider the contribution of ingredients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use (see section 4.3)

MyDekla 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 MyDekla.

Potential for interaction with other medicinal products

Daclatasvir is a substrate of CYP3A4, P-gp and organic cation transporter (OCT) 1. Strong or moderate inducers of CYP3A4 and P-gp may decrease the plasma levels and therapeutic effect of MyDekla. Coadministration with strong inducers of CYP3A4 and P-gp is contraindicated while dose adjustment of MyDekla is recommended when coadministered with moderate inducers of CYP3A4 and P-gp (see Table 4). Strong inhibitors of CYP3A4 may increase the plasma levels of MyDekla. Dose adjustment of MyDekla is recommended when coadministered with strong inhibitors of CYP3A4 (see Table 4). Coadministration of medicines that inhibit P-gp or OCT1 activity is likely to have a limited effect on daclatasvir exposure.

Daclatasvir is an inhibitor of P-gp, organic anion transporting polypeptide (OATP) 1B1, OCT1 and breast cancer resistance protein (BCRP). Administration of MyDekla may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B1, OCT1 or BCRP, which could increase or prolong their therapeutic effect and adverse reactions. Caution should be used if the medicinal product has a narrow therapeutic range (see Table 4).

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

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

Patients treated with vitamin K antagonists

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

Tabulated summary of interactions

Table 4 provides information from drug interaction studies with daclatasvir including clinical recommendations for established or potentially significant drug interactions. Clinically relevant increase in concentration is indicated as "↑", clinically relevant decrease as "↓", no clinically relevant change as "↔". If available, ratios of geometric means are shown, with 90% confidence intervals (CI) in parentheses. The studies presented in Table 4 were conducted in healthy adult subjects unless otherwise noted. The table is not all-inclusive.

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
ANTIVIRALS, HCV		
Nucleotide analogue polymerase inhibitor		
Sofosbuvir 400 mg once daily (daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir* AUC: 0.95 (0.82, 1.10) C_{max}: 0.88 (0.78, 0.99) C_{min}: 0.91 (0.71, 1.16) ↔ GS-331007 (major metabolite of sofosbuvir) AUC: 1.0 (0.95, 1.08) C_{max}: 0.8 (0.77, 0.90) C_{min}: 1.4 (1.35, 1.53)	No dose adjustment of MyDekla or sofosbuvir is required.
Other HCV antivirals		
Peginterferon alfa 180 µg once weekly and ribavirin 1000 mg or 1200 mg/day in two divided doses	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔*	No dose adjustment of MyDekla, peginterferon alfa, or ribavirin is required

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
(daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ 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)	
ANTIVIRALS, HIV or HBV		
Protease inhibitors (PIs)		
Atazanavir 300 mg/ritonavir 100 mg once daily	↑ Daclatasvir AUC*: 2.10 (1.95, 2.26) C_{max}*: 1.35 (1.24, 1.47) C_{min}*: 3.65 (3.25, 4.11) CYP3A4 inhibition by ritonavir *results are dose-normalised to 60 mg dose.	The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with atazanavir/ritonavir, atazanavir/cobicistat or other strong inhibitors of CYP3A4.
Atazanavir/cobicistat	Interaction not studied. *Expected due to CYP3A4 inhibition by atazanavir/cobicistat:* ↑ Daclatasvir	
Darunavir 800 mg/ritonavir 100 mg once daily (daclatasvir 30 mg once daily)	↑ Daclatasvir AUC: 1.41 (1.32, 1.50) C_{max}: 0.77 (0.70, 0.85) ↔ Darunavir AUC: 0.90 (0.73, 1.11) C_{max}: 0.97 (0.80, 1.17) C_{min}: 0.98 (0.67, 1.44)	The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with darunavir/ritonavir, darunavir/cobicistat or other strong inhibitors of CYP3A4.No dose adjustment of darunavir/ritonavir or darunavir/cobicistat is required.
Darunavir/cobicistat	Interaction not studied. *Expected:* ↑ Daclatasvir	
Lopinavir 400 mg/ritonavir 100 mg twice daily (daclatasvir 30 mg once daily)	↔ Daclatasvir AUC: 1.15 (1.07, 1.24) C_{max}: 0.67 (0.61, 0.74) ↔ Lopinavir AUC: 1.15 (0.77, 1.72) C_{max}: 1.22 (1.06, 1.41) C_{min}: 1.54 (0.46, 5.07)	The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with lopinavir/ritonavir, or other strong inhibitors of CYP3A4.No dose adjustment of lopinavir/ritonavir is required.
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil 245 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 MyDekla or tenofovir disoproxil is required.
Lamivudine **Zidovudine** **Emtricitabine** **Abacavir**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ NRTI	No dose adjustment of MyDekla or the NRTI is required.

