24 October 2013
EMA/697129/2013
Evaluation of Medicines for Human Use

Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring adressed to member states for Sofosbuvir available for compassionate use

1. MEDICINAL PRODUCT FOR COMPASSIONATE USE

- **Name of the medicinal product for Compassionate Use: Sofosbuvir Gilead**
- **Active substance(s): Sofosbuvir**
- **Pharmaceutical form: Film-coated tablet**
- **Route of administration: Oral use**
- **Strength: 400 mg**

2. NAME AND CONTACT DETAILS OF THE COMPANY

Gilead Sciences International Ltd
Granta Park
Abington
Cambridgeshire, CB21 6GT
UK
Tel: +44 1223 897496
Fax: +44 1223 897233

3. TARGET POPULATION

Sofosbuvir Gilead, when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C who are also:

- Actively on the waiting list for liver transplantation (documented) and require treatment to prevent graft reinfection with hepatitis C virus, or

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

- Who have undergone liver transplantation and have aggressive, recurrent hepatitis C infection resulting in progressive and worsening liver disease, and are at a high risk of death or decompensation within 12 months if left untreated.

4. CONDITIONS FOR DISTRIBUTION

Sofosbuvir Gilead should be prescribed only by clinicians experienced in the management of patients with chronic Hepatitis C virus (HCV) infection who are awaiting liver transplantation or have recently received a liver transplant.

5. CONDITIONS OF USE

5.1 Posology

Pre-transplant Patients: sofosbuvir 400 mg film-coated tablets (one tablet per day) should be used in combination with ribavirin (1,000 to 1,200 mg/day) until the time of liver transplantation.

Post-transplant Patients: sofosbuvir 400 mg film coated tablets (one tablet per day) should be used in combination with ribavirin (1,000 to 1,200 mg/day) for 24 weeks.

No dose adjustment is needed in hepatic impairment.

5.2 Contraindications

Patients with hypersensitivity to the active substance or any of the excipients.

5.3 Special warnings and precautions for use

For patients with mild to moderate renal impairment no dose adjustment is needed. In severe renal impairment / end stage renal disease the appropriate dose has not been identified (see section 6).

5.4 Interaction with other medicinal products and other forms of interaction

Potent intestinal inducers of Pgp ie rifampicin or St. John's wort (*Hypericum perforatum*) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect and thus should not be used together.

Sofosbuvir has no effect on the pharmacokinetics (PK) of co-administered oral contraceptives. No modification of dose of these agents is required.

Sofosbuvir has no or limited effect on the PK of co-administered ciclosporin, tacrolimus or methadone. No modification of the dose of these agents is required.

Ciclosporin (600 mg) increased sofosbuvir C_{max} and AUC 2.5-fold and 4.5-fold, respectively and decreased GS-331007 C_{max} by 40% while AUC was unchanged. No modification of the dose of is required.

Tacrolimus had a very limited effect on the PK of sofosbuvir, GS 566500 or GS 331007. No dose modification is required.

5.5 Pregnancy and lactation

Ribavirin may cause birth defects and/or death of the exposed foetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

When sofosbuvir is used in combination with ribavirin ± peginterferon alfa, women of childbearing potential and their male partners must an effective form of contraception during the treatment and for a period of time after the treatment, as recommended in the prescribing information for ribavirin. Refer to ribavirin prescribing information for additional information.

5.6 Incompatibilities

Not applicable.

5.7 Overdose

If an overdose occurs, the subject should be monitored for evidence of toxicity and standard supportive treatment administered as necessary. Haemodialysis can efficiently remove the predominant circulating metabolite GS-331007 with an extraction ratio of 53%. There is no known antidote for sofosbuvir.

5.8 Shelf life

2 years

5.9 Storage conditions

25°C

5.10 Special precautions for disposal

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

6. OTHER INFORMATION

- **Summary of relevant pharmacological properties**

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate (GS-461203), which can be incorporated by HCV NS5B and acts as a chain terminator.

