WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HP025 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 60 mg daclatasvir (as dihydrochloride) and 400 mg sofosbuvir.

Each tablet contains about 300 mg anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Peach-coloured, modified, capsule-shaped, biconvex, bevelled-edge film-coated tablet debossed with 'M' on one side and 'DTS' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HP025 trade name] is indicated 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

[HP025 trade name] treatment should be initiated and monitored by a health care provider experienced in the management of patients with chronic hepatitis C infection.

Posology

[HP025 trade name] should be taken once daily with food. The tablet should be taken whole and should not be crushed or chewed as they have an unpleasant bitter taste.

Table 1: Recommended treatment for daclatasvir/sofosbuvir 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 modification for concomitant medications

Strong inhibitors of cytochrome CYP3A4

The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4. [HP025 trade name] 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.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

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 [HP025 trade name]. Daclatasvir 30 mg tablets should be used. See section 4.5.

Missed doses

Patients should be instructed that, if they miss a dose of [HP025 trade name], the dose should be taken as soon as possible if remembered within 18 hours of the scheduled dose time. However, if the missed dose is remembered more than 18 hours after the scheduled dose, the dose should be skipped, and the next dose taken at the appropriate time. Patients should be instructed not to take a double dose.

Special populations

Elderly

No dose adjustment of [HP025 trade name] is required for patients aged ≥ 65 years (see section 5.2).

Renal impairment

No dose adjustment of [HP025 trade name] is required for patients with mild or moderate renal impairment.

There are limited data on the safety of sofosbuvir in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease requiring hemodialysis (see section 5.2). [HP025 trade name] may be used with no dose adjustment in these patients when no other treatment options are available.

Hepatic impairment

No dose adjustment of [HP025 trade name] is required for patients with any degree of hepatic impairment (see sections 4.4 and 5.2). The safety and efficacy of [HP025 trade name] have not been established in patents with decompensated cirrhosis.

Patients awaiting liver transplantation

The duration of administration of [HP025 trade name] in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient (see section 5.1).

Paediatric population

[HP025 trade name] is not indicated for the treatment of patients aged less than 18 years. Other combination therapies should be used.

4.3 Contraindications

[HP025 trade name] should not be given to patients with hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

[HP025 trade name] 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 [HP025 trade name]. 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

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 during the clinical development of sofosbuvir plus direct-acting antivirals (DAAs). Cases are potentially life threatening; therefore, amiodarone should only be used in patients taking [HP025 trade name] 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 [HP025 trade name]. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical

setting, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first two weeks of treatment.

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 [HP025 trade name].

All patients receiving [HP025 trade name] 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.

Pregnancy and contraception requirements

[HP025 trade name] 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 [HP025 trade name] therapy (see section 4.6).

Use in patients with diabetes

Patients with diabetes 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.

Renal impairment

There are limited safety data for the use of sofosbuvir in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and end stage renal disease requiring haemodialysis. [HP025 trade name] may be used in these patients with no dose adjustment when no other relevant treatment options are available.

Excipients

[HP025 trade name] contains lactose. 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 excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications to concomitant use (see section 4.3)

Daclatasvir/sofosbuvir is contraindicated in combination with medicinal products that strongly induce CYP3A4 and P-gp, including, but not limited to phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, rifapentine, systemic dexamethasone, and the herbal product St John's wort *(Hypericum perforatum)*. These products may lead to lower exposure and loss of efficacy of [HP025 trade name].

Potential for interaction with other medicinal products

- Daclatasvir is a substrate of CYP3A4, P-gp and organic cation transporter (OCT) 1.
- Sofosbuvir is a substrate of P-gp and breast cancer resistance protein (BCRP).

Co-administration of [HP025 trade name] with strong inducers of CYP3A4 and P-gp is contraindicated as they may decrease the plasma levels and therapeutic effect of [HP025 trade name].

Co-administration of [HP025 trade name] with moderate inducers of CYP3A4 and P-gp is not recommended because the required dose adjustment for daclatasvir cannot be made with [HP025 trade name] (see Table 2).

Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir and should not be coadministered with [HP025 trade name] because the required dose adjustment for daclatasvir cannot be made.