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

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
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 MyDekla is required.
ANTIBACTERIALS		
Clarithromycin **Telithromycin**	Interaction not studied. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ Daclatasvir	The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with clarithromycin, telithromycin or other strong inhibitors of CYP3A4.
Erythromycin	Interaction not studied. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ Daclatasvir	Administration of MyDekla 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 MyDekla 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 MyDekla in patients receiving dabigatran etexilate or other intestinal P-gp substrates that have a narrow therapeutic range.
Warfarin or other vitamin K antagonists	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Warfarin	No dose adjustment of MyDekla or warfarin is required. Close monitoring of INR values is recommended with all vitamin K antagonists. This is due to liver function that may change during treatment with MyDekla.
ANTICONVULSANTS		
Carbamazepine **Oxcarbazepine** **Phenobarbital** **Phenytoin**	Interaction not studied. *Expected due to CYP3A4 induction by the anticonvulsant:* ↓ Daclatasvir	Coadministration of MyDekla 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 MyDekla 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)	The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
	CYP3A4 inhibition by ketoconazole	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 MyDekla 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 MyDekla 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	
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 MyDekla. The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Amiodarone	Interaction not studied.	Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with MyDekla in combination with sofosbuvir (see sections 4.4 and 4.8).
Calcium channel blockers		
Diltiazem **Nifedipine** **Amlodipine**	Interaction not studied. *Expected due to CYP3A4 inhibition by the calcium channel blocker:* ↑ Daclatasvir	Caution is advised if MyDekla is coadministered with calcium channel blockers.
Verapamil	Interaction not studied. *Expected due to CYP3A4 and P-gp inhibition by verapamil:* ↑ Daclatasvir	Caution is advised if MyDekla is coadministered with calcium channel blockers.
CORTICOSTEROIDS		
Systemic dexamethasone	Interaction not studied. *Expected due to CYP3A4 induction by dexamethasone:* ↓ Daclatasvir	Coadministration of MyDekla with systemic dexamethasone or other strong inducers of CYP3A4 is contraindicated (see section 4.3).

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
HERBAL SUPPLEMENTS		
St. John's wort *(Hypericum perforatum)*	Interaction not studied. *Expected due to CYP3A4 induction by St. John's wort:* ↓ Daclatasvir	Coadministration of MyDekla 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)	If an oral contraceptive is needed during treatment with MyDekla, it should contain ethinylestradiol 35 µg and norgestimate 0.180/0.215/0.250 mg. Other oral contraceptives have not been studied.
IMMUNOSUPPRESSANTS		
Cyclosporine 400 mg single dose (daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.40 (1.29, 1.53) C_{max}: 1.04 (0.94, 1.15) C_{min}: 1.56 (1.41, 1.71) ↔ Cyclosporine AUC: 1.03 (0.97, 1.09) C_{max}: 0.96 (0.91, 1.02)	No dose adjustment of either medicinal product is required when MyDekla 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 MyDekla 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	
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	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↑ Buprenorphine AUC: 1.37 (1.24, 1.52)	No dose adjustment of MyDekla or buprenorphine may be required, but it is recommended that patients should be monitored for signs of opiate toxicity.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning coadministration
buprenorphine/naloxone maintenance therapy.	C_{max}: 1.30 (1.03, 1.64) C_{min}: 1.17 (1.03, 1.32) ↑ Norbuprenorphine AUC: 1.62 (1.30, 2.02) C_{max}: 1.65 (1.38, 1.99) C_{min}: 1.46 (1.12, 1.89) *Compared to historical data.	
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 MyDekla 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 MyDekla.
Triazolam **Alprazolam**	Interaction not studied. *Expected:* ↔ Triazolam ↔ Alprazolam	

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential

Pregnancy should be avoided in women treated with daclatasvir. Use of highly effective contraception should be continued for 5 weeks after completion of therapy with MyDekla (see section 4.5)

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.

MyDekla 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 therapy with (see section 4.5).

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

Breastfeeding

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 MyDekla.

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

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of daclatasvir is based on data from 476 patients with chronic HCV infection who received daclatasvir once daily in combination with sofosbuvir.

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

Tabulated list of adverse reactions

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

Table 5: Adverse reactions in clinical studies

System Organ Class	Adverse Reactions
Psychiatric disorders	
Common	insomnia
Nervous system disorders	
Very common	Headache
Common	dizziness, migraine
Gastrointestinal disorders	
Common	nausea, diarrhoea, abdominal pain
Musculoskeletal and connective tissue disorders	
Very common	arthralgia, myalgia
General disorders and administration site conditions	
Very common	fatigue

Laboratory abnormalities

Grade 3/4 increases in total bilirubin were observed in 5% of patients (all in patients with HIV coinfection who were receiving concomitant atazanavir, with Child-Pugh A, B, or C cirrhosis, or who were post-liver transplant).

