GRATEZIANO 400 MG

FILM COATED TABLET, for oral use
FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

GRATEZIANO 400 MG FILM COATED TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of sofosbuvir.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Pale yellow to yellow oblong biconvex film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GRATEZIANO is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2, 4.4 and 5.1).
For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.

4.2 Posology and method of administration

GRATEZIANO treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Posology

The recommended dose is one 400 mg tablet, taken orally, once daily with food (see section 5.2).
GRATEZIANO should be used in combination with other medicinal products. Monotherapy of GRATEZIANO is not recommended. Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with GRATEZIANO. The recommended co-administered medicinal product(s) and treatment duration for GRATEZIANO combination therapy are provided in Table 1.

Table 1: Recommended co-administered medicinal product(s) and treatment duration for GRATEZIANO combination therapy

Patient population*	Treatment	Duration
Patients with genotype 1 or 4 CHC	Sofosbuvir + ribavirin + peginterferon alfa	12 weeks[a,b]
Patients with genotype 2 CHC	Sofosbuvir + ribavirin	12 weeks[b]
Patients with genotype 3 CHC	Sofosbuvir + ribavirin + peginterferon alfa	12 weeks[b]
	Sofosbuvir + ribavirin	24 weeks
Patients with genotype 1, 2, 3 or 4 CHC awaiting liver transplantation	Sofosbuvir + ribavirin	Until liver transplantation[c]

* Includes patients co-infected with human immunodeficiency virus (HIV).
a.For previously treated patients with HCV genotype 1 infection, no data exists with the combination of GRATEZIANO, ribavirin and peginterferon alfa (see section 4.4).
b.Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alfa and ribavirin therapy).
c.See Special patient populations – Patients awaiting liver transplantation below.

GRATEZIANO in combination with ribavirin for 24 weeks can be considered as a therapeutic option for CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen (see sections 4.4 and 5.1). Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient.
The dose of ribavirin, when used in combination with GRATEZIANO is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg) and administered orally in two divided doses with food.
Concerning co-administration with other direct-acting antivirals against HCV, see section 4.4.

Dose modification

Dose reduction of GRATEZIANO is not recommended.
If sofosbuvir is used in combination with peginterferon alfa, and a patient has a serious adverse reaction potentially related to this medicinal product, the peginterferon alfa dose should be reduced or discontinued. Refer to the peginterferon alfa Summary of Product Characteristics for additional information about how to reduce and/or discontinue the peginterferon alfa dose.
If a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity.
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 GRATEZIANO

Laboratory values	Reduce ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Haemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
Haemoglobin in patients 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).

Discontinuation of dosing

If the other medicinal products used in combination with GRATEZIANO are permanently discontinued,GRATEZIANO should also be discontinued (see section 4.4).

Vomiting and missed doses

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 GS-331007 suggesting that the majority of the dose is absorbed within 2 hours after dosing.
If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed not to take a double dose.

Special patient populations

Elderly

No dose adjustment is warranted for elderly patients (see section 5.2).

Renal impairment

No dose adjustment of GRATEZIANO is required for patients with mild or moderate renal impairment.
Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) and end stage renal disease (ESRD) requiring haemodialysis. GRATEZIANO can be used in these patients with no dose adjustment when no other relevant treatment options are available (see section 4.4, 4.8, 5.1 and 5.2).

Hepatic impairment

No dose adjustment of GRATEZIANO is required for patients with mild, moderate or severe hepatic impairment (see section 5.2). The safety and efficacy of GRATEZIANO have not been established in patients with decompensated cirrhosis.

Patients awaiting liver transplantation

The duration of administration of GRATEZIANO in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient.

Liver transplant recipients

GRATEZIANO in combination with ribavirin is recommended for 24 weeks in liver transplant recipients. A starting ribavirin dose of 400 mg administered orally in two divided doses with food is recommended. If the starting dose of ribavirin is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (1,000 mg for patients weighing <75 kg and 1,200 mg for patients weighing ≥75 kg). If the starting dose of ribavirin is not well-tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels .

Paediatric population

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

Method of administration

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Medicinal products that are strong P-glycoprotein (P-gp) inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort). Co-administration will significantly decrease sofosbuvir plasma concentration and could result in loss of efficacy of GRATEZIANO (see section 4.5).

4.4 Special warnings and precautions for use

General

GRATEZIANO is not recommended for administration as monotherapy and should be prescribed in combination with other medicinal products for the treatment of hepatitis C infection. If the other medicinal products used in combination with GRATEZIANO are permanently discontinued, GRATEZIANO should also be discontinued (see section 4.2). Consult the Summary of Product Characteristics for co-prescribed medicinal products before starting therapy with GRATEZIANO.