Medicinal products that are moderate P-gp inducers in the intestine (e.g., oxcarbazepine and modafinil) may decrease sofosbuvir plasma concentrations leading to reduced therapeutic effect of [HP025 trade name]. Co-administration of [HP025 trade name] with such medicinal products is not recommended (see section 4.4).

Patients treated with vitamin K antagonists

As liver function may change during treatment with [HP025 trade name], close monitoring of International Normalised Ratio (INR) values is recommended.

Tabulated summary of interactions

Table 2 provides information from drug interaction studies with daclatasvir and sofosbuvir 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 "↔". The studies presented in Table 2 were conducted in healthy adult subjects unless otherwise noted. The table is not all-inclusive.

Table 2: Interactions between daclatasvir/sofosbuvir and other medicinal products

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANALEPTICS		
Modafinil	Interaction not studied. *Expected:* ↓ Daclatasvir ↓ Sofosbuvir ↔ GS-331007	Co-administration of [HP025 trade name] with modafinil is not recommended.
ANTIVIRALS, HCV		
Sofosbuvir 400 mg once daily Study conducted in patients with chronic HCV infection	↔ Daclatasvir ↔ GS-331007 (major metabolite of sofosbuvir)	No dose adjustment of daclatasvir or sofosbuvir is required.
Elbasvir/grazoprevir	Interaction not studied.	Elbasvir/grazoprevir is a complete regimen. There are no data to support the coadministration with another NS5A agent such as daclatasvir
Glecaprevir/pibrentasvir	Interaction not studied	Glecaprevir/pibrentasvir is a complete regimen. There are no data to support the coadministration with another NS5A agent such as daclatasvir.
ANTIVIRALS, HIV or HBV		
Protease inhibitors (PIs)		
Atazanavir 300 mg/ritonavir 100 mg once daily	↑ Daclatasvir ↔ Sofosbuvir (expected) CYP3A4 inhibition by ritonavir	Coadministration of [HP025 trade name] with atazanavir/ritonavir, atazanavir/cobicistat or other strong inhibitors of CYP3A4 is not recommended.
Darunavir 800 mg/ritonavir 100 mg once daily	↑ Daclatasvir ↑ Sofosbuvir ↔ Darunavir	No dose adjustment of [HP025 trade name] or darunavir/ritonavir is required
Darunavir/cobicistat	Interaction not studied. *Expected:* ↑ Daclatasvir	No dose adjustment of [HP025 trade name], or darunavir/cobicistat is required
Lopinavir 400 mg/ritonavir 100 mg twice daily	↔ Daclatasvir ↔ Sofosbuvir ↔ Lopinavir	No dose adjustment of [HP025 trade name] or lopinavir/ritonavir is required.
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil 245 mg once daily	↔ Daclatasvir ↔ Sofosbuvir (expected) ↔ Tenofovir	No dose adjustment of [HP025 trade name] or tenofovir disoproxil is required.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Tenofovir alafenamide	Interaction not studied *Expected:* ↔ Daclatasvir ↔ Sofosbuvir ↔ Tenofovir	No dose adjustment of [HP025 trade name] or tenofovir alafenamide is required.
Lamivudine **Zidovudine** **Emtricitabine** **Abacavir** **Didanosine** **Stavudine**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Sofosbuvir ↔ NRTI	No dose adjustment of [HP025 trade name] or the NRTI is required.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily	↓ Daclatasvir ↓ Sofosbuvir Induction of CYP3A4 by efavirenz	Coadministration of [HP025 trade name] with efavirenz is not recommended.
Etravirine **Nevirapine**	Interaction not studied. *Expected due to CYP3A4 induction by etravirine or nevirapine:* ↓ Daclatasvir	Due to the lack of data, co-administration of [HP025 trade name] and etravirine or nevirapine is not recommended.
Rilpivirine	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Sofosbuvir ↔ Rilpivirine	No dose adjustment of [HP025 trade name] or rilpivirine is required.
Integrase inhibitors		
Dolutegravir 50 mg once daily	↔ Daclatasvir ↔ Sofosbuvir (expected) ↑ Dolutegravir Inhibition of P-gp and BCRP by daclatasvir	No dose adjustment of [HP025 trade name] or dolutegravir is required.
Raltegravir	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Sofosbuvir ↔ Raltegravir	No dose adjustment of [HP025 trade name] or raltegravir is required.
Pharmacokinetic enhancer		
Cobicistat-containing regimen	Interaction not studied *Expected due to CYP3A4 inhibition by cobicistat:* ↑ Daclatasvir ↔ Sofosbuvir	Coadministration of [HP025 trade name] with cobicistat or other strong inhibitors of CYP3A4 is not recommended.
ACID REDUCING AGENTS		
H_2-receptor antagonists		
Famotidine 40 mg single dose	↔ Daclatasvir ↔ Sofosbuvir (expected)	No dose adjustment of [HP025 trade name] is required.
Proton pump inhibitors		
Omeprazole 40 mg once daily	↔ Daclatasvir ↔ Sofosbuvir (expected)	No dose adjustment of [HP025 trade name] is required.
ANTIBACTERIALS		
Clarithromycin	Interaction not studied.	Coadministration of [HP025 trade