- **Summary of relevant clinical properties**

Efficacy

SVR12 data are available from four phase III trials in patients with hepatitis C and compensated liver disease, including one single-armed study of sofosbuvir+peginterferon alfa+ribavirin for 12 weeks in treatment-naïve patients with genotype 1 infection and compensated liver disease (NEUTRINO); one randomised controlled non-inferiority study comparing 12 weeks of sofosbuvir+ribavirin with 24 weeks of peginterferon alfa+ribavirin (present standard-of-care) in treatment-naïve patients with genotype 2 or -3 infection and compensated liver disease

(FISSION); one randomised placebo-controlled study of sofosbuvir+ribavirin for 12 weeks in patients with genotype 2 or -3 infection deemed ineligible, intolerant or unwilling to take an interferon (POSITRON); and one randomised controlled comparison of sofosbuvir+ribavirin for 12 or 16 weeks in treatment-experienced patients with genotype 2 or -3 infection and compensated liver disease (FUSION). Treatment outcomes were as follows (tables 1 and 2):

Table 1. NEUTRINO (GS US 334 0110): Percentages of Subjects with SVR12 by HCV Genotype and Presence of Cirrhosis (Full Analysis Set)

	Number of Subjects with SVR12 n, %
	GS-334-0110 (NEUTRINO)
	Treatment Naive
	SOF+PEG+RBV 12 Weeks (N = 327)
Overall SVR12	296/327 (90.5%)
No Cirrhosis	252/273 (92.3%)
Cirrhosis	43/54 (79.6%)
Genotype 1 (1a, 1b, 1a/1b)	262/292 (89.7%)
Genotype 1a	206/225 (91.6%)
Genotype 1b	55/66 (83.3%)
Genotypes 4, 5, or 6	34/35 (97.1%)

27/28 patients with genotype 4 reached SVR12 A single subject with genotype 5 and all 6 subjects with genotype 6 HCV infection in this study achieved SVR12.

Table 2. FISSION (P7977-1231), POSITRON (GS US-334-0107), and FUSION (GS-US-334-0108): Percentages of Subjects with SVR12 by HCV Genotype and Presence of Cirrhosis (Full Analysis Set)

	Number of Subjects with SVR12 n, %				
	P7977-1231 (FISSION)		**GS-US-334-0107 (POSITRON)[a]**	**GS-US-334-0108 (FUSION)**	
	Treatment Naive		**Interferon Ineligible, Intolerant, Unwilling**	**Treatment Experienced**	
	SOF+RBV 12 Weeks	**PEG+RBV 24 Weeks**	**SOF+RBV 12 Weeks**	**SOF+RBV 12 Weeks**	**SOF+RBV 16 Weeks**
	N = 253	**N = 243**	**N = 207**	**N = 100**	**N = 95**
Overall SVR12	170/253 (67.2%)	162/243 (66.7%)	161/207 (77.8%)	50/100 (50.0%)	69/95 (72.6%)
No Cirrhosis	147/204 (72.1%)	143/193 (74.1%)	142/176 (80.7%)	39/64 (60.9%)	48/63 (76.2%)
Cirrhosis	23/49 (46.9%)	19/50 (38.0%)	19/31 (61.3%)	11/36 (30.6%)	21/32 (65.6%)
Genotype 2	68/70 (97.1%)	52/67 (77.6%)	101/109 (92.7%)	31/36 (86.1%)	30/32 (93.8%)
No Cirrhosis	58/59 (98.3%)	44/54 (81.5%)	85/92 (92.4%)	25/26 (96.2%)	23/23 (100.0%)
Cirrhosis	10/11 (90.9%)	8/13 (61.5%)	16/17 (94.1%)	6/10 (60.0%)	7/9 (77.8%)
Genotype 3	102/183 (55.7%)	110/176 (62.5%)	60/98 (61.2%)	19/64 (29.7%)	39/63 (61.9%)
No Cirrhosis	89/145 (61.4%)	99/139 (71.2%)	57/84 (67.9%)	14/38 (36.8%)	25/40 (62.5%)
Cirrhosis	13/38 (34.2%)	11/37 (29.7%)	3/14 (21.4%)	5/26 (19.2%)	14/23 (60.9%)

[a] None of the subjects in the placebo group in Study GS-US-334-0107 achieved SVR12.

