20 February 2014
EMA/181959/2014
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 Ledipasvir/Sofosbuvir available for compassionate use

1. MEDICINAL PRODUCT FOR COMPASSIONATE USE

- **Name of the medicinal product for Compassionate Use: ledipasvir/sofosbuvir FDC**
- **Active substance(s): ledipasvir, sofosbuvir**
- **Pharmaceutical form: Film-coated tablet**
- **Route of administration: Oral use**
- **Strength: 90mg/400mg**

2. NAME AND CONTACT DETAILS OF THE COMPANY

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3. TARGET POPULATION

Ledipasvir/sofosbuvir fixed dose combination (with or without ribavirin), when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C genotype 1 virus, with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated.

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to special medical prescription.

Ledipasvir/sofosbuvir fixed dose combination should be prescribed only by clinicians skilled in the management of patients with HCV.

5. CONDITIONS OF USE

5.1. Posology

Dosing recommendations

Ledipasvir/sofosbuvir film-coated tablets (one tablet per day) should be used for a duration of at least 12 weeks, up to 24 weeks, with or without ribavirin (1000/1200 mg per day if body weight is below or above 75 kg).

Method of administration

Ledipasvir/sofosbuvir may be taken with or without food.

5.2 Contraindications

Pregnant or nursing women;

Patients with history of significant drug allergy to the active substances of any of the exipients.

5.3 Special warnings and precautions for use

Drugs that are potent Pgp inducers (eg, rifampin, St. John's wort) in the intestine may significantly decrease ledipasvir and sofosbuvir plasma concentrations, leading to reduced therapeutic effect of LDV/SOF. Rifampin, rifapentine, rifabutin, and St John's Wort should not be used with LDV/SOF. Coadministration with other potent P-gp inducers (e.g. carbamazepine and phenytoin) is not recommended.

5.4 Interaction with other medicinal products and other forms of interaction

See also section 5.3 Special warnings and precautions for use.

Both ledipasvir and sofosbuvir are substrates of P-gp. 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.

Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentrations. Proton-pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with LDV/SOF or up to 2 hours after taking LDV/SOF. Proton-pump inhibitors should not be taken before LDV/SOF.

Coadministration of LDV/SOF with rosuvastatin may significantly increase rosuvastatin plasma concentrations, which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of LDV/SOF with rosuvastatin is not recommended.

Coadministration of LDV/SOF with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir, leading to reduced therapeutic effect of LDV/SOF. Coadministration is not recommended.

Coadminsitration of LDV/SOF with digoxin may increase digoxin plasma exposures. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with LDV/SOF.

Based on drug interaction studies conducted with ledipasvir or sofosbuvir single agents or LDV/SOF no clinically significant drug interactions have been either observed or are expected when LDV/SOF is combined with the following drugs: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, emtricitabine, efavirenz, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir disoproxil fumarate or verapamil.

5.5 Pregnancy and lactation

Ledipasvir/sofosbuvir should not be used in pregnant or nursing women.

5.6 Incompatibilities

Not applicable.

5.7 Overdose

There is no known antidote for the LDV/SOF. In the case of overdose, the subject should receive standard treatment for overdose and supportive therapy based on the subject's signs and symptoms.

It is unknown whether the LDV/SOF can be removed by dialysis. It is also unknown if LDV can be removed by dialysis. Hemodialysis can efficiently remove the predominant SOF circulating metabolite GS-331007 with an extraction ratio of 53%.

5.8 Shelf life

2 years

5.9 Storage condition

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 pharmacokinetic properties

Ledipasvir

The absolute bioavailability of ledipasvir is unknown. Following oral administration of LDV/SOF, ledipasvir median peak concentrations were observed 4.0 to 4.5 hours post-dose. The median terminal half-life of ledipasvir following administration of LDV/SOF is 47 hours. Ledipasvir is subject to slow oxidative metabolism via an unknown mechanism. Unchanged ledipasvir is the major species present in the feces. Biliary excretion of unchanged ledipasvir is a major route of elimination with renal excretion beinga minor pathway (approximately 1%). The overall ledipasvir exposure (AUC_{inf}) is similar in subjects with severe hepatic impairment and healthy controls with normal hepatic function.