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Telithromycin	*Expected due to CYP3A4 inhibition by the antibacterial:* ↑ Daclatasvir ↔ Sofosbuvir (expected)	name] is not recommended with clarithromycin, telithromycin or other strong inhibitors of CYP3A4.
Erythromycin	Interaction not studied. *Expected due to CYP3A4 inhibition by the antibacterial:* ↑ Daclatasvir ↔ Sofosbuvir (expected)	Coadministration of erythromycin with [HP025 trade name] may result in increased concentrations of daclatasvir. Caution is advised.
Azithromycin **Ciprofloxacin**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Sofosbuvir ↔ Azithromycin or Ciprofloxacin	No dose adjustment of [HP025 trade name] or azithromycin or ciprofloxacin is required.
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied. *Expected due to inhibition of P-gp by daclatasvir:* ↑ Dabigatran etexilate ↔ Sofosbuvir (expected)	Safety monitoring is advised when initiating treatment with [HP025 trade name] 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 ↔ Sofosbuvir ↔ Warfarin	No dose adjustment of [HP025 trade name] or warfarin is required. Close monitoring of INR values is recommended with all vitamin K antagonists. This is because liver function may change during treatment with daclatasvir.
ANTICONVULSANTS		
Carbamazepine **Oxcarbazepine** **Phenobarbital** **Phenytoin**	Interaction not studied. *Expected due to CYP3A4 and P-gp induction by the anticonvulsant:* ↓ Daclatasvir ↓ Sofosbuvir	Co-administration of [HP025 trade name] 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 ↔ Sofosbuvir (expected) ↔Escitalopram	No dose adjustment of [HP025 trade name] or escitalopram is required.
ANTIFUNGALS		
Ketoconazole 400 mg once daily	↑ Daclatasvir ↑ Sofosbuvir (expected)	Coadministration of [HP025 trade name] with ketoconazole or other strong inhibitors of CYP3A4 is not recommended.
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 ↔ Sofosbuvir ↔ Fluconazole	Modest increases in concentrations of daclatasvir are expected, but no dose adjustment of [HP025 trade name] or fluconazole is required.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTIMYCOBACTERIALS		
Rifampicin 600 mg once daily	↓ Daclatasvir ↓ Sofosbuvir (expected)	Co-administration of [HP025 trade name] 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 and P-gp induction by the antimycobacterial:* ↓ Daclatasvir ↓ Sofosbuvir (expected)	
CARDIOVASCULAR AGENTS		
Antiarrhythmics		
Digoxin 0.125 mg once daily	↑ Digoxin P-gp inhibition by daclatasvir	Digoxin should be used with caution when co-administered with [HP025 trade name]. 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 coadministered with [HP025 trade name] (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 ↔ Sofosbuvir	Caution is advised if [HP025 trade name] is co-administered with calcium channel blockers.
Verapamil	Interaction not studied. *Expected due to CYP3A4 and P-gp inhibition by verapamil:* ↑ Daclatasvir ↔ Sofosbuvir	Caution is advised if [HP025 trade name] is co-administered with calcium channel blockers.
CORTICOSTEROIDS		
Systemic dexamethasone	Interaction not studied. *Expected due to CYP3A4 induction by dexamethasone:* ↓ Daclatasvir ↓ Sofosbuvir	Co-administration of [HP025 trade name] 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 ↓ Sofosbuvir	Co-administration of [HP025 trade name] 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	↔ Ethinylestradiol ↔ Norelgestromin ↔ Norgestrel	If an oral contraceptive is needed during treatment with [HP025 trade name], it should contain ethinylestradiol 35 µg and

