מאי 2023

הודעה על עדכון עלונים:

Epclusa film coated tablets

(SOFOSBUVIR 400 MG/ VELPATASVIR 100 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:

Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection 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:

גיליאד סיאנסז ישראל בע"מ, רחוב החרש 4 ,ת.ד. 6090, פארק העסקים הוד השרון 4524075, ישראל .

התכשיר משווק ע"י חברת סל"א.

בברכה,

ילנה קפלן

רוקחת ממונה

גיליאד סיאנסז ישראל בע"מ

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העדכונים המהותיים בעלון לרופא:

4.2 Posology and method of administration

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Renal impairment

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~~The s~~Safety ~~and efficacy of Epclusa has not been assessed~~ data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2) ~~or~~ and end stage renal disease (ESRD) requiring haemodialysis. Epclusa can be used in these patients with no dose adjustment when no other relevant treatment options are available (see sections 4.4, 4.8, 5.1 and 5.2).

Epclusa has not been studied in patients with severe renal impairment not requiring dialysis.

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4.4 Special warnings and precautions for use

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Renal impairment

Safety data are limited ~~No dose adjustment of Epclusa is required for patients with mild or moderate renal impairment. The safety of Epclusa has not been assessed~~ in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) ~~or~~ and ESRD requiring haemodialysis. Epclusa 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 Epclusa is used in combination with ribavirin refer also to the Physicians Leaflet for ribavirin for patients with creatinine clearance < 50 mL/min (see section 5.2).

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5.1 Pharmacodynamic properties

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Clinical efficacy and safety

The efficacy of Epclusa was evaluated in three Phase 3 studies in patients with genotype 1 to 6 HCV infection with or without compensated cirrhosis, one Phase 3 study in patients with genotype 1 to 6 HCV infection with decompensated cirrhosis, ~~and~~ one Phase 3 study in HCV/HIV-1 co-infected patients with genotype 1 to 6 HCV infection and one Phase 2 study in patients with HCV infection and ESRD requiring dialysis, as summarised in Table 10.

Table 10: Studies conducted with Epclusa in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection

Study	Population	Study arms (Number of patients treated)
ASTRAL-1	Genotype 1, 2, 4, 5 and 6 TN and TE, without cirrhosis or with compensated cirrhosis	Epclusa 12 weeks (624) Placebo 12 weeks (116)
ASTRAL-2	Genotype 2 TN and TE, without cirrhosis or with compensated cirrhosis	Epclusa 12 weeks (134) SOF+RBV 12 weeks (132)
ASTRAL-3	Genotype 3 TN and TE, without cirrhosis or with compensated cirrhosis	Epclusa 12 weeks (277) SOF+RBV 24 weeks (275)
ASTRAL-4	Genotype 1, 2, 3, 4, 5 and 6 TN and TE, with CPT Class B decompensated cirrhosis	Epclusa 12 weeks (90) Epclusa + RBV 12 weeks (87) Epclusa 24 weeks (90)
ASTRAL-5	Genotype 1, 2, 3, 4, 5 and 6 TN and TE, without cirrhosis or with compensated cirrhosis, with HCV/HIV-1 co-infection	Epclusa 12 weeks (106)
GS-US-342-4062	TN and TE with or without cirrhosis, with ESRD requiring dialysis	Epclusa 12 weeks (59)

TN = treatment-naïve patients; TE = treatment-experienced patients (including those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor)

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Clinical studies in patients with Renal Impairment – study 4062

Study 4062 was an open-label clinical study that evaluated 12 weeks of treatment with Epclusa in 59 HCV-infected patients with ESRD requiring dialysis. The proportions of patients with genotype 1, 2, 3, 4, 6 or indeterminate HCV infection were 42%, 12%, 27%, 7% , 3%, and 9%, respectively. At baseline, 29% of patients had cirrhosis, 22% were treatment experienced, 32% had received a kidney transplant, 92% were on haemodialysis, and 8% were on peritoneal dialysis; mean duration on dialysis was 7.3 years (range: 0 to 40 years). The overall SVR rate was 95% (56/59); of the three patients that did not achieve SVR12, one had completed Epclusa treatment and relapsed and two did not meet virologic failure criteria.

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 Epclusa 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 Velpatasvir 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/1.73m^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↑	1.8-fold↑
GS-331007	1.6-fold↑	1.9-fold↑	5.5-fold↑	≥10-fold↑	≥20-fold↑	~7-fold↑	18-fold↑
Velpatasvir	-	-	1.5-fold↑	-	-	-	1.4-fold↑

The pharmacokinetics of sofosbuvir was 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 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively. In patients with ESRD, sofosbuvir $AUC_{0\text{-}inf}$ was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when dosed 1 hour after haemodialysis, respectively. The $AUC_{0\text{-}inf}$ 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%. Following a single 400 mg dose of sofosbuvir, a 4 hour haemodialysis removed 18% of administered dose ~~(see section 4.2).~~

In HCV-infected patients with severe renal impairment treated with sofosbuvir 200 mg with ribavirin (n=10) or sofosbuvir 400 mg with ribavirin (n=10) for 24 weeks or ledipasvir/sofosbuvir 90/400 mg (n=18) 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 velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). ~~Relative to subjects with normal renal function, velpatasvir AUC_{inf} was 50% higher in subjects with severe renal impairment (see section 4.2).~~

The pharmacokinetics of sofosbuvir, GS-331007, and velpatasvir were studied in HCV-infected patients with ESRD requiring dialysis treated with Epclusa (n=59) for 12 weeks, and compared to patients without renal impairment in the sofosbuvir/velpatasvir Phase 2/3 studies.

העדכונים המהותיים בעלון לצרכן:

2. לפני השימוש באפקלוזה

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אזהרות מיוחדות הנוגעות לשימוש בתרופה

היוועץ ברופא אם אתה:

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- סובל מבעיות בכליות/או אם הינך עובר דיאליזה בכליות, מאחר שהשפעות של אפקלוזה על חולים הסובלים מבעיות כלייתיות חמורות לא נבדקו במלואן