Sofosbuvir

Sofosbuvir is a nucleotide prodrug that is extensively metabolised. The active metabolite is not observed. The predominant (>90%) metabolite, GS-331007, is inactive. Renal clearance is the major

elimination pathway for GS-331007 with a large part actively secreted. Following administration of LDV/SOF, the median terminal half-lives of sofosbuvir and GS-331007 are 0.4 and 27 hours, respectively. Relative to subjects with normal hepatic function, the sofosbuvir AUC(0-24) was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC(0-24) was 18% and 9% higher, respectively.

LDV/SOF may be administered to patients with mild, moderate or severe hepatic impairment without dose adjustment.

Summary of relevant pharmacological properties

- Ledipasvir is an inhibitor of NS5A, a mulitfunctional protein necessary for HCV replication. NS5A is an essential component of HCV replication complex.
- Sofosbuvir is an inhibitor of the HCV NS5B RNA polymerase.
- As individual components, both LDV and SOF displayed potent inhibition of HCV replicon RNA replication. Ledipasvir demonstrated picomolar potency in HCV genotypes 1a and 1b, with mean EC_{50} values of 0.031 and 0.004 nM, respectively. In addition, LDV had differing levels of antiviral activity against genotypes 2 to 6, with EC_{50} values ranging from 0.15 to 530 nM. Sofosbuvir demonstrated potent activity against all HCV genotypes with a range of activities observed in replicon assay (14–241 nM) depending on the genotype and testing method used. The combination of LDV and SOF has been shown to exhibit additive antiviral activity in vitro.

Summary of relevant Clinical properties

Clinical efficacy and safety

LONESTAR (GS-US-337-0118)

This is an ongoing Phase 2, randomized, open-label study. The study assessed the safety, tolerability, and antiviral efficacy of LDV/SOF administered with and without RBV for 8 or 12 weeks. The study had 2 parallel cohorts.

In Cohort 1, noncirrhotic treatment-naive subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups:

- LDV/SOF 8 Week TN group (Group 1): LDV/SOF 400 mg/90 mg (1 tablet) once daily for 8 weeks in treatment-naive subjects
- LDV/SOF+RBV 8 Week TN group (Group 2): LDV/SOF 400 mg/90 mg (1 tablet) once daily + RBV total daily dose of 1000 mg for subjects weighing $<$ 75 kg (5 $\times$ 200-mg tablets) or 1200 mg for subjects weighing $\geq$ 75 kg (6 $\times$ 200-mg tablets) administered in a divided daily dose for 8 weeks in treatment-naive subjects
- LDV/SOF 12 Week TN group (Group 3): LDV/SOF 400 mg/90 mg (1 tablet) once daily for 12 weeks in treatment-naive subjects

In Cohort 2, cirrhotic and noncirrhotic subjects who had previously failed PI+Peg-IFN+RBV therapy were randomized in a 1:1 ratio to 1 of 2 treatment groups:

- LDV/SOF 12 Week TE group (Group 4): LDV/SOF 400 mg/90 mg (1 tablet) once daily for 12 weeks in treatment-experienced subjects
- LDV/SOF+RBV 12 Week TE group (Group 5): LDV/SOF 400 mg/90 mg (1 tablet) once daily + RBV total daily dose of 1000 mg for subjects weighing $<$ 75 kg (5 $\times$ 200-mg tablets) or 1200 mg for

subjects weighing ≥ 75 kg (6 × 200-mg tablets) administered in a divided daily dose for 12 weeks in treatment-experienced subjects.

A total of 97 of 100 subjects achieved SVR12 across all groups; individual group proportions of subjects who achieved SVR12 ranged from 94.7% to 100%. Of note, 21 of the 22 cirrhotic subjects who had previously failed treatment with a PI-based regimen achieved SVR12.

Overall, the highest percentage of subjects with any AE was observed in the 2 RBV-containing groups (LDV/SOF+RBV 8 Week TN and LDV/SOF+RBV 12 Week TE groups [57.1% in both]), followed by the RBV-free groups (LDV/SOF 8 Week TN group [45.0%], the LDV/SOF 12 Week TN group [42.1%], and the LDV/SOF 12 Week TE group [36.8%]).

ION-1 (GS-US-337-0102)

This ongoing Phase 3, randomized, open-label, international, multicenter study assessed the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in treatment-naive subjects with chronic genotype 1 HCV infection.