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
		norgestimate 0.180/0.215/0.250 mg. Other oral contraceptives have not been studied.
IMMUNOSUPPRESSANTS		
Cyclosporine 400 mg single dose	↔ Daclatasvir ↔ Sofosbuvir ↔ Cyclosporine	No dose adjustment of either medicinal product is required when [HP025 trade name] is co-administered with cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil.
Tacrolimus 5 mg single dose	↔ Daclatasvir ↔ Sofosbuvir ↔ Tacrolimus	
Sirolimus **Mycophenolate mofetil**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Sofosbuvir ↔ Immunosuppressant	
LIPID LOWERING AGENTS		
HMG-CoA reductase inhibitors		
Rosuvastatin 10 mg single dose	↑ Rosuvastatin *Inhibition of OATP1B1 and BCRP by daclatasvir*	Caution should be used when [HP025 trade name] is co-administered 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* *** Evaluated in opioid-dependent adults on stable buprenorphine/naloxone maintenance therapy**	↔ Daclatasvir ↔ Sofosbuvir ↔ Buprenorphine ↔ Norbuprenorphine	No dose adjustment of [HP025 trade name] or buprenorphine is required, but it is recommended that patients should be monitored for signs of opiate toxicity.
Methadone, 40-120 mg once daily individualized dose*	↔ Daclatasvir ↔ Sofosbuvir ↔ R-methadone	No dose adjustment of [HP025 trade name] or methadone is required.
SEDATIVES		
Benzodiazepines		
Midazolam 5 mg single dose	↔ Midazolam	No dose adjustment of midazolam or other benzodiazepines is required when co-administered with [HP025 trade name].
Triazolam **Alprazolam**	Interaction not studied. *Expected:* ↔ Triazolam ↔ Alprazolam	

No clinically relevant effect on the pharmacokinetics of either medicinal product is expected when daclatasvir is co-administered 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/sofosbuvir. Use of highly effective contraception should be continued for 5 weeks after completion of therapy with [HP025 trade name] (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.

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir in pregnant women.

Animal studies do not indicate direct or indirect harmful effects from sofosbuvir with respect to reproductive toxicity. No effects on fetal development have been observed in rats and rabbits at the highest doses tested. However, it has not been possible to fully estimate exposure margins achieved for sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose (see section 5.3).

[HP025 trade name] should not be used during pregnancy or in women of childbearing potential who are not using contraception (see section 4.4). Use of highly effective contraception should be continued for 5 weeks after completion of therapy (see section 4.5).

Breastfeeding

It is not known whether daclatasvir, sofosbuvir or their metabolites are 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 [HP025 trade name].

Fertility

No human data on the effect of daclatasvir and sofosbuvir 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.

If affected, this may influence a patient's ability to drive and use machines.

4.8 Undesirable effects

The overall safety profile of [HP025 trade name] 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 treatment for adverse events, only one of which was considered related to study therapy.

Adverse reactions attributable to daclatasvir/sofosbuvir are listed below by system organ class and frequency: very common (≥ 1/10), or common (≥ 1/100 to < 1/10).

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	
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).

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/sofosbuvir in children and adolescents aged <18 years have not yet been established.

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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

There is limited experience of accidental overdose of daclatasvir/sofosbuvir. Healthy subjects who received up to 100 mg daclatasvir once daily for up to 14 days or single doses of daclatasvir up to 200 mg had no unexpected adverse reactions. Healthy subjects who received a single dose of 1,200 mg sofosbuvir had no unexpected adverse reactions.

There is no known antidote for overdose of daclatasvir/sofosbuvir. Treatment of overdose 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. Haemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007. A 4-hour haemodialysis session removed 18% of the administered dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Daclatasvir

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.

Sofosbuvir

Pharmacotherapeutic group: Direct-acting antiviral; ATC code: J05AP08

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 (the active metabolite of sofosbuvir) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Clinical efficacy and safety

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 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 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 managed by a specialist.