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when daclatasvir is used in combination with sofosbuvir and concomitant amiodarone and/or other drugs that lower the heart rate (see sections 4.4 and 4.5).

Paediatric population

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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

There is limited experience of accidental overdose of daclatasvir in clinical studies. In phase 1 clinical studies, healthy subjects who received up to 100 mg once daily for up to 14 days or single doses up to 200 mg had no unexpected adverse reactions.

Treatment

There is no known antidote for overdose of daclatasvir. Treatment of overdose with daclatasvir should consist of general supportive measures, including monitoring of vital signs, and observation of the patient's clinical status. Because daclatasvir is highly protein bound (99%) and has a molecular weight >500, dialysis is unlikely to significantly reduce plasma concentrations of daclatasvir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Daclatasvir is an inhibitor of non-structural 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.

Clinical efficacy and safety

A WHO-commissioned systematic review identified 142 clinical studies that evaluated the safety and efficacy of various FDA- and EMA-approved DAA regimens, including sofosbuvir/daclatasvir.

Sofosbuvir/daclatasvir in HCV infected adults without cirrhosis:

In a combined analysis of treatment-naïve and treatment-experienced persons treated with sofosbuvir/daclatasvir, the pooled SVR rates exceeded 92% for infection with genotypes 1, 2, 3 and 4. Data from an observational study (MSF demonstration project) provided information on the less commonly reported genotypes 5 and 6. A total of eight persons with genotype 5 and 123 persons with genotype 6 infection were treated with sofosbuvir/daclatasvir for 12 weeks. SVR rates were 88% and 94% for genotypes 5 and 6 respectively.

Sofosbuvir/daclatasvir in HCV infected adults with compensated cirrhosis:

In a combined analysis of treatment-naive and treatment-experienced persons with compensated cirrhosis (Child Pugh A or B) treated with sofosbuvir/daclatasvir for 12 weeks, the pooled SVR rates exceeded 93% for infection with genotypes 1 and 2. SVR rates for infection with genotype 3 were low, ranging from 79% to 82%. However, after 24 weeks of treatment, SVR rates increased to 90%. Data from an observational study (MSF demonstration project) provided information on genotypes 5 and 6, and real-world data from Egypt provided information on genotype 4. One cirrhotic person with genotype 5 infection treated with sofosbuvir/daclatasvir for 12 weeks reached SVR. Among 185 cirrhotic persons with genotype 6 infection treated with sofosbuvir/daclatasvir for 12 weeks, 92% reached SVR. Cirrhotic persons with genotype 4 infection had SVR rates that exceeded 98% after 12 weeks of treatment.

Sofosbuvir/daclatasvir in HCV infected adults with decompensated cirrhosis:

There are currently insufficient data to provide definitive treatment guidelines for HCV infected adults with decompensated cirrhosis (Child Pugh C). It is recommended that such individuals are

treated with sofosbuvir/daclatasvir for 24 weeks using the same regimen as used for individuals with compensated cirrhosis.

HCV/HIV co-infection

HCV treatment outcomes with daclatasvir/sofosbuvir are comparable in persons with HIV/HCV coinfection to those with HCV monoinfection. Because DAAs are safe and effective for people with HIV/HCV, there is no longer any need to consider them as a special or difficult-to-treat population. However, there are important DDIs (drug-drug interactions) with pangenotypic HCV regimens and antiretroviral therapies for HIV. Therefore, checking for DDIs between HCV and HIV medications should be emphasized. The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See Section 4-5.

Safety of sofosbuvir/daclatasvir

Treatment discontinuation due to adverse events was very low in persons without and with cirrhosis (<1%). Similar results were observed in treatment-naive and treatment-experienced persons.

Long term efficacy data

In a follow-up study of 258 patients who achieved SVR12 with daclatasvir and sofosbuvir with a median duration of post-SVR12 follow-up of 38 months, no relapses occurred (with relapses defined as confirmed or last available HCV RNA ≥ LLOQ).

Impact of baseline NS5A RAVs on cure rates

Baseline NS5A resistance-associated variants (RAVs) had no major impact on cure rates in patients treated with sofosbuvir + daclatasvir, with the exception of the Y93H RAV in genotype 3 infection (seen in 16/192 [8%] of patients). The SVR12 rate in genotype-3 infected patients with this RAV is reduced (in practice as relapse after end of treatment response), especially in patients with cirrhosis. The overall cure rate for genotype-3 infected patients who were treated for 12 weeks with sofosbuvir + daclatasvir in the presence and absence of the Y93H RAV was 7/13 (54%) and 134/145 (92%), respectively.