Following screening and confirmation of eligibility by the investigators, approximately 800 subjects were randomized (1:1:1:1) to 1 of the following 4 treatment groups:

LDV/SOF 24 Week group (Group 1): LDV/SOF FDC (400 mg/90 mg) tablet once daily for 24 weeks

LDV/SOF+RBV 24 Week group (Group 2): LDV/SOF FDC (400 mg/90 mg) tablet once daily + RBV (1000 or 1200 mg/day divided twice daily [BID]) for 24 weeks

LDV/SOF 12 Week group (Group 3): LDV/SOF FDC (400 mg/90 mg) tablet once daily for 12 weeks

LDV/SOF+RBV 12 Week group (Group 4): LDV/SOF FDC (400 mg/90 mg) tablet once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks.

Randomization was stratified by HCV genotype (1a, 1b, or mixed 1a/1b) and cirrhosis status (presence or absence) at screening. Enrollment was managed so that approximately 20% of randomized subjects had cirrhosis.

SVR12 data have been presented for patients randomized to 12 week treatment arms

	LDV/SOF 12 Weeks (N = 214)	**LDV/SOF+RBV 12 Weeks (N = 217)**
SVR12	209/214 (97.7%)	211/217 (97.2%)
Overall Virologic Failure	1/214 (0.5%)	0/217

Note: HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL.

ION-2 (GS-US-337-0109)

This ongoing Phase 3, randomized, open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in treatment-experienced subjects with chronic genotype 1 HCV infection.

Following screening and confirmation of eligibility by the investigator, approximately 400 subjects were randomized (1:1:1:1) to 1 of the following 4 treatment groups:

LDV/SOF 24 Week group (Group 1): LDV/SOF FDC (400 mg/90 mg) tablet once daily for 24 weeks

LDV/SOF+RBV 24 Week group (Group 2): LDV/SOF FDC (400 mg/90 mg) tablet once daily + RBV (1000 or 1200 mg/day divided BID) for 24 weeks

LDV/SOF 12 Week group (Group 3): LDV/SOF FDC (400 mg/90 mg) tablet once daily for 12 weeks

LDV/SOF+RBV 12 Week group (Group 4): LDV/SOF FDC (400 mg/90 mg) tablet once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks.

Eligible subjects were males or nonpregnant/nonlactating females ≥ 18 years of age with chronic genotype 1 HCV infection who had screening HCV RNA levels ≥ 10^4 IU/mL, had virologic failure to prior treatment with a Peg-IFN+RBV regimen (including regimens containing nonstructural protein 3/4A [NS3/4A] PIs), had documentation of the presence or absence of cirrhosis, and had BMI ≥ 18 kg/m^2. Subjects were enrolled across 64 sites in the US.

Subjects who had discontinued their prior HCV therapy due to an AE were prohibited from enrolling in this study; therefore, all subjects in this study were prior virologic failures, classified as either relapse/breakthrough (55.7%) or nonresponse (44.3%). These treatment-experienced subjects had failed a prior Peg-IFN+RBV regimen, with approximately half having failed prior PI+Peg-IFN+RBV therapy (52.5%).

Of the 231 subjects who failed prior PI+Peg-IFN+RBV therapy (58.4% failed telaprevir; 29.4% failed boceprevir; 12.1% failed investigational PIs), 62.3% of subjects had relapse/breakthrough and 37.7% of subjects had nonresponse.

Of the 207 subjects who failed prior Peg-IFN+RBV therapy, 48.8% of subjects had relapse/breakthrough and 51.2% of subjects had nonresponse. The majority of these prior Peg-IFN+RBV nonresponders (60.4%) were null responders (ie, subjects who did not achieve undetectable HCV RNA levels while on treatment and who had < 2 $\log_{10}$ reduction during the first 12 weeks of treatment), and 39.6% were partial responders.

88 patients had cirrhosis.

The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS.

	LDV/SOF 12 Weeks (N=109)	LDV/SOF+RBV 12 Weeks (N=111)	LDV/SOF 24 Weeks (N=109)	LDV/SOF+RBV 24 Weeks (N=111)
SVR12	102/109 (93.6%)	107/111 (96.4%)	108/109 (99.1%)	110/111 (99.1%)
Overall Virologic Failure	7/109 (6.4%)	4/111 (3.6%)	0/109	1/111 (0.9%)

Note: HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL.