HCV/HIV co-infection

HCV treatment outcomes with daclatasvir/sofosbuvir are comparable in persons with HIV/HCV coinfection to those with HCV monoinfection. 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.

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.

5.2 Pharmacokinetic properties

Absorption of [HP025 trade name]

The absorption characteristics of [HP025 trade name] have been determined after administration of a single dose tablet in healthy subjects in the fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**	
	Daclatasvir	**Sofosbuvir**
Maximum concentration (C_{max})	1545 ± 421 ng/mL	1816 ± 848 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	18258 ± 5889 ng·h/mL	2045 ± 829 ng·h/mL
Time to attain maximum concentration (Tmax)	1.65 ± 0.79 hours	1.00 ± 0.70 hours

Pharmacokinetics of daclatasvir and sofosbuvir

	Daclatasvir	**Sofosbuvir**
General		
	The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in patients with chronic HCV.	Sofosbuvir is a nucleotide prodrug that is extensively metabolised.
Absorption		
Absolute bioavailability	The absolute bioavailability of the tablet formulation is 67%.	NA*
Oral Bioavailability	At least 67%.	At least 82.5%.
Food effect	<table><tr><th></th><th>$AUC_{(0-\infty)}$</th><th>C_{max}</th><th>T_{max}</th></tr><tr><td>High fat</td><td>23%↓</td><td>28%↓</td><td>NA*</td></tr><tr><td>Light meal</td><td>↔</td><td>↔</td><td>NA*</td></tr></table>	<table><tr><th></th><th>$AUC_{(0-\infty)}$</th><th>C_{max}</th><th>T_{max}</th></tr><tr><td>High fat:</td><td>180%↑</td><td>↔</td><td>↓</td></tr></table>
Distribution		
General note		
Volume of distribution (mean)	Approximately 47 L.	NA*
Plasma protein binding *in vitro*	Approximately 99% (independent of dose between 1 mg to 100 mg)	85% (*ex vivo data*) Binding is independent of drug concentration over the range of 1 to 20 μg/mL.
Tissue distribution	Active and passive transport into hepatocytes.	No human data available. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.
Metabolism		
	Substrate of CYP3A with CYP3A4 being the major isoform responsible for metabolism.	The active triphosphate metabolite GS-461203 is formed in the liver by extensive metabolism via sequential hydrolysis (Cat A or CES1) and phosphoramidate cleavage (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of the inactive nucleoside metabolite GS-331007. Sofosbuvir and GS-331007 are not substrates of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes
Active metabolite(s)	None	The active metabolite GS-461203 is formed in hepatocytes

		and not observed in plasma.
Elimination		
General note	Mainly cleared by the liver.	
Elimination half life	12 to 15 hours	Sofosbuvir 0.4 hours
Means systemic clearance (Cl/F)	4.24 L/hr	NA*
% of dose excreted in urine	6.6% (primarily as unchanged drug)	80% (3.5% as sofosbuvir)
% of dose excreted in faeces	88% (53% as unchanged drug)	14%
Pharmacokinetic linearity	C_{max}, AUC and C_{min} increase in a near dose-proportional manner	AUC is near dose proportional over the dose range of 200 mg to 400 mg (in fasted healthy subjects)
Drug interactions *(in vitro)*	NA*	NA*
Transporters	Substrate of P-gp. Inhibitor of P-gp, OATP 1B1 and BCRP (in vitro and in vivo) Active transport into hepatocytes by OCT1 and other unidentified uptake transporters. Inhibitor of renal uptake transporters, OAT1 and 3, and OCT2, (in vitro) but not expected to have a clinical effect on the pharmacokinetics of substrates of these transporters.	Substrate of P-gp and BCRP
Metabolising enzymes	Substrate of CYP3A, with CYP3A4 being the major CYP isoform responsible for the metabolism (in vitro and in vivo) Not an inhibitor of CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 (in vitro)	Substrate for CatA and CES1, followed by HINT1, however no interaction in vivo is expected involving this pathway.

Renal impairment

Daclatasvir:

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.

