מאי 2023

הודעה על עדכון עלונים:

Harvoni film coated tablets

(SOFOSBUVIR 400 MG/ LEDIPASVIR 90 MG)

רופאים ורוקחים נכבדים,

חברת גיליאד סיאנסז ישראל בע"מ מבקשת להודיעכם כי חל עדכון בעלון לרופא ועלון לצרכן של התכשיר בנדון.

ההתוויה הרשומה לתכשיר בישראל:

Harvoni is indicated for the treatment of chronic hepatitis C (CHC) in adults.

השינויים מסומנים בעלונים המצורפים כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו חוצה~~ נגרע ממנו.

העדכונים המשמעותיים ביותר מופיעים במכתב זה, קיימים עדכונים מינוריים נוספים.

העלונים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://israeldrugs.health.gov.il/#!/byDrug

כמו כן ,ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

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התכשיר משווק ע"י חברת סל"א.

בברכה,

ילנה קפלן

רוקחת ממונה

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העדכונים המהותיים בעלון לרופא:

4.2 Posology and method of administration

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Renal impairment

No dose adjustment of Harvoni 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 dialysis. Harvoni 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).

~~The safety of ledipasvir/sofosbuvir has not been assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis (see section 5.2).~~

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4.4 Special warnings and precautions for use

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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 ESRD requiring haemodialysis. Harvoni 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). ~~No dose adjustment of Harvoni is required for patients with mild or moderate renal impairment. The safety of Harvoni has not been assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis.~~ When Harvoni is used in combination with ribavirin refer also to the Physicians Leaflet for ribavirin for patients with creatinine clearance (CrCl) < 50 mL/min (see section 5.2).

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4.8 Undesirable effects

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Patients with renal impairment

Ledipasvir/sofosbuvir was administered for 12 weeks to 18 patients with genotype 1 CHC and severe renal impairment in an open-label study (Study 0154). In this limited clinical safety data set, the rate of adverse events was not clearly elevated from what is expected in patients with severe renal impairment.

The safety of Harvoni has been evaluated in a 12-week non-controlled study including 95 patients with ESRD requiring dialysis (Study 4063). In this setting, exposure of sofosbuvir metabolite GS-331007 is 20-fold increased, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not clearly elevated from what is expected in ESRD patients.

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5.1 Pharmacodynamic properties

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Patients with renal impairment

Study 0154 was an open-label clinical study that evaluated the safety and efficacy of 12 weeks of treatment with ledipasvir/sofosbuvir in 18 genotype 1 HCV-infected patients with severe renal impairment not requiring dialysis. At baseline, two patients had cirrhosis and the mean eGFR was 24.9 mL/min (range: 9.0-39.6). SVR12 was achieved in 18/18 patients.

Study 4063 was an open-label three-arm clinical study that evaluated 8, 12, and 24 weeks of treatment with ledipasvir/sofosbuvir in a total of 95 patients with genotype 1 (72%), 2 (22%), 4 (2%), 5 (1%), or 6 (2%) CHC and ESRD requiring dialysis: 45 treatment-naïve genotype 1 HCV-infected patients without cirrhosis received ledipasvir/sofosbuvir for 8 weeks; 31 treatment-experienced genotype 1 HCV-infected patients and treatment-naïve or treatment-experienced patients with genotype 2, 5, and 6 infection without cirrhosis received ledipasvir/sofosbuvir for 12 weeks; and 19 genotype 1, 2, and 4 HCV-infected patients with compensated cirrhosis received ledipasvir/sofosbuvir for 24 weeks. Of the 95 total patients, at baseline, 20% of patients had cirrhosis, 22% were treatment experienced, 21% had received a kidney transplant, 92% were on hemodialysis, and 8% were on peritoneal dialysis; mean duration on dialysis was 11.5 years (range: 0.2 to 43.0 years). The SVR rates for the 8, 12, and 24 week ledipasvir/sofosbuvir treatment groups were 93% (42/45), 100% (31/31), and 79% (15/19), respectively. Of the seven patients who did not achieve SVR12, none experienced virologic failure or relapsed.

5.2 Pharmacokinetic properties

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Renal impairment

A summary of the effect of varying degrees of renal impairment (RI) on the exposures of the components of Harvoni compared to subjects with normal renal function, as described in the text below, are provided in Table 18.

Table 18: Effect of Varying Degrees of Renal Impairment on Exposures (AUC) of Sofosbuvir, GS-331007, and Ledipasvir Compared to Subjects with Normal Renal Function

	HCV-Negative Subjects					HCV-Infected Subjects	
	Mild RI (eGFR ≥ 50 and <80 mL/min/1.73m^2)	Moderate RI (eGFR ≥30 and <50 mL/min/1.73 m^2)	Severe RI (eGFR <30 mL/min/1.73 m^2)	ESRD Requiring Dialysis		Severe RI (eGFR <30 mL/min/1.73m^2)	ESRD Requiring Dialysis
				Dosed 1 hr Before Dialysis	Dosed 1 hr After Dialysis		
Sofosbuvir	1.6-fold ↑	2.1-fold ↑	2.7-fold ↑	1.3-fold ↑	1.6-fold ↑	~2-fold ↑	1.9-fold ↑
GS-331007	1.6-fold ↑	1.9-fold ↑	5.5-fold ↑	≥10-fold ↑	≥20-fold ↑	~6-fold ↑	23-fold ↑
Ledipasvir	-	-	↔	-	-	-	1.6-fold ↑

↔ indicates no clinically relevant change in the exposure of Ledipasvir.

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault, median [range] CrCl 22 [17-29] mL/min). ~~No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment.~~

The pharmacokinetics of sofosbuvir were studied in HCV negative patients 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 patients with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir~~. R~~relative to patients 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-inf} was 55%, 88% and 451% higher, respectively. In patients with ESRD, relative to patients with normal renal function, sofosbuvir AUC_{0-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_{0-inf} of GS-331007 in patients with ESRD administered with sofosbuvir 1 hour before or 1 hour after haemodialysis was at least 10-fold and 20-fold higher, respectively. GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%.~~ 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. ~~The safety and efficacy of sofosbuvir have not been established in patients with severe renal impairment or ESRD.~~

In HCV-infected patients with severe renal impairment treated with ledipasvir/sofosbuvir for 12 weeks (n = 18), the pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 were consistent with that observed in HCV negative patients with severe renal impairment.

The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 were studied in HCV-infected patients with ESRD requiring dialysis treated with ledipasvir/sofosbuvir (n=94) for 8, 12, or 24 weeks, and compared to patients without renal impairment in the ledipasvir/sofosbuvir Phase 2/3 trials.

Hepatic impairment

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Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to ledipasvir.

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Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to sofosbuvir and GS-331007.

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העדכונים המהותיים בעלון לצרכן:

2. לפני שימוש בתרופה

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אזהרות מיוחדות הנוגעות לשימוש בתרופה

הרופא שלך יידע האם אחד מהמצבים הרפואיים הבאים תקף לגביך. מצבים אלה יהוו שיקול לפני תחילת הטיפול בהרוונ.

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- **בעיות בכליות / או אם הינך עובר דיאליזה של כליות.**