The following is a summary of safety in the LONESTAR study. The 3 most frequently reported overall AEs were nausea, anemia, and upper respiratory tract infection. The LDV/SOF+RBV 12 Week TE group had the highest numbers of subjects with nausea, anemia, and upper respiratory tract infection (19.0%, 4 subjects; 28.6%, 6 subjects; 19.0%, 4 subjects; respectively); all other AEs were reported in ≤ 2 subjects in any group, with the exception of headache (14.3%, 3 subjects) in the LDV/SOF+RBV 8 Week TN group. Anemia was only reported in subjects receiving RBV.

Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Grade 3 AEs were only reported in subjects receiving RBV. A total of 4 subjects (19.0%) in the LDV/SOF+RBV 8 Week TN group and 2 subjects (9.5%) in the LDV/SOF+RBV 12 Week TE group had a Grade 3 (severe) AE. Anemia was the only Grade 3 AE reported in > 1 subject; Grade 3 anemia was reported for 2 subjects (9.5%) in the LDV/SOF+RBV 12 Week TE group. No Grade 4 AEs were reported.

No deaths, pregnancies, or permanent study drug discontinuations due to AEs were reported during this study. A total of 5 SAEs were reported in 4 subjects on or after the first dose of study drug through the date of last dose of study drug plus 30 days. No SAEs were reported in the LDV/SOF 8 Week TN group on or after the first dose of study drug through the date of last dose of study drug plus 30 days. No trends in SAE type or onset time were observed, as no individual SAE was experienced by more than 1 subject. All SAEs were considered unrelated to study drug with the exception of anemia reported in 1 subject in the LDV/SOF+RBV 12 Week TE group.

All AEs leading to dose modifications led to modification of RBV only. The most frequently reported AE leading to modification or interruption of study drug was anemia, which was observed only in subjects treated with LDV/SOF+RBV (6 subjects [28.6%] in the LDV/SOF+RBV 12 Week TE group and 2 subjects [9.5%] in the LDV/SOF +RBV 8 Week TN group). Each of the other AEs that led to modification or interruption of study drug (dyspnea exertional, edema, and peptic ulcer) was reported in 1 subject only. One subject had LDV/SOF interrupted due to an SAE of peptic ulcer.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 laboratory abnormalities were reported in 2 subjects in each 12 Week TE group and in 1 subject in each 8 Week TN group (none in the 12 Week TN group). Grade 4 laboratory abnormalities were only reported in the 12 Week TE groups (2 subjects in the LDV/SOF+RBV group and 1 subject in the LDV/SOF group).

Consistent with the expected safety profile of RBV, corresponding decreases in hemoglobin and elevations in reticulocytes, bilirubin, and platelets were observed in subjects who received RBV as a component of the treatment regimen for the duration of treatment. Regarding the LDV/SOF+RBV groups, 4 subjects had a Grade 3 (3 subjects) or 4 (1 subject) decrease in hemoglobin, and 8 subjects had post baseline hemoglobin values < 10 g/dL, of whom 2 had hemoglobin values < 8.5 g/dL; no subjects in the RBV-free groups met these criteria. Median hemoglobin, reticulocytes, bilirubin, and platelets returned towards baseline values within 4 weeks after the last dose of study drug.

Grade 3 chemistry laboratory abnormalities were reported for lipase and serum glucose (hyperglycemia and hypoglycemia). Grade 4 chemistry laboratory abnormalities were reported for serum glucose (hyperglycemia) and serum potassium (hyperkalemia). The most common Grade 3 or 4 chemistry laboratory abnormality was increased serum glucose; all such subjects with hyperglycemia had a medical history of diabetes (the subject with a Grade 3 decrease in serum glucose [hypoglycemia] also had a medical history of diabetes). All other Grade 3 and 4 laboratory abnormalities occurred in 1 subject across the groups.

No subject in any group had Grade 3 or 4 ALT or total bilirubin changes (increases) from baseline. Three subjects had bilirubin > 2 × ULN while on treatment, 2 who received LDV/SOF+RBV and 1 who received LDV/SOF (this subject had elevated bilirubin at baseline). No notable changes in total bilirubin values were observed in the other groups.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) were reported during the study.

7. CONDITIONS FOR SAFETY MONITORING

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 24(1) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the company will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

8. DATE OF CHMP OPINION

20 February 2014