MPIVIROPACK

Sofosbuvir 400mg

1. Name of the medicinal product

MPIVIROPACK 400 mg F.C.T

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.

4. Clinical particulars

4.1 Therapeutic indications

MPIVIROPACK 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

MPIVIROPACK 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).

MPIVIROPACK should be used in combination with other medicinal products. Monotherapy of MPIVIROPACK is not recommended (see section 5.1). Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with MPIVIROPACK. The recommended co-administered medicinal product(s) and treatment duration for MPIVIROPACK combination therapy are provided in Table 1.

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

Patient population*	Treatment	Duration
Patients with genotype 1, 4, 5 or 6 CHC	MPIVIROPACK + ribavirin + peginterferon alfa MPIVIROPACK + ribavirin Only for use in patients ineligible or intolerant to peginterferon alfa (see section 4.4)	12 weeks[a,b] 24 weeks
Patients with genotype 2 CHC	MPIVIROPACK + ribavirin	12 weeks[b]
Patients with genotype 3 CHC	MPIVIROPACK + ribavirin + peginterferon alfa MPIVIROPACK + ribavirin	12 weeks[b] 24 weeks
Patients with CHC awaiting liver transplantation	MPIVIROPACK + 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 MPIVIROPACK, 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.

The dose of ribavirin, when used in combination with MPIVIROPACK, 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 MPIVIROPACK is not recommended.

If sofosbuvir is used in combination with peginterferon alfa, and a patient has a serious adverse reaction potentially related to this drug, 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 MPIVIROPACK

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 period treatment	<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 MPIVIROPACK are permanently discontinued, MPIVIROPACK should also be discontinued (see 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 potent P-gp inducers

Medicinal products that are potent P-glycoprotein (P-gp) inducers in the intestine (e.g. rifampicin, St. John's wort [Hypericum perforatum], carbamazepine and phenytoin) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of MPIVIROPACK. Such medicinal products should not be used with MPIVIROPACK (see section 4.5).

Renal impairment

The safety of MPIVIROPACK 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. When MPIVIROPACK 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).

HCV/HBV (hepatitis B virus) co-infection

There are no data on the use of MPIVIROPACK in patients with HCV/HBV co-infection.

Paediatric population

MPIVIROPACK is not recommended for use in children and adolescents under 18 years of age because the safety and efficacy have not been established in this population.

4.5 Interaction with other medicinal products and other forms of interaction

Sofosbuvir is a nucleotide prodrug. After oral administration of MPIVIROPACK, 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 (e.g. rifampicin, St. John's wort, carbamazepine and phenytoin) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of MPIVIROPACK and thus should not be used with MPIVIROPACK (see section 4.4). Co-administration of MPIVIROPACK with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus MPIVIROPACK 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 MPIVIROPACK 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 MPIVIROPACK and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{tau}[a]	Recommendation concerning co-administration with MPIVIROPACK
ANALEPTICS		
Modafinil	Interaction not studied. Expected: ↓ Sofosbuvir ↓ GS-331007	Co-administration of MPIVIROPACK with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of MPIVIROPACK. Such co-administration is not recommended.
ANTICONVULSANTS		
Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	Interaction not studied. Expected: ↓ Sofosbuvir ↓ GS-331007	Co-administration of MPIVIROPACK with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of MPIVIROPACK. Such co-administration is not recommended. MPIVIROPACK should not be used with carbamazepine, phenytoin, phenobarbital or oxcarbazepine, potent intestinal P-gp inducers (see section 4.4).
ANTIMYCOBACTERIALS		
Rifabutin Rifampicin Rifapentine	Interaction not studied. Expected: ↓ Sofosbuvir ↓ GS-331007	Co-administration of MPIVIROPACK with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of MPIVIROPACK. Such co-administration is not recommended. MPIVIROPACK should not be used with rifampicin, a potent intestinal P-gp inducer (see section 4.4).
HERBAL SUPPLEMENTS		
St. John's wort (Hypericum perforatum)	Interaction not studied. Expected: ↓ Sofosbuvir ↓ GS-331007	MPIVIROPACK should not be used with St. John's wort, a potent intestinal P-gp inducer (see section 4.4).
HCV ANTIVIRAL AGENTS: NS5A INHIBITORS		
Elbasvir (EBR) Telaprevir (TPV)	Interaction not studied. Expected: ↑ Sofosbuvir (TPV)	No drug-drug interaction data exists regarding the co-administration of MPIVIROPACK with ombitasvir or telaprevir.

HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS		
Raltegravir[c] (400 mg once daily) *	Raltegravir ↓ C_{max} 0.57 (0.44, 0.75) ↓ AUC 0.73 (0.59, 0.91) ↔ C_{24} 0.95 (0.81, 1.12) Sofosbuvir ↔ C_{max} 0.87 (0.71, 1.08) ↔ AUC 0.95 (0.82, 1.09) C_{max} (NA) GS-331007 ↔ C_{max} 1.09 (0.99, 1.20) ↔ AUC 1.03 (0.97, 1.08) C_{max} (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_{max} (NA) Norgestrel ↔ C_{max} 1.18 (0.98, 1.41) ↔ AUC 1.19 (0.98, 1.44) C_{max} (NA) Ethinyl estradiol ↔ C_{max} 1.14 (0.96, 1.36) ↔ AUC 1.08 (0.93, 1.25) C_{max} (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%

Medicinal products that are potent P-gp inducers in the intestine (rifampicin, St. John's wort, carbamazepine and phenytoin) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect. For this reason, sofosbuvir should not be co-administered with known inducers of P-gp.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

When MPIVIROPACK 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.

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 MPIVIROPACK 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. 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, MPIVIROPACK should not be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

MPIVIROPACK 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

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 proportion of subjects who permanently discontinued treatment due to adverse reactions was 1.4% for subjects receiving placebo, 0.5% for subjects receiving sofosbuvir + ribavirin for 12 weeks, 0% for subjects receiving sofosbuvir + ribavirin for 16 weeks, 11.1% for subjects receiving peginterferon alfa + ribavirin for 24 weeks and 2.4% for subjects receiving sofosbuvir + peginterferon alfa + ribavirin for 12 weeks.

Tabulated summary of adverse reactions

MPIVIROPACK has mainly 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 subjects receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin

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 (IC50) 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.

5.2 Pharmacokinetic properties

Sofosbuvir is a nucleotide prodrug that is extensively metabolised. The active metabolite is not observed. 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. 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. Based on population pharmacokinetic analysis in subjects with genotypes 1 to 6 HCV infection (n = 986), steady-state AUC_{0-24} 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 AUC_{0-24} was 57% higher and 39% lower, respectively in HCV infected subjects.

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 transporters including the organic anion-transporting polypeptide (OATP) 1B1 or 1B3. While subject to active tubular secretion, GS-331007 is not a substrate for renal transporters including organic anion transporter (OAT) 1 or 3, or organic cation transporter (OCT) 2.

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.

After a single 400 mg oral dose of [14C]-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 [14C]-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.

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 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

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects 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 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 m2), the sofosbuvir AUC_{inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{inf} was 55%, 88% and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir AUC_{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_{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