Sofosbuvir was studied in HCV-infected subjects prior to undergoing liver transplantation in an open-label clinical study evaluating the safety and efficacy of sofosbuvir and ribavirin administered pre-transplant to prevent post-transplant HCV reinfection. The primary endpoint of the study was

post-transplant virologic response (pTVR, HCV-RNA <LLOQ at 12 weeks post-transplant). HCV-infected subjects, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the MILAN criteria received 400 mg sofosbuvir and 1,000-1,200 mg ribavirin daily for a maximum of 24 weeks or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 subjects who received sofosbuvir and ribavirin; the majority of subjects had HCV genotype 1, 44 subjects had a baseline CPT score less than 7. Among 41 patients that underwent transplantation with plasma HCV-RNA <LLOQ (regardless of treatment duration), outcomes were as follows:

Table 3. Virologic response post-transplant in subjects with HCV-RNA <LLOQ at the time of liver transplantation

	Week 2 post-transplant	**Week 4 post-transplant**	**Week 8 post-transplant**	**Week 12 post-transplant (pTVR)[b]**
Virologic response in evaluable subjects[a]	32/40 (80%)	27/39 (69%)	26/38 (68%)	23/37 (62%)

a. Evaluable subjects are defined as those who have reached the specified time point at the time of the interim analysis.
b. pTVR: post-transplant virologic response (HCV-RNA < LLOQ at 12 weeks post-procedure).

Pre-transplant treatment duration with sofosbuvir and ribavirin did not appear to influence treatment outcome provided the HCV-RNA was < LLOQ at the time of transplantation.

Drug resistance data

Resistance analyses were attempted on plasma HCV isolates from all subjects with HCV-RNA >1,000 IU/ml at the virologic failure time point or early discontinuation time point for those who had a plasma sample available. Among all sofosbuvir-treated subjects in the Phase 2 and 3 studies, a total of 302 of 1662 subjects qualified to be part of the resistance analysis population (RAP) with NS5B sequences available from 300 of 302 subjects in the RAP (deep sequencing from 294 with > 1000 × coverage at NS5B position 282 in 272/294 subjects; population sequencing from 6 subjects). The S282T substitution (conferring resistance to sofosbuvir) was detected in one subject who received sofosbuvir monotherapy, not in any of the remaining 299 subjects in the RAP with sequence data. There were other NS5B substitutions observed in samples from >2 subjects. However, none of these substitutions were associated with a phenotypic change in sofosbuvir or ribavirin susceptibility.

Safety

The most common side effects reported with the combination of peginterferon alfa+ribavirin include fatigue, headache, nausea and insomnia. In the sofosbuvir+ribavirin containing arms of phase III trials, irritability, anaemia, cough and dyspnoea were more common than with placebo.

No specific safety signal has been identified in the pre-transplant population (P7977-2025 study). A summary of reported serious adverse events (SAE) in the interim analysis is as follows:

Table 4. P7977-2025: Treatment-Emergent Serious Adverse Events (Safety Analysis Set)

Preferred Term	**SOF + RBV (N=61) N(%)**
Subjects Experiencing Any Serious Adverse Event	11 (18.0%)
Hepatocellular carcinoma	2 (3.3%)
Pyrexia	2 (3.3%)
Umbilical Hernia, Obstructive	2 (3.3%)
Atrial Fibrillation	1 (1.6%)
Abdominal Pain	1 (1.6%)
Abdominal Strangulated Hernia	1 (1.6%)
Cellulitis	1 (1.6%)
Confusional State	1 (1.6%)
Hepatic Encephalopathy	1 (1.6%)
Hyponatraemia	1 (1.6%)
Intervertebral Disc Degeneration	1 (1.6%)
Nausea	1 (1.6%)
Osteoarthritis	1 (1.6%)
Peritonitis Bacterial	1 (1.6%)
Pneumonitis	1 (1.6%)
Prostate Cancer	1 (1.6%)
Renal Failure Acute	1 (1.6%)
Sepsis	1 (1.6%)
Tumour Thrombosis	1 (1.6%)
Vomiting	1 (1.6%)

Pharmacokinetics

Absorption

Peak sofosbuvir concentrations were generally observed approximately 0.5 to 2 hours post-dose, regardless of dose level, in HCV-infected subjects and healthy subjects. Peak plasma concentrations of the metabolite GS-331007 were generally observed between 2 to 4 hours after sofosbuvir administration. No absolute bioavailability data is available.

