MyHep DVIR
(Daclatasvir and Sofosbuvir Film-Coated Tablets 60mg/400 mg)

1. NAME OF THE MEDICINAL PRODUCT

Daclatasvir and Sofosbuvir Film-Coated Tablets 60mg/400 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Daclatasvir Dihydrochloride equivalent to Daclatasvir……. 60 mg
Sofosbuvir…….. 400 mg

Excipient(s) with known effect:

Each film-coated tablet contains 300 mg of lactose (as anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Peach colored, modified capsule shaped, biconvex beveled edge film-coated tablet debossed with "M" on one side and "DTS" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Daclatasvir and Sofosbuvir Film-Coated Tablets 60mg/400 mg is indicated in treatment of chronic hepatitis C (CHC) 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

Daclatasvir and Sofosbuvir Film-Coated Tablets 60mg/400 mg should be initiated and monitored by a health care provider experienced in the management of chronic hepatitis C.

Posology

The recommended dose of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets is one tablet, taken orally, once daily with food (see section 5.2).

Table 1: Recommended regimens and treatment duration for Daclatasvir/Sofosbuvir 60 mg/400 mg tablets

Patient population[1]	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

GT: Genotype; CP: Child Pugh

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

Dose modification

Dose modification of the fixed dose combination Daclatasvir/Sofosbuvir 60 mg/400 mg tablets to manage adverse reactions is not recommended.

Ribavirin Dosing Guidelines

Table 2 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 2: Ribavirin dose modification guideline for co-administration with sofosbuvir

Laboratory values	Reduce ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Haemoglobin in subjects with no cardiac disease	<10 g/dL	<8.5 g/dL
Haemoglobin in subjects with history of stable cardiac disease	≥2 g/dL decrease in haemoglobin during any 4 week treatment period	<12 g/dL despite 4 weeks at reduced dose

Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the original assigned dose (1,000 mg to 1,200 mg daily).

Dose recommendation for concomitant medicines

Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)

Daclatasvir/Sofosbuvir 60 mg/400 mg tablets should not be used in combination with strong inhibitors of CYP3A4 since appropriate dose adjustments cannot be made.

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 the Daclatasvir 60 mg/Sofosbuvir 400mg tablets, 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 patient populations

Elderly
No dose adjustment of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets is warranted for elderly patients (see section 5.2).

Renal impairment
No dose adjustment of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets is required for patients with mild or moderate renal impairment. The safety and appropriate dose of Sofosbuvir have not been established in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis (see section 5.2).

Hepatic impairment
No dose adjustment of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C) (see section 5.2). The safety and efficacy of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets have not been established in patients with decompensated cirrhosis.

Paediatric population
The safety and efficacy of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets in children and adolescents aged below 18 years have not yet been established. No data are available.

Patients awaiting liver transplantation
The duration of administration of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets 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).

Method of administration

The film-coated tablet is for oral use. Patients should be instructed to swallow the tablet whole. The film-coated tablet should not be chewed or crushed, due to the bitter taste of the active substance. The tablet should be taken with food (see section 5.2).

Patients should be instructed that if vomiting occurs within 2 hours of dosing an additional tablet should be taken. If vomiting occurs more than 2 hours after dosing, no further dose is needed. These recommendations are based on the absorption kinetics of sofosbuvir and its

predominant inactive metabolite GS-331007 suggesting that the majority of the dose is absorbed within 2 hours after dosing.

4.3 Contraindications

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

Use with potent P-gp inducers

Daclatasvir
Daclatasvir 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 Daclatasvir. 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*).

Sofosbuvir
Medicinal products that are potent P-glycoprotein (P-gp) inducers in the intestine (rifampicin, rifabutin, St. John's wort [*Hypericum perforatum*], carbamazepine, phenobarbital and phenytoin).

Co-administration will significantly decrease Daclatasvir/Sofosbuvir 60 mg/400 mg tablets plasma concentration and could result in loss of efficacy of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets (see section 4.5).

4.4 Special warnings and precautions for use

General

As a fixed combination, Daclatasvir/Sofosbuvir 60 mg/400 mg tablets should not be administered concomitantly with other medicinal products containing the same active components, Daclatasvir or Sofosbuvir.

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/Sofosbuvir 60 mg/400 mg tablets

The efficacy of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets as part of a retreatment regimen in patients with prior exposure to a NS5A inhibitor has not been established.

Pregnancy and contraception requirements

Daclatasvir/Sofosbuvir 60 mg/400 mg tablets 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 Daclatasvir/Sofosbuvir 60 mg/400 mg tablets therapy (see section 4.6).

Interactions with medicinal products

Co-administration of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets can alter the concentration of other medicinal products and other medicinal products may alter the concentration of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets. Refer to section 4.3 for a listing of medicinal products that are contraindicated for use with Daclatasvir/Sofosbuvir 60 mg/400 mg tablets due to potential loss of therapeutic effect. Refer to section 4.5 for established and other potentially significant drug-drug interactions.

Use with moderate P-gp inducers

Medicinal products that are moderate P-gp inducers in the intestine (e.g. oxcarbazepine and modafinil) may decrease Sofosbuvir 400 mg tablets plasma concentration leading to reduced therapeutic effect of Sofosbuvir. Co-administration of such medicinal products is not recommended with Daclatasvir/Sofosbuvir 60 mg/400 mg tablet (see section 4.5).

Renal impairment

The safety of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets has not been assessed in subjects with severe renal impairment (eGFR <30 mL/min/1.73 m2) or ESRD requiring haemodialysis. Furthermore, the appropriate dose has not been established

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

The safety and efficacy of Daclatasvir/Sofosbuvir 60 mg/400 mg tablets in children and adolescents aged <18 years have not yet been established. No data are available.

Important information about some of the ingredients in Daclatasvir/Sofosbuvir 60 mg/400 mg tablets

Daclatasvir/Sofosbuvir 60 mg/400 mg tablets 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

As Daclatasvir/Sofosbuvir 60 mg/400 mg tablets contains Daclatasvir and sofosbuvir, any interactions that have been identified with these active substances individually may occur with Daclatasvir/Sofosbuvir 60 mg/400 mg tablets.

Daclatasvir

Contraindications of concomitant use (see section 4.3)
Daclatasvir 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 Daclatasvir.

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

Daclatasvir is an inhibitor of P-gp, organic anion transporting polypeptide (OATP) 1B1, OCT1 and breast cancer resistance protein (BCRP). Administration of Daclatasvir 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 [HP016 trade name], a close monitoring of International Normalized Ratio (INR) values is recommended.

Sofosbuvir

Sofosbuvir is a nucleotide prodrug. After oral administration of Sofosbuvir, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic and intestinal metabolism. Intracellular hydrolytic prodrug cleavage catalysed by enzymes including carboxylesterase 1 and sequential phosphorylation steps catalysed by nucleotide kinases result in formation of the pharmacologically active uridine nucleoside analogue triphosphate. The predominant inactive circulating metabolite GS-331007 that accounts for greater than 90% of drug-related material systemic exposure is formed through pathways sequential and parallel to formation of active metabolite. The parent sofosbuvir accounts for approximately 4% of drug-related material systemic exposure (see section 5.2). In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not.

Medicinal products that are potent P-gp inducers in the intestine (rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sofosbuvir and thus are contraindicated with Sofosbuvir (see section 4.3). Medicinal products that are moderate P-gp inducers in the intestine (e.g. oxcarbazepine and modafinil) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sofosbuvir. Co-administration with such medicinal products is not recommended with Sofosbuvir (see section 4.4). Co-administration of Sofosbuvir with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus Sofosbuvir may be co-administered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of medicinal products that are substrates of these transporters.

The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low affinity and high capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant medicinal products (see section 5.2).

Other interactions

Drug interaction information for Sofosbuvir & daclatasvir with potential concomitant medicinal products is summarised in Table 3 below (where 90% confidence interval (CI) of the geometric least-squares mean (GLSM) ratio were within "↔", extended above "↑", or extended below "↓" the predetermined equivalence boundaries). The table is not all-inclusive.

Table 3: Interactions between Daclatasvir/Sofosbuvir and other medicinal products

Medicinal products by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]**	**Recommendations concerning co-administration**
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 Daclatasvir 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 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)	No dose adjustment of Daclatasvir, peginterferon alfa, or ribavirin is required
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 co-administered 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 co-administered 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 co-administered 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 Daclatasvir or tenofovir disoproxil is required.
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 co-administered with efavirenz.
Etravirine Nevirapine	Interaction not studied. Expected due to CYP3A4 induction by etravirine or nevirapine: ↓ Daclatasvir	Due to the lack of data, co-administration of Daclatasvir and etravirine or nevirapine is not recommended.
Rilpivirine	Interaction not studied. Expected: ↔ Daclatasvir ↔ Rilpivirine	No dose adjustment of Daclatasvir 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 Daclatasvir or dolutegravir is required.
Raltegravir	Interaction not studied. Expected: ↔ Daclatasvir ↔ Raltegravir	No dose adjustment of Daclatasvir 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 co-administered with cobicistat or other strong inhibitors of CYP3A4.
Fusion inhibitor		
Enfuvirtide	Interaction not studied. Expected: ↔ Daclatasvir ↔ Enfuvirtide	No dose adjustment of Daclatasvir or enfuvirtide is required.

ACID REDUCING AGENTS		
H2-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 Daclatasvir 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 daclatasvir 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 co-administered with clarithromycin, telithromycin or other strong inhibitors of CYP3A4
Erythromycin	Interaction not studied. Expected due to CYP3A4 inhibition by the antibacterial: ↑ Daclatasvir	Administration of daclatasvir 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 Daclatasvir 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 Daclatasvir 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 Daclatasvir 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 Daclatasvir.
ANTICONVULSANTS		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied. Expected due to CYP3A4 induction by the anticonvulsant: ↓ Daclatasvir	Co-administration of Daclatasvir 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 Daclatasvir 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 daclatasvir should be reduced to 30 mg once daily when co-administered 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 Daclatasvir 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	Co-administration of Daclatasvir 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 co-administered with Daclatasvir. 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 Daclatasvir 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 Daclatasvir is co-administered with calcium channel blockers.
Verapamil	Interaction not studied. Expected due to CYP3A4 and P-gp inhibition by verapamil: ↑ Daclatasvir	Caution is advised if Daclatasvir is co-administered with calcium channel blockers.
CORTICOSTEROIDS		
Systemic dexamethasone	Interaction not studied. Expected due to CYP3A4 induction by dexamethasone: ↓ Daclatasvir	Co-administration of Daclatasvir 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	Co-administration of Daclatasvir 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 Daclatasvir, 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 Daclatasvir is co-administered 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 Daclatasvir 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* (daclatasvir 60 mg once daily) * Evaluated in opioid-dependent adults on stable buprenorphine/naloxone maintenance therapy.	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↑ Buprenorphine AUC: 1.37 (1.24, 1.52) 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.	No dose adjustment of Daclatasvir or buprenorphine may be required, but it is recommended that patients should be monitored for signs of opiate toxicity.
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 Daclatasvir 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 co-administered with Daclatasvir.
Triazolam Alprazolam	Interaction not studied. Expected: ↔ Triazolam ↔ Alprazolam	
Interactions between sofosbuvir and other medicinal products		
ANALEPTICS		

Modafinil	Interaction not studied. Expected: ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of sofosbuvir with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.
ANTIARRHYTHMICS		
Amiodarone	Interaction not studied.	Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with sofosbuvir and another DAA (see sections 4.4 and 4.8).
ANTICOAGULANTS		
Vitamin K antagonists	Interaction not studied	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with sofosbuvir.
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Interaction not studied. Expected: ↓ Sofosbuvir ↔ GS-331007	Sofosbuvir is contraindicated with carbamazepine, phenobarbital and phenytoin, potent intestinal P-gp inducers (see section 4.3).
Oxcarbazepine	Interaction not studied. Expected: ↓ Sofosbuvir ↔ GS-331007	Co-administration of sofosbuvir with oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to a reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended (see section 4.4).
ANTIMYCOBACTERIALS		
Rifampicin[f] (600 mg single dose)	Sofosbuvir ↓↓ C_{max} ↓↓ AUC C_{min} (NA) GS-331007 ↔ C_{max} ↔ AUC C_{min} (NA)	Sofosbuvir is contraindicated with rifampicin, a potent intestinal P-gp inducer (see section 4.3).

Rifabutin Rifapentine	Interaction not studied. Expected: ↓ Sofosbuvir ↔ GS-331007	Sofosbuvir is contraindicated with rifabutin, a potent intestinal P-gp inducer (see section 4.3). Co-administration of sofosbuvir with rifapentine is expected to decrease the concentration of sofosbuvir, leading to a reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.
HERBAL SUPPLEMENTS		
St. John's wort (Hypericum perforatum)	Interaction not studied. Expected: ↓ Sofosbuvir ↔ GS-331007	Sofosbuvir is contraindicated with St. John's wort, a potent intestinal P-gp inducer (see section 4.3).
HBV ANTIVIRAL AGENTS		
Entecavir	Interaction not studied. Based on the metabolism and clearance a clinically significant drug-drug interaction is unlikely.	No dose adjustment of sofosbuvir or entecavir is required when these agents are used concomitantly.
HCV ANITIVIRAL AGENTS: HCV PROTEASE INHIBITORS		
Boceprevir (BOC)	Interaction not studied. Expected: ↔ Sofosbuvir (BOC) ↔ GS-331007 (BOC)	No drug-drug interaction data exists regarding the co-administration of sofosbuvir with boceprevir.
Elbasvir/grazoprevir (50mg + 200mg)	Sofosbuvir ↑ AUC ↑ C_{max} GS-331007 ↔ AUC ↔ C_{max} ↑ C_{trough} Elbasvir/grazoprevir	No dose adjustments of elbasvir/grazoprevir or sofosbuvir are needed.

Glecaprevir/pibrentasvir	Sofosbuvir ↑ AUC ↑ C_{max} GS-331007 ↔ AUC ↔ C_{max} ↑ C_{trough} Glecaprevir/pibrentasvir ↔ AUC ↔ C_{max}	No dose adjustments of glecaprevir/pibrentasvir or sofosbuvir are needed.
NARCOTIC ANALGESICS		
Methadone[f] (Methadone maintenance therapy [30 to 130 mg/daily])	R-methadone ↔ C_{max} 0.99 (0.85, 1.16) ↔ AUC 1.01 (0.85, 1.21) ↔ C_{min} 0.94 (0.77, 1.14) S-methadone ↔ C_{max} 0.95 (0.79, 1.13) ↔ AUC 0.95 (0.77, 1.17) ↔ C_{min} 0.95 (0.74, 1.22) Sofosbuvir ↓ C_{max} 0.95[c] (0.68, 1.33) ↑ AUC 1.30[c] (1.00, 1.69) C_{min} (NA) GS-331007 ↓ C_{max} 0.73[c] (0.65, 0.83) ↔ AUC 1.04[c] (0.89, 1.22) C_{min} (NA)	No dose adjustment of sofosbuvir or methadone is required when sofosbuvir and methadone are used concomitantly.
IMMUNOSUPPRESSANTS		
Ciclosporin[e] (600 mg single dose)	Ciclosporin ↔ C_{max} 1.06 (0.94, 1.18) ↔ AUC 0.98 (0.85, 1.14) C_{min} (NA) Sofosbuvir ↑ C_{max} 2.54 (1.87, 3.45) ↑ AUC 4.53 (3.26, 6.30) C_{min} (NA) GS-331007 ↓ C_{max} 0.60 (0.53, 0.69) ↔ AUC 1.04 (0.90, 1.20) C_{min} (NA)	No dose adjustment of sofosbuvir or ciclosporin is required when sofosbuvir and ciclosporin are used concomitantly.

Tacrolimus[e] (5 mg single dose)	Tacrolimus ↓ C_{max} 0.73 (0.59, 0.90) ↔ AUC 1.09 (0.84, 1.40) C_{min} (NA) Sofosbuvir ↓ C_{max} 0.97 (0.65, 1.43) ↑ AUC 1.13 (0.81, 1.57) C_{min} (NA) GS-331007 ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13) C_{min} (NA)	No dose adjustment of sofosbuvir or tacrolimus is required when sofosbuvir and tacrolimus are used concomitantly.
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz[f] (600 mg once daily) [d]	Efavirenz ↔ C_{max} 0.95 (0.85, 1.06) ↔ AUC 0.96 (0.91, 1.03) ↔ C_{min} 0.96 (0.93, 0.98) Sofosbuvir ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) GS-331007 ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or efavirenz is required when sofosbuvir and efavirenz are used concomitantly.
Emtricitabine [f] (200 mg once daily) [d]	Emtricitabine ↔ C_{max} 0.97 (0.88, 1.07) ↔ AUC 0.99 (0.94, 1.05) ↔ C_{min} 1.04 (0.98, 1.11) Sofosbuvir ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) GS-331007 ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or emtricitabine is required when sofosbuvir and emtricitabine are used concomitantly.

Tenofovir disoproxil [f] (245 mg once daily)[d]	Tenofovir ↑ C_{max} 1.25 (1.08, 1.45) ↔ AUC 0.98 (0.91, 1.05) ↔ C_{min} 0.99 (0.91, 1.07) Sofosbuvir ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) GS-331007 ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or tenofovir disoproxil is required when sofosbuvir and tenofovir disoproxil are used concomitantly.
Rilpivirine [f] (25 mg once daily)	Rilpivirine ↔ C_{max} 1.05 (0.97, 1.15) ↔ AUC 1.06 (1.02, 1.09) ↔ C_{min} 0.99 (0.94, 1.04) Sofosbuvir ↑ C_{max} 1.21 (0.90, 1.62) ↔ AUC 1.09 (0.94, 1.27) C_{min} (NA) GS-331007 ↔ C_{max} 1.06 (0.99, 1.14) ↔ AUC 1.01 (0.97, 1.04) C_{min} (NA)	No dose adjustment of sofosbuvir or rilpivirine is required when sofosbuvir and rilpivirine are used concomitantly.
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Darunavir boosted with ritonavir [f] (800/100 mg once daily)	Darunavir ↔ C_{max} 0.97 (0.94, 1.01) ↔ AUC 0.97 (0.94, 1.00) ↔ C_{min} 0.86 (0.78, 0.96) Sofosbuvir ↑ C_{max} 1.45 (1.10, 1.92) ↑ AUC 1.34 (1.12, 1.59) C_{min} (NA) GS-331007 ↔ C_{max} 0.97 (0.90, 1.05) ↔ AUC 1.24 (1.18, 1.30) C_{min} (NA)	No dose adjustment of sofosbuvir or darunavir (ritonavir boosted) is required when sofosbuvir and darunavir are used concomitantly. Co-administration with darunavir boosted with cobicistat has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Sofosbuvir is a prodrug and formation of its active metabolite is unlikely to be affected by cobicistat.
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS		

Raltegravir [f] (400 mg twice daily)	Raltegravir ↓ C_{max} 0.57 (0.44, 0.75) ↓ AUC 0.73 (0.59, 0.91) ↔ C_{min} 0.95 (0.81, 1.12) Sofosbuvir ↔ C_{max} 0.87 (0.71, 1.08) ↔ AUC 0.95 (0.82, 1.09) C_{min} (NA) GS-331007 ↔ C_{max} 1.09 (0.99, 1.20) ↔ AUC 1.03 (0.97, 1.08) C_{min} (NA)	No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly.
ORAL CONTRACEPTIVES		
Norgestimate/ethinyl estradiol	Norgestromin ↔ C_{max} 1.06 (0.93, 1.22) ↔ AUC 1.05 (0.92, 1.20) C_{min} (NA) Norgestrel ↔ C_{max} 1.18 (0.99, 1.41) ↔ AUC 1.19 (0.98, 1.44) C_{min} (NA) Ethinyl estradiol ↔ C_{max} 1.14 (0.96, 1.36) ↔ AUC 1.08 (0.93, 1.25) C_{min} (NA)	No dose adjustment of norgestimate/ethinyl estradiol is required when sofosbuvir and norgestimate/ethinyl estradiol are used concomitantly.

NA = not available

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics with/without sofosbuvir and mean ratio of sofosbuvir and GS-331007 with/without co-administered drug. No effect = 1.00
b. All interaction studies conducted in healthy volunteers
c. Comparison based on historical control
d. Administered as Atripla
e. Bioequivalence boundary 80%-125%
f. Equivalence boundary 70%-143%

No clinically relevant effects on the pharmacokinetics of either medicinal product are 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 lactation

Women of childbearing potential / contraception in males and females

When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin (see section 4.4). Women of childbearing potential or their male partners must use an effective form of contraception during treatment and for a period of time after the treatment has concluded. Refer to the summary of product characteristics for ribavirin for additional information.
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 Daclatasvir/Sofosbuvir 60 mg/400 mg tablets (see section 4.5)

Pregnancy

Daclatasvir
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.

Daclatasvir 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 daclatasvir therapy (see section 4.5).

Since daclatasvir 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.

Sofosbuvir
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 with respect to reproductive toxicity. No effects on foetal 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).

As a precautionary measure, it is preferable to avoid the use of Sofosbuvir during pregnancy.

However, if ribavirin is co-administered with sofosbuvir, the contraindications regarding use of ribavirin during pregnancy apply (see also the Summary of Product Characteristics for ribavirin).

Breast-feeding

It is unknown whether daclatasvir /sofosbuvir and its metabolites are excreted in human milk.

Available pharmacokinetic data in animals has shown excretion of metabolites in milk (for details see section 5.3)

A risk to newborns/infants cannot be excluded. Therefore, daclatasvir /sofosbuvir should not be used during breast-feeding.

Fertility

No human data on the effect of daclatasvir /sofosbuvir on fertility are available. Animal studies do not indicate harmful effects on fertility.

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 Din combination with peginterferon alfa and ribavirin.

4.8 Undesirable effects

Summary of the safety profile

During treatment with sofosbuvir in combination with ribavirin or with peginterferon alfa and ribavirin, the most frequently reported adverse drug reactions were consistent with the expected safety profile of ribavirin and peginterferon alfa treatment, without increasing the frequency or severity of the expected adverse drug reactions.

Assessment of adverse reactions is based on pooled data from five Phase 3 clinical studies (both controlled and uncontrolled).

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.

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

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 heart rate (see sections 4.4 and 4.5).

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

Paediatric population

The safety and efficacy of Daclatasvir/Sofosbuvir 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.

4.9 Overdose

Daclatasvir

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

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

Sofosbuvir

The highest documented dose of sofosbuvir was a single supratherapeutic dose of sofosbuvir 1,200 mg administered to 59 healthy subjects. In that study, there were no untoward effects observed at this dose level, and adverse reactions were similar in frequency and severity to those reported in the placebo and sofosbuvir 400 mg treatment groups. The effects of higher doses are unknown.

No specific antidote is available for overdose with Sofosbuvir. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Haemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite 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

Sofosbuvir

Pharmacotherapeutic group: Antivirals for systemic use, direct-acting antiviral; ATC code: J05AP08

Namibia Pharmacological Classification: 20.2.8 - Antivirals

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.

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. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with a 50% inhibitory concentration (IC_{50}) value ranging from 0.7 to 2.6 µM. GS-461203 (the active metabolite of sofosbuvir) is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral activity

Sofosbuvir

Resistance

In cell culture

Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T

substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In clinical studies
In a pooled analysis of 221 samples with post-baseline NS5B sequences and deep sequencing data (assay cutoff of 1%) the sofosbuvir-associated resistance substitution S282T was not detected by deep sequencing or population sequencing. The S282T substitution in NS5B was detected in a single subject receiving sofosbuvir monotherapy in a Phase 2 study. This subject harboured <1% HCV S282T at baseline and developed S282T (>99%) at 4 weeks post-treatment which resulted in a 13.5-fold change in sofosbuvir EC50 and reduced viral replication capacity. The S282T substitution reverted to wild-type over the next 8 weeks and was no longer detectable by deep sequencing at 12 weeks post-treatment.

Two NS5B substitutions, L159F and V321A, were detected in post-treatment relapse samples from multiple genotype 3 HCV infected subjects in the Phase 3 clinical studies. No shift in the phenotypic susceptibility to sofosbuvir or ribavirin of subject isolates with these substitutions was detected. In addition, S282R and L320F substitutions were detected on treatment by deep sequencing in a pre-transplant subject with a partial treatment response. The clinical significance of these findings is unknown.

Effect of baseline HCV polymorphisms on treatment outcome
Baseline NS5B sequences were obtained for 1,292 subjects from Phase 3 studies by population sequencing and the S282T substitution was not detected No statistically significant association was observed between the presence of any HCV NS5B variant at baseline and treatment outcome.

Paediatric population
Baseline NS5B sequences were obtained for 47 patients in the Phase 2 study. Among these, one patient was found to have a NS5B RAV substitution (F289L). This patient achieved SVR12.

Cross-resistance
HCV replicons expressing the sofosbuvir-associated resistance substitution S282T were fully susceptible to other classes of anti-HCV agents. Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors.
Sofosbuvir was fully active against substitutions associated with resistance to other direct-acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors, NS3 protease inhibitors and NS5A inhibitors.

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

Daclatasvir

The absorption characteristics of [HP016 trade name] 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%.
Oral bioavailability	At least 67%.
Food effect	<table><tr><td></td><td>$AUC_{(0-\infty)}$</td><td>C_{max}</td><td>T_{max}</td></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>

Distribution	
Volume of distribution (mean)	Approximately 47 L.
Plasma protein binding	Approximately 99% (independent of dose between 1 mg to 100 mg)
Tissue distribution	Active and passive transport into hepatocytes.
Metabolism	
	Substrate of CYP3A with CYP3A4 being the major isoform responsible for metabolism.
Active metabolite(s)	None.
Elimination	
General note	Daclatasvir is mainly cleared by the liver.
Elimination half life	12 to 15 h
Mean systemic clearance (Cl/F)	4.24 L/h
% of dose excreted in urine	6.6% (primarily as unchanged drug)
% of dose excreted in faeces	88% (53% as unchanged drug)
Pharmacokinetic linearity	Daclatasvir C_{max}, AUC and C_{min} increase in a near dose-proportional manner
Drug interactions *(in vitro*)	NA*
Transporters	*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.
Metabolizing enzymes	*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.

*Information not available

Sofosbuvir

Sofosbuvir is a nucleotide prodrug that is extensively metabolised. The active metabolite is formed in hepatocytes and not observed in plasma. The predominant (>90%) metabolite, GS-331007, is inactive. It is formed through sequential and parallel pathways to the formation of active metabolite.

Absorption

The pharmacokinetic properties of sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C.

Based on population pharmacokinetic analysis in subjects with genotypes 1 to 6 HCV infection (n = 986), steady-state AUC0-24 for sofosbuvir and GS-331007 was 1,010 ng•h/mL and 7,200 ng•h/mL, respectively. Relative to healthy subjects (n = 284), the sofosbuvir and GS-331007 AUC0-24 was 57% higher and 39% lower, respectively in HCV infected subjects.

Following single dose of administration of Sofosbuvir Tablets, Film-coated 400 mg in healthy volunteers, mean (± SD) sofosbuvir C_{max} value was 1287 (± 572) ng/ml and the corresponding value for AUC_{0-t} was 1503 (±415) ng·hour/ml. The mean sofosbuvir t_{max} value was 1.53 ± 0.67 hours.

Effects of food

Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardised high fat meal slowed the rate of absorption of sofosbuvir. The extent of absorption of sofosbuvir was increased approximately 1.8-fold, with little effect on peak concentration. The exposure to GS-331007 was not altered in the presence of a high-fat meal.

Distribution

Sofosbuvir is not a substrate for hepatic uptake transporters, organic anion-transporting polypeptide (OATP) 1B1 or 1B3, and organic cation transporter (OCT) 1. While subject to active tubular secretion, GS-331007 is not a substrate for renal transporters including organic anion transporter (OAT) 1 or 3, OCT2, MRP2, P-gp, BCRP or MATE1. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1. GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Sofosbuvir is approximately 85% bound to human plasma proteins (*ex vivo* data) and the binding is independent of drug concentration over the range of 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [14C]-sofosbuvir in healthy subjects, the blood to plasma ratio of 14C-radioactivity was approximately 0.7.

Biotransformation

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. Sofosbuvir and GS-331007 are not substrates or inhibitors of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes.

After a single 400 mg oral dose of [^{14}C]-sofosbuvir, sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug-related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

Elimination

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, faeces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. This data indicate that renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

Linearity/non-linearity
The dose linearity of sofosbuvir and its primary metabolite, GS-331007, was evaluated in fasted healthy subjects. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 400 mg.

Special populations
Gender and race
Daclatasvir
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

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

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

Sofosbuvir
Population pharmacokinetic analysis in HCV infected subjects showed that within the age range (19 to 75 years) analysed, age did not have a clinically relevant effect on the exposure to sofosbuvir and GS-331007. Clinical studies of sofosbuvir included 65 subjects aged 65 and over. The response rates observed for subjects over 65 years of age were similar to that of younger subjects across treatment groups

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 (see section 4.2).

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 400 mg film-coated tablets was administered 1 hour before or 1 hour after haemodialysis, respectively.

Haemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. A 4-hour haemodialysis session removed approximately 18% of administered dose. No dose adjustment is required for patients with mild or moderate renal impairment. The safety of Sofosbuvir 400 mg film-coated tablets has not been assessed in patients with severe renal impairment or ESRD (see section 4.4).

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 (see section 4.2).

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 $AUC_{0\text{-}24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ 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).

Paediatric population

Daclatasvir

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

Sofosbuvir

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.

Pharmacokinetic/pharmacodynamic relationship(s)

Efficacy, in terms of rapid virologic response, has been shown to correlate with exposure to sofosbuvir as well as GS 331007. However, neither of these entities has been evidenced to be a general surrogate marker for efficacy (SVR12) at the therapeutic 400 mg dose.

Bioequivalence study
Single-Dose Fasting Bioequivalence Study of Daclatasvir and Sofosbuvir Film-Coated Tablets (60 mg/400 mg; Mylan) versus DAKLINZA™ Tablets (60 mg; Bristol-Myers Squibb) and SOVALDI® Tablets (400 mg; Gilead) in Healthy Adult Volunteers

Pharmacokinetic Results:

Daclatasvir n = 58				
Parameter	Arithmetic Mean (%CV) A = Mylan	Arithmetic Mean (%CV) B = DAKLINZA™	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCL (ng•hr/mL)	13541 (37.66)	13209 (40.16)	1.03	99.35% – 106.85%
AUCINF (ng•hr/mL)	14125 (38.64)	13771 (40.59)	1.03	99.46% – 106.69%
CPEAK (ng/mL)	1326 (35.53)	1312 (37.79)	1.02	97.02% – 106.42%
KEL (hr^{-1})	0.0701 (20.79)	0.0707 (20.02)		
HALFLIFE (hr)	10.37 (25.60)	10.22 (21.58)		
TPEAK (hr)	1.707 (63.59)	1.566 (67.52)		

* Ratio (A/B) = $e^{[LSMEAN\ of\ (LNA - LNB)]}$
**Used Natural Log Transformed Parameter

Sofosbuvir n = 58				
Parameter	Arithmetic Mean (%CV) A = Mylan	Arithmetic Mean (%CV) B = SOVALDI®	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCL (ng•hr/mL)	1179 (47.57)	1221 (43.39)	0.95	89.75% – 100.06%
AUCINF (ng•hr/mL)	1196 (47.15)[o]	1237 (42.88)	0.95[o]	90.30% – 100.52%[o]
CPEAK (ng/mL)	1228 (46.29)	1269 (44.00)	0.96	85.74% – 106.53%
KEL (hr^{-1})	1.532 (25.47)[o]	1.609 (22.66)		
HALFLIFE (hr)	0.488 (32.82)[o]	0.455 (25.22)		
TPEAK (hr)	0.866 (78.35)	0.835 (66.97)		

[o]n=57
* Ratio (A/B) = $e^{[LSMEAN\ of\ (LNA - LNB)]}$
**Used Natural Log Transformed Parameter

5.3 Preclinical safety data

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.

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.
Sofosbuvir had no effects on embryo-foetal 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.

Daclatasvir: -

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

Tablet core

Anhydrose Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate.

Film-coating

Polyvinyl Alcohol, Titanium Dioxide, Polyethylene Glycol, Talc, Red Iron Oxide, Yellow Iron Oxide & Black Iron Oxide.

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

Bottle of 28's.

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

Mylan Laboratories Limited, INDIA.

Manufactured at

Mylan Laboratories Limited
F-4 & F-12, MIDC, Malegaon, Sinnar,
Nashik - 422 113, Maharashtra, INDIA

8. DATE OF REVISION OF THE TEXT

March 24,2020.

Reference
https://extranet.who.int/prequal/sites/default/files/HP001part4.pdf ,
https://extranet.who.int/prequal/sites/default/files/HP016part4v1.pdf,
accessed on March23,2020

Zambia Regn No.:
Zimbabwe Regn No.:
Botswana Regn No.:
Namibia Regn No.:
Namibia Scheduling Status: NS2

POM	Schedule 2	PP	List - 1

Mylan

Daclatasvir is manufactured under a license from BMS and MPP
Sofosbuvir is manufactured under a license from Gilead Sciences Ireland UC