Paediatric population

No data are available on the safety and efficacy of daclatasvir in children and adolescents aged below 18 years (see section 4.2).

5.2 Pharmacokinetic properties

The absorption characteristics of MyDekla have been determined after administration of one daclatasvir (as dihydrochloride) 60 mg tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**
	Daclatasvir
Maximum concentration (C_{max})	2.003 ± 0.492 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	21.786 ± 6.287 µg.h/mL
Time to attain maximum concentration (T_{max})	1.28 ± 0.54 h

*arithmetic mean

Pharmacokinetics of daclatasvir

	Daclatasvir
General	
	The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in patients with chronic HCV.
Absorption	
Absolute bioavailability	The absolute bioavailability of the tablet formulation is 67%.

<table>
<tr><td>Oral bioavailability</td><td>At least 67%.</td></tr>
<tr><td>Food effect</td><td>
<table>
<tr><th></th><th>$AUC_{(0-\infty)}$</th><th>C_{max}</th><th>T_{max}</th></tr>
<tr><td>With high-fat meal</td><td>23%↓</td><td>28%↓</td><td>NA*</td></tr>
<tr><td>With light meal</td><td>No change</td><td>No change</td><td>NA*</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of distribution (mean)</td><td>Approximately 47 L.</td></tr>
<tr><td>Plasma protein binding</td><td>Approximately 99% (independent of dose between 1 mg to 100 mg)</td></tr>
<tr><td>Tissue distribution</td><td>Active and passive transport into hepatocytes.</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td></td><td>Substrate of CYP3A with CYP3A4 being the major isoform responsible for metabolism.</td></tr>
<tr><td>Active metabolite(s)</td><td>None.</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>General note</td><td>Daclatasvir is mainly cleared by the liver.</td></tr>
<tr><td>Elimination half life</td><td>12 to 15 h</td></tr>
<tr><td>Mean systemic clearance (Cl/F)</td><td>4.24 L/h</td></tr>
<tr><td>% of dose excreted in urine</td><td>6.6% (primarily as unchanged drug)</td></tr>
<tr><td>% of dose excreted in faeces</td><td>88% (53% as unchanged drug)</td></tr>
<tr><td>Pharmacokinetic linearity</td><td>Daclatasvir C_{max}, AUC and C_{min} increase in a near dose-proportional manner</td></tr>
<tr><td>Drug interactions (in vitro)</td><td>NA*</td></tr>
<tr><td>Transporters</td><td>In vitro and in vivo studies showed that daclatasvir is a substrate of P-gp. Daclatasvir is an inhibitor of P-gp, OATP 1B1 and BCRP.
Active transport into hepatocytes by OCT1 and other unidentified uptake transporters.
In vitro daclatasvir is an inhibitor of renal uptake transporters, OAT1 and 3, and OCT2, but is not expected to have a clinical effect on the pharmacokinetics of substrates of these transporters.</td></tr>
<tr><td>Metabolizing enzymes</td><td>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. Daclatasvir in vitro did not inhibit CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6.</td></tr>
</table>

*Information not available

Pharmacokinetics in special clinical situations:

Renal impairment

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

Hepatic impairment

The pharmacokinetics of daclatasvir following a single 30 mg oral dose were studied in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with unimpaired subjects. The C_{max} and AUC of total daclatasvir

(free and protein-bound drug) were lower in subjects with hepatic impairment; however, hepatic impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir.

Elderly

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

Paediatric population

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

Gender

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

Race

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

5.3 Preclinical safety data

General toxicity

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.

Mutagenicity/ Carcinogenicity

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.

Reproductive toxicity

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.

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 nor the

number of viable conceptuses sired. The AUC associated with this dose in males is 19-fold the clinical AUC exposure.
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

Core tablet:
Anhydrous lactose
Silicified microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Colloidal anhydrous silica

Film coat:
Hypromellose
Titanium dioxide
Macrogol
Iron oxide yellow
FD&C blue #2 / Indigo carmine aluminium lake

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Round, blue, opaque high density polyethylene (HDPE) bottle with a blue, opaque polypropylene screw cap or child-resistant closure, with wad containing aluminium induction sealing liner.

Pack size: 28 tablets.

6.6 Instructions for use, handling and disposal

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

7. SUPPLIER

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Telangana
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8. DATE OF REVISION OF THE TEXT

October 2023

References

General:

Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection, Section 4.2.1: July 2018

https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf

European SmPC (2014)

https://www.ema.europa.eu/en/documents/product-information/daklinza-epar-product-information_en.pdf

Section 4.5

University of Liverpool, HEP and HIV Drug interactions, available at:

http://www.hep-druginteractions.org

http://www.hiv-druginteractions.org

All web links last accessed 23rd February 2020.

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/ .