After a high fat meal the exposure to sofosbuvir and GS-566500 was increased 1.8-fold and 1.6-fold. The bioequivalence criteria were met for GS-331007 which was the primary analysis in this study (P7977 1318- food-effect study).

In the pivotal Phase III protocols, sofosbuvir could be taken without regard to food. For the combination with ribavirin, however, the recommendation was to take ribavirin with food. Therefore, in practice sofosbuvir was administered with food in the pivotal clinical studies.

Distribution

The apparent oral volume of distribution for sofosbuvir was estimated to 127 L using population PK modelling (Pop-PK sofosbuvir).

Protein binding of GS-331007 was minimal in all evaluated species. There was a discrepancy between ex vivo (fu 18%) and in vitro (38%) determination of plasma protein binding (PPB) for sofosbuvir due to unknown reasons. The main binding protein is probably albumin.

Sofosbuvir is transported by BCRP and Pgp based on in vitro data.

Elimination

Sofosbuvir can be hydrolysed to GS-566500 by both human cathepsin A (CatA) and Carboxylesterase 1 (CES1).

GS-331007 was the major radioactive component in the plasma of all subjects, and accounted for an average of 90% of the total drug-related AUC. Sofosbuvir and GS-566500 accounted for the average of 6% and 3% of the total drug-related AUC, respectively.

Following a single 400 mg oral dose of [^{14}C] sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 76%, 14%, and 2.5% recovered in urine, faeces, and expired air, respectively. The majority of the sofosbuvir dose was recovered in the urine as GS-331007 (78%) with GS-566500 (3.7%), sofosbuvir (3.5%) and GS-606965 (nucleoside analogue monophosphate) contributing minimally to the overall urine recovery. This data indicate that renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. The median terminal half-life of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

The total recovery of all faecal components was between 5.7 and 27% of the administered dose. GS-331007 was the dominant radioactive component in all faecal samples and neither sofosbuvir nor GS-566500 were detected in the faeces of any subject.

Special populations

- *Renal impairment*

The PK of sofosbuvir were studied in HCV-negative subjects with mild (eGFR ≥50 and <80 ml/min/1.73 m^2), moderate (eGFR ≥30 and <50 ml/min/1.73 m^2), severe renal impairment (eGFR <30 ml/min/1.73 m^2) and subjects with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR >80 ml/min/1.73 m^2), the sofosbuvir $AUC_{0\text{-inf}}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-inf}}$ was 55%, 88% and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir $AUC_{0\text{-inf}}$ was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis

compared with 60% when sofosbuvir was dosed 1 hour after haemodialysis. The AUC_{0-inf} of GS-331007 in subjects with ESRD could not be reliably determined However, data indicate at least 10-fold and 20-fold higher exposure to GS-331007 in ESRD compared to normal subjects when sofosbuvir was administered 1 hour before or 1 hour after haemodialysis, respectively.

No dose adjustment is needed in mild or moderate renal impairment. No dose recommendation can be given in patients with severe renal impairment and subjects with ESRD.

- *Hepatic impairment*

The PK of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, sofosbuvir AUC_{0-24h} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24h} was 18% and 9% higher, respectively. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment.

7. CONDITIONS FOR SAFETY MONITORING

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Article 28(1) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use in accordance with Article 83(4) of Regulation (EC) No 726/2004 has been adopted. The Member State(s) will ensure that these pharmacovigilance obligations are fulfilled

8. DATE OF CHMP OPINION

24 October 2013