Sofosbuvir:

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥50 and <80 mL/min/1.73 m^2), moderate (eGFR ≥30 and <50 mL/min/1.73 m^2), severe renal impairment (eGFR <30 mL/min/1.73 m^2) and subjects with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR >80 mL/min/1.73 m^2), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir $AUC_{0\text{-}inf}$ was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when sofosbuvir was dosed 1 hour after haemodialysis. The $AUC_{0\text{-}inf}$ of GS-331007 in subjects with ESRD could not be reliably determined. However, data indicate at

least 10-fold and 20-fold higher exposure to GS-331007 in ESRD compared to normal subjects when sofosbuvir was administered 1 hour before or 1 hour after haemodialysis, respectively.

Haemodialysis can efficiently remove the predominant circulating metabolite GS-331007. A 4-hour haemodialysis session removed approximately 18% of administered dose.

Hepatic impairment

Daclatasvir:

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.

Sofosbuvir:

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV infected subjects with moderate and severe hepatic impairment (CPT class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV infected subjects indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate, and severe hepatic impairment (see section 4.2).

Elderly population

Population pharmacokinetic analysis of data from clinical studies indicated that age had no apparent effect on the pharmacokinetics of daclatasvir, sofosbuvir or GS-331007.

Paediatric population

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

Sofosbuvir and GS-331007 exposures in adolescents aged 12 to <18 years were similar to those in adults from Phase 2/3 studies following administration of sofosbuvir (400 mg). The pharmacokinetics of sofosbuvir and GS-331007 have not been established in paediatric patients < 12 years of age.

Race and gender

No clinically relevant pharmacokinetic differences due to race or gender have been identified for daclatasvir, sofosbuvir or GS-331007.

5.3 Preclinical safety data

Daclatasvir

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 embryofetal lethality, reduced fetal body weights and increased incidence of fetal 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.

Sofosbuvir

In repeat dose toxicology studies in rat and dog, high doses of the 1:1 diastereomeric mixture caused adverse liver (dog) and heart (rat) effects and gastrointestinal reactions (dog). Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity; however, exposure to the major metabolite GS-331007 at the adverse dose was 29 times (rat) and 123 times (dog) higher than the clinical exposure at 400 mg sofosbuvir. No liver or heart findings were observed in chronic toxicity studies at exposures 9 times (rat) and 27 times (dog) higher than the clinical exposure.

Mutagenicity/ Carcinogenicity

Sofosbuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* mouse micronucleus assays.

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 600 mg/kg/day in mouse and 750 mg/kg/day in rat. Exposure to GS-331007 in these studies was up to 30 times (mouse) and 15 times (rat) higher than the clinical exposure at 400 mg sofosbuvir.

Reproductive toxicity

Sofosbuvir had no effects on embryo-fetal viability or on fertility in rat and was not teratogenic in rat and rabbit development studies. No adverse effects on behaviour, reproduction or development of offspring in rat were reported. In rabbit studies exposure to sofosbuvir was 9 times the expected clinical exposure. In the rat studies, exposure to sofosbuvir could not be determined but exposure margins based on the major human metabolite ranged from 8 to 28 times higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir-derived material was transferred through the placenta in pregnant rats and into the milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core tablet: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate.
Film coat: polyvinyl alcohol partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol, talc iron oxide yellow, iron oxide red and iron oxide black

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 HDPE bottle with either a blue opaque polypropylene screw or child resistant cap.
Pack sizes: 28 tablets

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed off in accordance with local requirements.

7. SUPPLIER

Mylan Laboratories Limited
Plot No.564/A/22, Road No. 92, Jubilee Hills
Hyderabad – 500096
Telangana
India
E-mail: Imtiyaz.Basade@viatris.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HP025

9. DATE OF PREQUALIFICATION

27 October 2020

10. DATE OF REVISION OF THE TEXT

February 2021

References

Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version April 2016, available at:
http://apps.who.int/iris/bitstream/handle/10665/205035/9789241549615_eng.pdf;jsessionid=F890AC78D569AB632C49293BFC910732?sequence=1

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

European SmPC Sovaldi, available at:
https://www.ema.europa.eu/en/documents/product-information/sovaldi-epar-product-information_en.pdf

University of Liverpool, HEP and HIV Drug interactions, available at:
http://www.hep-druginteractions.org
http://www.hiv-druginteractions.org

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines