SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Andodaclata 60 mg FC Tablets

2. QUALITATIVE AND QUANTITATIVE

Each film-coated tablet contains daclatasvir dihydrochloride 65.92 mg equivalent to 60 mg daclatasvir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Andodaclata is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

4.2. Posology and method of administration

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

Posology

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

Andodaclata must be administered in combination with other medicinal products. The Summary of Product Characteristics for the other medicinal products in the regimen should also be consulted before initiation of therapy with Andodaclata.

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

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

Patients without cirrhosis	Andodaclata + sofosbuvir + ribavirin for 12 weeks (see section 5.1)
Patients with CP A or B cirrhosis GT 1 or 4 GT 3	 Andodaclata + sofosbuvir + ribavirin for 12 weeks Andodaclata + sofosbuvir +/- ribavirin for 24 weeks
Patients with CP C cirrhosis	Andodaclata + sofosbuvir +/- ribavirin for 24 weeks (see sections 4.4 and 5.1)

GT: Genotype; CP: Child Pugh

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

Andodaclata + peginterferon alfa + ribavirin

This regimen is an alternative recommended regimen for patients with genotype 4 infection, without cirrhosis or with compensated cirrhosis. Andodaclata is given for 24 weeks, in combination with 24-48 weeks of peginterferon alfa and ribavirin:

- If HCV RNA is undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks.

- If undetectable HCV RNA is achieved, but not at both treatment weeks 4 and 12, Andodaclata should be discontinued at 24 weeks and peginterferon alfa and ribavirin continued for a total duration of 48 weeks.

Ribavirin Dosing Guidelines

The dose of ribavirin, when combined with Andodaclata, is weight-based (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively). Refer to the Summary of Product Characteristics of ribavirin.

For patients with Child-Pugh A, B, or C cirrhosis or recurrence of HCV infection after liver transplantation, the recommended initial dose of ribavirin is 600 mg daily with food. If the starting dose is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (breakpoint 75 kg). If the starting dose is not well-tolerated, the dose should be reduced as clinically indicated, based on haemoglobin and creatinine clearance measurements (see Table 2).

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

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

Dose modification, interruption and discontinuation

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

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

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

It is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR); therefore, discontinuation of treatment is recommended in these patients. The HCV RNA thresholds that trigger discontinuation of treatment (i.e., treatment stopping rules) are presented in Table 3.

Table 3: Treatment stopping rules in patients receiving Andodaclata in combination with peginterferon alfa and ribavirin with inadequate on-treatment virologic response

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

Dose recommendation for concomitant medicines

Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)

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

Moderate inducers of CYP3A4

The dose of Daclatasvir should be increased to 90 mg once daily when coadministered with moderate inducers of CYP3A4.

Missed doses

Patients should be instructed that, if they miss a dose of Andodaclata, the dose should be taken as soon as possible if remembered within 20 hours of the scheduled dose time. However, if the missed dose is remembered more than 20 hours after the scheduled dose, the dose should be skipped and the next dose taken at the appropriate time.

Special populations

Elderly

No dose adjustment of Andodaclata is required for patients aged ≥65 years.

Renal impairment

No dose adjustment of Andodaclata is required for patients with any degree of renal impairment.

Hepatic impairment

No dose adjustment of Andodaclata is required for patients with mild (Child-Pugh A, score 5-6), moderate (Child-Pugh B, score 7-9) or severe (Child-Pugh C, score ≥10) hepatic impairment.

Paediatric population

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

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Coadministration with medicinal products that strongly induce cytochrome P450 3A4 (CYP3A4) and P-glycoprotein transporter (P-gp) and thus may lead to lower exposure and loss of efficacy of Andodaclata. 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 special precautions for use

Andodaclata must not be administered as monotherapy. Andodaclata must be administered in combination with other medicinal products for the treatment of chronic HCV infection.

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 Andodaclata 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 Andodaclata 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 Andodaclata in combination with sofosbuvir.

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

Genotype-specific activity

Concerning recommended regimens with different HCV genotypes, see section 4.2. Concerning genotype-specific virological and clinical activity, see section 5.1.

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

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

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

Patients with Child-Pugh C liver disease

The safety and efficacy of Daclatasvir in the treatment of HCV infection in patients with Child-Pugh C liver disease have been established in the clinical study ALLY-1 (AI444215, Daclatasvir + sofosbuvir + ribavirin for 12 weeks); however, SVR rates were lower than in patients with Child-Pugh A and B. Therefore, a conservative treatment regimen of Andodaclata + sofosbuvir +/- ribavirin for 24 weeks is proposed for patients with Child-Pugh C. Ribavirin may be added based on clinical assessment of an individual patient.

HCV/HBV (hepatitis B virus) co-infection

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

Retreatment with Andodaclata

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

Pregnancy and contraception requirements

Andodaclata 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 Andodaclata therapy (see section 4.6).

When Andodaclata is used in combination with ribavirin, the contraindications and warnings for that medicinal product are applicable. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients (see the Summary of Product Characteristics for ribavirin).

4.5 Interaction with other FPPs and other forms of interaction:

Coadministration of Daclatasvir can alter the concentration of other medicinal products and other medicinal products may alter the concentration of daclatasvir. Refer to section 4.3 for a listing of

medicinal products that are contraindicated for use with Daclatasvir due to potential loss of therapeutic effect. Refer to section 4.5 for established and other potentially significant drug-drug interactions.

Paediatric population

Andodaclata is not recommended for use in children and adolescents aged below 18 years because the safety and efficacy have not been established in this population.

Important information about some of the ingredients in Andodaclata

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

Interaction with other FPPs and other forms of interaction Contraindications of concomitant use

Andodaclata 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 Andodaclata.

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. Coadministration with strong inducers of CYP3A4 and P-gp is contraindicated while dose adjustment of Andodaclata 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 Andodaclata is recommended when coadministered with strong inhibitors of CYP3A4 (see Table 4). Coadministration of medicines that inhibit P-gp or OCT1 activity is likely to have a limited effect on daclatasvir exposure.

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

Tabulated summary of interactions

Table 4 provides information from drug interaction studies with daclatasvir including clinical recommendations for established or potentially significant drug interactions. Clinically relevant increase

in concentration is indicated as "↑", clinically relevant decrease as "↓", no clinically relevant change as "↔". If available, ratios of geometric means are shown, with 90% confidence intervals (CI) in parentheses. The studies presented in Table 4 were conducted in healthy adult subjects unless otherwise noted. The table is not all-inclusive.

Table 4: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning coadministration**
ANTIVIRALS, HCV		
Nucleotide analogue polymerase inhibitor		
Sofosbuvir 400 mg once daily (Daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir* AUC: 0.95 (0.82, 1.10) C_{max}: 0.88 (0.78, 0.99) C_{min}: 0.91 (0.71, 1.16) ↔ GS-331007** AUC: 1.0 (0.95, 1.08) C_{max}: 0.8 (0.77, 0.90) C_{min}: 1.4 (1.35, 1.53) *Comparison for daclatasvir was to a historical reference (data from 3 studies of daclatasvir 60 mg once daily with peginterferon alfa and ribavirin). **GS-331007 is the major circulating metabolite of the prodrug sofosbuvir.	No dose adjustment of daclatasvir or sofosbuvir is required.
Protease inhibitors (PIs)		
Boceprevir	Interaction not studied. *Expected due to CYP3A4 inhibition by boceprevir:* ↑ Daclatasvir	The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with boceprevir or other strong inhibitors of CYP3A4.
Simeprevir 150 mg once daily (Daclatasvir 60 mg once daily)	↑ Daclatasvir AUC: 1.96 (1.84, 2.10) C_{max}: 1.50 (1.39, 1.62) C_{min}: 2.68 (2.42, 2.98) ↑ Simeprevir AUC: 1.44 (1.32, 1.56) C_{max}: 1.39 (1.27, 1.52) C_{min}: 1.49 (1.33, 1.67)	No dose adjustment of daclatasvir or simeprevir is required.
Telaprevir 500 mg q12h (Daclatasvir 20 mg once daily) **Telaprevir 750 mg q8h** (Daclatasvir 20 mg once daily)	↑ Daclatasvir AUC: 2.32 (2.06, 2.62) C_{max}: 1.46 (1.28, 1.66) ↔ Telaprevir AUC: 0.94 (0.84, 1.04) C_{max}: 1.01 (0.89, 1.14) ↑ Daclatasvir AUC: 2.15 (1.87, 2.48) C_{max}: 1.22 (1.04, 1.44) ↔ Telaprevir AUC: 0.99 (0.95, 1.03)	The dose of daclatasvir should be reduced to 30 mg once daily when co-administered with telaprevir or other strong inhibitors of CYP3A4.