Severe bradycardia and heart block

Cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone with or without other medicinal products that lower heart rate. The mechanism is not established.
The concomitant use of amiodarone was limited through the clinical development of sofosbuvir. Cases are potentially life threatening, therefore amiodarone should only be used in patients on GRATEZIANO when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone.
Should concomitant use of amiodarone be considered necessary it is recommended that patients are closely monitored when initiating GRATEZIANO. 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 GRATEZIANO.
All patients receiving GRATEZIANO in combination with amiodarone with or without other medicinal products 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.

Treatment-experienced patients with genotype 1 and 4 HCV infection

The optimal treatment duration in this population has not been established (see also sections 4.2 and 5.1). Consideration should be given to treating these patients, and potentially extending the duration of therapy with sofosbuvir, peginterferon alfa and ribavirin beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype).

Patients with genotype 5 or 6 HCV infection

There is very limited data regarding the use of GRATEZIANO in patients with genotype 5 and 6 HCV infection. Available data on subjects with genotype 5 or 6 HCV infection are insufficient for dosing recommendations.

Interferon-free therapy for genotype 1 HCV infection

The optimal regimen and treatment duration have not been established. Such regimens should only be used for patients that are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment.

Co-administration with other direct-acting antivirals against HCV

GRATEZIANO should only be co-administered with other direct-acting antiviral medicinal products if the benefit is considered to outweigh the risks based upon available data. There are no data to support the co-administration of GRATEZIANO and telaprevir or boceprevir. Such co-administration is not recommended (see also section 4.5).

Pregnancy and concomitant use with ribavirin

When GRATEZIANO is used in combination with ribavirin or peginterferon alfa/ribavirin, women of childbearing potential or their male partners must use an effective form of contraception during the treatment and for a period of time after the treatment as recommended in the Summary of Product Characteristics for ribavirin. Refer to the Summary of Product Characteristics for ribavirin for additional information.

Use with moderate P-gp inducers

Medicinal products that are moderate P- gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of GRATEZIANO. Co-administration of such medicinal products is not recommended with GRATEZIANO (see section 4.5).

Use in diabetic patients

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

Renal impairment

Safety data are limited in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and ESRD requiring haemodialysis. GRATEZIANO can be used in these patients with no dose adjustment when no other relevant treatment options are available (see sections 4.8, 5.1 and 5.2). When GRATEZIANO is used in combination with ribavirin or peginterferon alfa/ribavirin, refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance (CrCl) <50 mL/min (see also section 5.2).

Elderly patients

In general, caution should be exercised when administering sofosbuvir in elderly patients reflecting the greater frequency of anaemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

4.5 interactions with other medicinal products and other forms of interactions

Sofosbuvir is a nucleotide prodrug. After oral administration of GRATEZIANO, 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). Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not. Medicinal products that are strong P-gp inducers in the intestine (carbamazepine, phenobarbital,phenytoin, rifampicin and St. John's wort) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of GRATEZIANO and thus are contraindicated with GRATEZIANO (see section 4.3). Medicinal products that are moderate P-gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of GRATEZIANO. Co-administration with such medicinal products is not recommended with GRATEZIANO (see section 4.4). Co-administration of GRATEZIANO with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus GRATEZIANO 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).

Patients treated with vitamin K antagonists

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

Impact of DAA therapy on drugs metabolized by the liver

The pharmacokinetics of drugs that are metabolized by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV.

Other interactions

Drug interaction information for GRATEZIANO with potential concomitant medicinal products is summarized 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 GRATEZIANO and other medicinal products

