מאי 2023

הודעה על עדכון עלונים:

Vosevi film coated tablets

(SOFOSBUVIR 400 MG/ VOXILAPREVIR 100 MG/ VELPATASVIR 100 MG)

רופאים ורוקחים נכבדים,

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

ההתוויה הרשומה לתכשיר בישראל:

Vosevi is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

השינויים מסומנים בעלון המצורף 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

~~The s~~Safety ~~and efficacy of Vosevi has not been assessed~~ data are limited in patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] < 30 mL/min/1.73 m^2) ~~or~~ and end stage renal disease (ESRD) requiring haemodialysis. Vosevi has not been studied in patients with ESRD requiring dialysis. Vosevi 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).

Vosevi 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 in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) and ESRD requiring haemodialysis. Vosevi 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).

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4.8 Undesirable effects

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Patients with renal impairment

The safety of sofosbuvir in a fixed dose combination with either ledipasvir or velpatasvir has been studied in 154 patients with ESRD requiring dialysis (Study 4062 and 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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5.2 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 Vosevi compared to subjects with normal renal function, as described in the text below, are provided in Table 15.

Table 15: Effect of varying degrees of renal impairment on exposures (AUC) of SOF, GS-331007, velpatasvir and voxilaprevir 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↑	1.8-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↑
Voxilaprevir	-	-	1.7-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. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73 m^2), ~~the sofosbuvir AUC0-inf was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC0-inf was 55%, 88% and 451% higher, respectively. In patients with ESRD, sofosbuvir AUC0-inf was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when dosed 1 hour after haemodialysis, respectively. The AUC0-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 were studied with a single dose of 100 mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Voxilaprevir is not renally eliminated. ~~Relative to subjects with normal renal function, velpatasvir AUCinf was 50% higher in subjects with severe renal impairment (see section 4.2).~~

Additionally, ~~T~~the pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). The pharmacokinetics of voxilaprevir have not been studied in subjects with ESRD requiring dialysis ~~Relative to subjects with normal renal function, voxilaprevir AUCinf was 71% 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 once daily sofosbuvir/velpatasvir 400/100 mg for 12 weeks, and compared to patients without renal impairment in the sofosbuvir/velpatasvir Phase 2/3 trials.

Although exposures of the fixed-dose combination sofosbuvir, GS-331007, velpatasvir, and voxilaprevir were not directly evaluated in HCV-infected patients with ESRD requiring dialysis after administration of Vosevi, the exposures of sofosbuvir, GS-331007, and velpatasvir are expected to be similar to those observed after administration of sofosbuvir/velpatasvir 400/100 mg in HCV-infected patients with ESRD requiring dialysis.

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