	C_{max}: 1.02 (0.95, 1.09) CYP3A4 inhibition by telaprevir	
Other HCV antivirals		
Peginterferon alfa 180 µg once weekly and ribavirin 1000 mg or 1200 mg/day in two divided doses (Daclatasvir 60 mg once daily) Study conducted in patients with chronic HCV infection	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↔ Peginterferon alfa C_{min}: ↔* ↔ Ribavirin AUC: 0.94 (0.80,1.11) C_{max}: 0.94 (0.79, 1.11) C_{min}: 0.98 (0.82, 1.17) *PK parameters for daclatasvir when administered with peginterferon alfa and ribavirin in this study were similar to those observed in a study of HCV-infected subjects administered daclatasvir monotherapy for 14 days. PK trough levels for peginterferon alfa in patients who received peginterferon alfa, ribavirin, and daclatasvir were similar to those in patients who received peginterferon alfa, ribavirin, and placebo.	No dose adjustment of daclatasvir, peginterferon alfa, or ribavirin is required.
ANTIVIRALS, HIV or HBV		
Protease inhibitors (PIs)		
Atazanavir 300 mg/ritonavir 100 mg once daily (Daclatasvir 20 mg once daily)	↑ Daclatasvir AUC*: 2.10 (1.95, 2.26) C_{max}*: 1.35 (1.24, 1.47) C_{min}*: 3.65 (3.25, 4.11) CYP3A4 inhibition by ritonavir *Results are dose-normalized 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)	No dose adjustment of daclatasvir 60 mg once daily, darunavir/ritonavir (800/100 mg once daily or 600/100 mg twice daily) or darunavir/cobicistat is required.
Darunavir/cobicistat	Interaction not studied. *Expected:* ↔ Daclatasvir	
Lopinavir 400 mg/ritonavir 100	↔ Daclatasvir	No dose adjustment of

mg twice daily (Daclatasvir 30 mg once daily)	AUC: 1.15 (1.07, 1.24) C_{max}: 0.67 (0.61, 0.74) ↔ Lopinavir* AUC: 1.15 (0.77, 1.72) C_{max}: 1.22 (1.06, 1.41) C_{min}: 1.54 (0.46, 5.07) * the effect of 60 mg daclatasvir on lopinavir may be higher.	daclatasvir 60 mg once daily or lopinavir/ritonavir is required.
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil fumarate 300 mg once daily (Daclatasvir 60 mg once daily)	↔ Daclatasvir AUC: 1.10 (1.01, 1.21) C_{max}: 1.06 (0.98, 1.15) C_{min}: 1.15 (1.02, 1.30) ↔ Tenofovir AUC: 1.10 (1.05, 1.15) C_{max}: 0.95 (0.89, 1.02) C_{min}: 1.17 (1.10, 1.24)	No dose adjustment of daclatasvir or tenofovir is required.
Lamivudine **Zidovudine** **Emtricitabine** **Abacavir** **Didanosine** **Stavudine**	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ NRTI	No dose adjustment of daclatasvir or the NRTI is required.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (Daclatasvir 60 mg once daily/120 mg once daily)	↓ Daclatasvir AUC*: 0.68 (0.60, 0.78) C_{max}*: 0.83 (0.76, 0.92) C_{min}*: 0.41 (0.34, 0.50) Induction of CYP3A4 by efavirenz *Results are dose-normalized 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, coadministration 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 fumarate	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.
CCR5 receptor antagonist		
Maraviroc	Interaction not studied. *Expected:* ↔ Daclatasvir ↔ Maraviroc	No dose adjustment of daclatasvir or maraviroc is required.
ACID REDUCING AGENTS		
H_2-receptor antagonists		
Famotidine 40 mg single dose (Daclatasvir 60 mg single dose)	↔ Daclatasvir AUC: 0.82 (0.70, 0.96) C_{max}: 0.56 (0.46, 0.67) C_{min}: 0.89 (0.75, 1.06) Increase in gastric pH	No dose adjustment of 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	Coadministration 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	Coadministration 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 coadministered 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	Administration of daclatasvir with any of these calcium channel blockers may result in increased concentrations of daclatasvir. Caution is advised.
Verapamil	Interaction not studied. *Expected due to CYP3A4 and P-gp inhibition by verapamil:* ↑ Daclatasvir	Administration of daclatasvir with verapamil may result in increased concentrations of daclatasvir. Caution is advised.
CORTICOSTEROIDS		
Systemic dexamethasone	Interaction not studied. *Expected due to CYP3A4 induction by dexamethasone:* ↓ Daclatasvir	Coadministration of 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*	Coadministration of daclatasvir with St. John's

	by St. John's wort: ↓ Daclatasvir	wort or other strong inducers of CYP3A4 is contraindicated (see section 4.3).
HORMONAL CONTRACEPTIVES		
Ethinylestradiol 35 µg once daily for 21 days + norgestimate 0.180/0.215/0.250 mg once daily for 7/7/7 days (Daclatasvir 60 mg once daily)	↔ Ethinylestradiol AUC: 1.01 (0.95, 1.07) C_{max}: 1.11 (1.02, 1.20) ↔ Norelgestromin AUC: 1.12 (1.06, 1.17) $C_{max:}$ 1.06 (0.99, 1.14) ↔ Norgestrel AUC: 1.12 (1.02, 1.23) C_{max}: 1.07 (0.99, 1.16)	An oral contraceptive containing ethinylestradiol 35 µg and norgestimate 0.180/0.215/0.250 mg is recommended with daclatasvir. 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)	↔ Daclatasvir AUC: ↔* C_{max}: ↔* C_{min}: ↔* ↑ Buprenorphine	No dose adjustment of Daclatasvir or buprenorphine may be required, but it is recommended that patients should be monitored for signs

* Evaluated in opioid-dependent adults on stable buprenorphine/naloxone maintenance therapy.	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.	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	

No clinically relevant effects 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 Pregnancy and lactation (*See example below*)

Use during 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.

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 Andodaclata therapy (see section 4.5).

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

Use during lactation:

It is not known whether daclatasvir is excreted in human milk. Available pharmacokinetic and toxicological data in animals have shown excretion of daclatasvir and metabolites in milk (see section 5.3). A risk to the newborn/infant cannot be excluded. Mothers should be instructed not to breastfeed if they are taking daclatasvir.

Fertility

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Daclatasvir 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.

Daclatasvir in combination with peginterferon alfa and ribavirin

The most frequently reported adverse reactions were fatigue, headache, pruritus, anaemia, influenza-like illness, nausea, insomnia, neutropenia, asthenia, rash, decreased appetite, dry skin, alopecia, pyrexia, myalgia, irritability, cough, diarrhoea, dyspnoea and arthralgia. The most frequently reported adverse reactions of at least Grade 3 severity (frequency of 1% or greater) were neutropenia, anaemia, lymphopenia and thrombocytopenia. The safety profile of daclatasvir in combination with peginterferon alfa and ribavirin was similar to that seen with peginterferon alfa and ribavirin alone, including among patients with cirrhosis.

Tabulated list of adverse reactions

Adverse reactions are listed in Table 5 by regimen, system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions

System Organ Class	**Adverse Reactions**	
Frequency	*Daclatasvir +sofosbuvir + ribavirin*	*Daclatasvir +sofosbuvir*
Blood and lymphatic system disorders		
very common	anaemia	

Metabolism and nutrition disorders		
common	decreased appetite	
Psychiatric disorders		
common	insomnia, irritability	insomnia
Nervous system disorders		
very common	headache	headache
common	dizziness, migraine	dizziness, migraine
Vascular disorders		
common	hot flush	
Respiratory, thoracic and mediastinal disorders		
common	dyspnoea, dyspnoea exertional, cough, nasal congestion	
Gastrointestinal disorders		
very common	nausea	
common	diarrhoea, vomiting, abdominal pain, gastrooesophageal reflux disease, constipation, dry mouth, flatulence	nausea, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders		
common	rash, alopecia, pruritus, dry skin	
Musculoskeletal and connective tissue disorders		
common	arthralgia, myalgia	arthralgia, myalgia
General disorders and administration site conditions		
very common	fatigue	fatigue

Laboratory abnormalities

Daclatasvir in combination with sofosbuvir with or without ribavirin, 2% of patients had Grade 3 haemoglobin decreases; all of these patients received Daclatasvir + sofosbuvir + ribavirin. Grade 3/4 increases in total bilirubin were observed in 5% of patients (all in patients with HIV co-infection who were receiving concomitant atazanavir, with Child-Pugh A, B, or C cirrhosis, or who were post-liver transplant).