Medicinal product by therapeutic areas	Mean ratio (90% confidence interval) for AUC, C_{max}, $C_{min a,b}$	Recommendation concerning co-administration with GRATEZIANO
ANALEPTICS		
Modafinil	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of GRATEZIANO with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of GRATEZIANO. 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 GRATEZIANO (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 GRATEZIANO.
ANTICONVULSANTS		
Phenobarbital Phenytoin	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	GRATEZIANO is contraindicated with phenobarbital and phenytoin (see section 4.3).
Carbamazepine	*Sofosbuvir* ↓ C_{max} 0.52 (0.43, 0.62) ↓ AUC 0.52 (0.46, 0.59) C_{min} (NA) GS 331007 ↔ C_{max} 1.04 (0.97,1.11) ↔ AUC 0.99 (0.94, 1.04) C_{min} (NA) (Induction of P-gp)	GRATEZIANO is contraindicated with carbamazepine (see section 4.3).
Oxcarbazepine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of GRATEZIANO with oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of GRATEZIANO. Such co-administration is not recommended (see section 4.4).
ANTIMYCOBACTERIALS		
Rifampicin[f] (600 mg single dose)	*Sofosbuvir* ↓ C_{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) C_{min} (NA) *GS-331007* ↔ C_{max} 1.23 (1.14,1.34) ↔ AUC 0.95 (0.88, 1.03) C_{min} (NA) (Induction of P-gp)	GRATEZIANO is contraindicated with rifampicin (see section 4.3).
Rifabutin	*Sofosbuvir* ↓ C_{max} 0.64 (0.53, 0.77) ↓ AUC 0.76 (0.63, 0.91) C_{min} (NA) GS 331007 ↔ C_{max} 1.15 (1.03,1.27) ↔ AUC 1.03 (0.95, 1.12) C_{min} (NA) (Induction of P-gp)	No dose adjustment of GRATEZIANO is required when concomitantly used with rifabutin.
Rifapentine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of GRATEZIANO with rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of GRATEZIANO. Such co-administration is not recommended (see section 4.4).
HERBAL SUPPLEMENTS		
St. John's wort	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	GRATEZIANO is contraindicated with St. John's wort (see section 4.4).
HCV ANITIVIRAL AGENTS: HCV PROTEASE INHIBITORS		
Boceprevir (BOC) Telaprevir (TPV)	Interaction not studied. *Expected:* ↑ Sofosbuvir (TPV) ↔ Sofosbuvir (BOC) ↔ GS-331007 (TPV or BOC)	No drug-drug interaction data exists regarding the co-administration of GRATEZIANO with boceprevir or telaprevir.
NARCOTIC ANALGESICS		
Methadone[f] (Methadone maintenance therapy [30 to 130 mg/daily])	Change to be: 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} 0.95c (0.68,1.33) ↑ AUC 1.30c (1.00, 1.69) C_{min} (NA) GS-331007 ↓ C_{max} 0.73c (0.65,0.83) ↔ AUC 1.04c (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 at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required.
Tacrolimuse (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 at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.
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_{mi}n (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.
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/not applicable
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%

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

When GRATEZIANO 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 as recommended in the Summary of Product Characteristics for ribavirin. Refer to the Summary of Product Characteristics for ribavirin for additional information.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir in pregnant women.
As a precautionary measure, it is preferable to avoid the use of GRATEZIANO 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 sofosbuvir and its metabolites are excreted in human milk.
A risk to newborns/infants cannot be excluded. Therefore, GRATEZIANO should not be used during breast-feeding.

Fertility

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

4.7 Effect on the ability to drive and use machines

GRATEZIANO has moderate influence on the ability to drive and use machines. Patients should be informed that fatigue and disturbance in attention, dizziness and blurred vision have been reported during treatment with sofosbuvir in combination with peginterferon alfa and ribavirin (see section 4.8).

4.8 undesirable effects

Summary of the safety profile

Sofosbuvir has been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. The most common adverse drug reactions occurring in patients receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin and peginterferon alfa were fatigue, headache, nausea and insomnia.

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with sofosbuvir in combination with ribavirin or in combination with peginterferon alfa and ribavirin (Table 4). The adverse reactions are listed below by body system organ class and frequency.

Table 4: Adverse drug reactions identified with sofosbuvir in combination with ribavirin or peginterferon alfa and ribavirin

Frequency	SOF[a] + RBV[b]	SOF + PEG[c] + RBV
Infections and infestations:		
Common	nasopharyngitis	
Blood and lymphatic system disorders:		
Very common	haemoglobin decreased	anaemia, neutropenia, lymphocyte count decreased, platelet count decreased
Common	anaemia	
Metabolism and nutrition disorders:		
Very common		decreased appetite
Common		weight decreased
Psychiatric disorders:		
Very common	insomnia	insomnia
Common	depression	depression, anxiety, agitation
Nervous system disorders:		
Very common	headache	dizziness, headache
Common	disturbance in attention	migraine, memory impairment,disturbance in attention
Eye disorders:		
Common		vision blurred
Respiratory, thoracic and mediastinal disorders:		
Very common		dyspnoea, cough
Common	dyspnoea, dyspnoea exertional, cough	dyspnoea exertional
Gastrointestinal disorders:		
Very common	nausea	diarrhoea, nausea, vomiting
Common	abdominal discomfort, constipation, dyspepsia	constipation, dry mouth, gastroesophageal reflux
Hepatobiliary disorders:		
Very common	blood bilirubin increased	blood bilirubin increased
Skin and subcutaneous tissue disorders:		
Very common		rash, pruritus
Common	alopecia, dry skin, pruritus	alopecia, dry skin
Musculoskeletal and connective tissue disorders:		
Very common		arthralgia, myalgia
Common	arthralgia, back pain, muscle spasms, myalgia	back pain, muscle spasms
General disorders and administration site conditions:		
Very common	fatigue, irritability	chills, fatigue, influenza-like illness, irritability, pain, pyrexia
Common	pyrexia, asthenia	chest pain, asthenia

a. SOF = sofosbuvir; b. RBV = ribavirin; c. PEG = peginterferon alfa.
Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when sofosbuvir containing-regimes are used in combination with amiodarone and/or other medicinal products that lower heart rate (see sections 4.4 and 4.5).

Skin disorders

Frequency not known: Stevens-Johnson syndrome

4.9 Overdose

No specific antidote is available for overdose with GRATEZIANO. If overdose occurs the patients must be monitored for evidence of toxicity. Treatment of overdose with GRATEZIANO consists of general supportive measures including monitoring of vitals signs as well as observation of the clinical status of the patient. A 4-hour hemodialysis session removed 18% of the administered dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

Sofosbuvir is a direct-acting antiviral; agent against the hepatitis C virus.
Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 is not an inhibitor of human DNA and RNA polymerases nor and inhibitor of mitochondrial RNA polymerase.

5.2 Pharmacokinetic properties

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

Absorption

Following oral administration, sofosbuvir was absorbed quickly and the peak plasma concentration was observed ~0.5-2 hour post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 to 4 hours post-dose.

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, OCT 2, 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. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

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 GtS-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.

Pharmacokinetics in special populations

Gender and race

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

Elderly

Population pharmacokinetic analysis in HCV infected patients 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.

Renal impairment

A summary of the effect of varying degrees of renal impairment (RI) on the exposures of sofosbuvir and GS-331007 compared to subjects with normal renal function, as described in the text below, are provided in Table 5.

Table 5: Effect of varying degrees of renal impairment on exposures (AUC) of sofosbuvir and GS-331007 compared to subjects with normal renal function

	HCV-Negative Subjects					HCV-Infected Subjects	
	Mild RI (eGFR ≥50 and <80 mL/min/1.73 m2)	Moderate RI (eGFR ≥30 and <50 mL/min/1.73 m2)	Severe RI (eGFR <30 mL/min/1.7 3m2)	ESRD Requiring Dialysis		Severe RI (eGFR <30 mL/min/1. 73m2)	ESRD Requiring Dialysis
				Dosed 1hr Before Dialysis	Dosed 1hr After Dialysis		
Sofosbuvir	1.6-fold↑	2.1-fold↑	2.7-fold↑	1.3-fold↑	1.6-fold↑	~2-fold↑	1.9-fold↑
GS331007	1.6-fold↑	1.9-fold↑	5.5-fold↑	≥10-fold↑	≥20-fold↑	~7-fold↑	21-fold↑

The pharmacokinetics of sofosbuvir were studied in HCV negative patients with mild (eGFR ≥50 and<80 mL/min/1.73 m2), moderate (eGFR ≥30 and <50 mL/min/1.73 m2), severe renal impairment (eGFR <30 mL/min/1.73 m2) and patients with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir, relative to patients with normal renal function (eGFR >80 mL/min/1.73 m2). GS 331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%. Following a single 400 mg dose of sofosbuvir, a 4 hour haemodialysis removed 18% of administered sofosbuvir dose.
In HCV-infected patients with severe renal impairment treated with sofosbuvir 200 mg with ribavirin or sofosbuvir 400 mg with ribavirin for 24 weeks or ledipasvir/sofosbuvir 90/400 mg for 12 weeks, the pharmacokinetics of sofosbuvir and GS-331007 were consistent with that observed in HCV negative patients with severe renal impairment.
The pharmacokinetics of sofosbuvir, and GS-331007 were studied in HCV-infected patients with ESRD requiring dialysis treated with ledipasvir/sofosbuvir for 8, 12, or 24 weeks or sofosbuvir/velpatasvir for 12 weeks, and compared to patients without renal impairment in the ledipasvir/sofosbuvir and sofosbuvir/velpatasvir (see section 4.4).

Hepatic impairment

No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment (see section 4.2).

Paediatric population

The pharmacokinetics of sofosbuvir and GS-331007 in paediatric patients have not been established (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Mannitol
Microcrystalline cellulose
Croscarmellose sodium
Colloidal silicon dioxide
Magnesium stearate
Film-coating:
Opadry 85F 92259 yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at room temperature not exceeding 30ºC, in dry place.
Dispense only in original container
Do not use if seal over bottle opening is broken or missing

6.5 Nature and contents of container

GRATEZIANO tablets are supplied in a carton box containing plastic HDPE bottle, Aluminum sealed containing 28 film coated tablets, and a desiccant with plastic HDPE cap+ insert leaflet

6.6 Special precautions for disposal

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

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EUROPEAN PHARMACEUTICALS

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