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when 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).

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. You can report any suspected adverse reactions via:

1- Al Andalous website: (www.alandalous.org).

2- The Egyptian Pharmaceutical Vigilance Center (EPVC)

Address: 21 Abd Elaziz Al Seoud-Manial-Cairo, PO box: 11451

Tel: (+2) 02 23684288/ (+2) 02 23640368, ext. 1303

Fax: (02) 2368 4194

Email: pv.center@eda.mohealth.gov.eg

Website: www.epvc.gov.eg

4.9 Over dose

There is limited experience of accidental overdose of daclatasvir in clinical studies.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral

Mechanism of action

Daclatasvir is an inhibitor of nonstructural protein 5A (NS5A), a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir inhibits both viral RNA replication and virion assembly.

Antiviral activity in cell culture

Daclatasvir is an inhibitor of HCV genotypes 1a and 1b replication in cell-based replicon assays with effective concentration (50% reduction, EC50) values of 0.003-0.050 and 0.001-0.009 nM, respectively, depending on the assay method. The daclatasvir EC50 values in the replicon system were 0.003-1.25 nM for genotypes 3a, 4a, 5a and 6a, and 0.034-19 nM for genotype 2a as well as 0.020 nM for infectious genotype 2a (JFH-1) virus.

Daclatasvir showed additive to synergistic interactions with interferon alfa, HCV nonstructural protein 3 (NS3) PIs, HCV nonstructural protein 5B (NS5B) non-nucleoside inhibitors, and HCV NS5B nucleoside analogues in combination studies using the cell-based HCV replicon system. No antagonism of antiviral activity was observed.

No clinically relevant antiviral activity was observed against a variety of RNA and DNA viruses, including HIV, confirming that daclatasvir, which inhibits a HCV-specific target, is highly selective for HCV.

Resistance in cell culture

Substitutions conferring daclatasvir resistance in genotypes 1-4 were observed in the N-terminal 100 amino acid region of NS5A in a cell-based replicon system. L31V and Y93H were frequently observed resistance substitutions in genotype 1b, while M28T, L31V/M, Q30E/H/R, and Y93C/H/N were frequently observed resistance substitutions in genotype 1a. These substitutions conferred low level resistance (EC50 <1 nM) for genotype 1b, and higher levels of resistance for genotype 1a (EC50 up to 350 nM). The most resistant variants with single amino acid substitution in genotype 2a and genotype 3a were F28S (EC50 >300 nM) and Y93H (EC50 >1,000 nM), respectively. In genotype 4, amino acid substitutions at 30 and 93 (EC50 < 16 nM) were frequently selected.

Cross-resistance

HCV replicons expressing daclatasvir-associated resistance substitutions remained fully sensitive to interferon alfa and other anti-HCV agents with different mechanisms of action, such as NS3 protease and NS5B polymerase (nucleoside and non-nucleoside) inhibitors.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in patients with chronic HCV. Following multiple oral doses of daclatasvir 60 mg once daily in combination with peginterferon alfa and ribavirin in treatment-naïve patients with genotype 1 chronic HCV, the geometric mean (CV%) daclatasvir C_{max} was 1534 (58) ng/ml, AUC0-24h was 14122 (70) ng•h/ml, and C_{min} was 232 (83) ng/ml.

Absorption

Daclatasvir administered as a tablet was readily absorbed following multiple oral doses with peak plasma concentrations occurring between 1 and 2 hours.

Daclatasvir C_{max}, AUC, and C_{min} increased in a near dose-proportional manner. Steady state was achieved after 4 days of once-daily administration. At the 60 mg dose, exposure to daclatasvir was similar between healthy subjects and HCV-infected patients.

In vitro and *in vivo* studies showed that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.

Effect of food on oral absorption

In healthy subjects, administration of daclatasvir 60 mg tablet after a high-fat meal decreased daclatasvir C_{max} and AUC by 28% and 23%, respectively, compared with administration under fasting conditions. Administration of daclatasvir 60 mg tablet after a light meal resulted in no reduction in daclatasvir exposure.

Distribution

At steady state, protein binding of daclatasvir in HCV-infected patients was approximately 99% and independent of dose at the dose range studied (1 mg to 100 mg). In patients who received daclatasvir 60

mg tablet orally followed by 100 µg [13C,15N]-daclatasvir intravenous dose, estimated volume of distribution at steady state was 47 l. In vitro studies indicate that daclatasvir is actively and passively transported into hepatocytes. The active transport is mediated by OCT1 and other unidentified uptake transporters, but not by organic anion transporter (OAT) 2, sodium-taurocholate cotransporting p Daclatasvir is an inhibitor of P-gp, OATP 1B1 and BCRP. *In vitro* daclatasvir is an inhibitor of renal uptake transporters, OAT1 and 3, and OCT2, but is not expected to have a clinical effect on the pharmacokinetics of substrates of these transporters.

Biotransformation

In vitro and *in vivo* studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 being the major CYP isoform responsible for the metabolism. No metabolites circulated at levels more than 5% of the parent concentration. Daclatasvir *in vitro* did not inhibit (IC50 >40 µM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6.

Elimination

Following single-dose oral administration of 14C–daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% as unchanged drug) and 6.6% was excreted in the urine (primarily as unchanged drug). These data indicate that the liver is the major clearance organ for daclatasvir in humans. *In vitro* studies indicate that daclatasvir is actively and passively transported into hepatocytes. The active transport is mediated by OCT1 and other unidentified uptake transporters. Following multiple-dose administration of daclatasvir in HCV-infected patients, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours. In patients who received daclatasvir 60 mg tablet orally followed by 100 µg [13C,15N]-daclatasvir intravenous dose, the total clearance was 4.24 l/h.

Special populations

Renal impairment

The pharmacokinetics of daclatasvir following a single 60 mg oral dose were studied in non-HCV infected subjects with renal impairment. Daclatasvir unbound AUC was estimated to be 18%, 39% and 51% higher for subjects with creatinine clearance (CLcr) values of 60, 30 and 15 ml/min, respectively, relative to subjects with normal renal function. Subjects with end-stage renal disease requiring haemodialysis had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to subjects with normal renal function (see section 4.2).

Hepatic impairment

The pharmacokinetics of daclatasvir following a single 30 mg oral dose were studied in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with unimpaired subjects. The C_{max} and AUC of total daclatasvir (free and protein-bound drug) were lower in subjects with hepatic impairment; however, hepatic impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir (see section 4.2).

Elderly

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

Paediatric population

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

Gender

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

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.

6. PHARMACEUTICAL PARTICULARS:

6.1. List of excipients:

Lactose anhydrous spray dried, Microcrystalline cellulose (Avicel PH 102), Croscarmellose sodium, Colloidal Silicon Dioxide (Aerosil 200), Magnesium stearate, Opadry green II (Polyvinyl alcohol-part hydrolyzed, macrogol/PEG (4000), talc, quinoline yellow aluminium lake (CI:47005), titanium dioxide, FD&C blue #2/indigo carmine aluminium lake, FD&C yellow # 6/ sunset yellow FCF aluminium lake.

6.2. Incompatibilities:

Not applicable.

6.3. Shelf life:

2 years.

6.4. Special precautions for storage:

Store at temperature not exceeding 30 º C, in dry place.

6.5. Nature and contents of container

Carton box containing 4 (AL/AL) strips each of 7 film coated tablets with insert leaflet.

6.6. Instructions for use and handling and disposal

None.

7. MARKETING AUTHORISATION HOLDER:

Al Andalous for pharmaceutical industries.

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS:

32777/2018.

9. DATE OF FIRST AUTHORISATION/RENEWALOF THE AUTHORISATION:

02/08/2018.

10. DATE OF REVISION OF THE TEXT:

10/2021.