אוגוסט 2025

הודעה על עדכון עלונים:

Veklury® 100 mg Powder for Concentrate for Solution for Infusion

(remdesivir 100 mg/vial)

רופאים ורוקחים נכבדים,

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

ההתוויה הרשומה לתכשיר בישראל:

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in:

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו חוצה~~ נגרע ממנו. הסימונים בצהוב הינם החמרות במידע הבטיחותי.

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

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://israeldrugs.health.gov.il/#!/byDrug/drugs/index.html

כמו כן, ניתן לקבלו מודפס 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 סל"א.

בברכה,

מריה חורגין

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 remdesivir is required in patients with renal impairment, including those on dialysis. However, safety data in patients with severe renal impairment and end stage renal disease (ESRD) are limited (see section 4.4) and based on a 5-day treatment duration (for clinical efficacy data in patients with an eGFR <30 mL/min, see section 5.1). ~~The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Patients with eGFR ≥ 30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment. Remdesivir should not be used in patients with eGFR < 30 mL/min (see sections 4.4 and 5.2).~~ The timing of administration of remdesivir is without regard to dialysis (see section 5.2).

The use of Veklury in pediatric patients with renal impairment is supported by safety data in adults. Limited data are available regarding the safety of Veklury in pediatric patients with mild or moderate renal impairment. No data are available regarding the safety of Veklury in pediatric patients with severe renal impairment.

4.4 Special warnings and precautions for use

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Renal impairment

~~In animal studies on rats and monkeys, severe renal toxicity was observed (see section 5.3). The mechanism of this renal toxicity is not fully understood. A relevance for humans cannot be excluded.~~

~~All patients should have eGFR determined prior to starting remdesivir and while receiving it as clinically appropriate. Remdesivir should not be used in patients with eGFR < 30 mL/min.~~ As clinically appropriate, patients should have eGFR determined prior to starting remdesivir and while receiving it. Safety data from patients with severe renal impairment and ESRD reported during Study GS-US-540-5912 were comparable to the known safety profile of remdesivir. However, there are limited safety data in this patient population. Therefore, taking the significant higher exposure of the metabolite GS-441524 into account, patients with severe renal impairment and ESRD should be closely monitored for adverse events during treatment with remdesivir (see section 5.2).

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Excipients

This medicinal product contains 212 mg sodium per 100 mg dose, equivalent to 10.6% of the WHO recommended maximum daily intake of 2g sodium for an adult.

~~Veklury contains betadex sulfobutyl ether sodium, which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Therefore Veklury should not be used in patients with eGFR < 30 mL/min (see sections 4.2 and 5.2).~~

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4.8 Undesirable effects

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Patients with renal impairment

In Study GS-US-540-5912, 163 hospitalised patients with confirmed COVID-19 and acute kidney injury, chronic kidney disease or ESRD on haemodialysis received remdesivir for up to 5 days (see sections 4.4 and 5.2). Safety data from these patients were comparable to the known safety profile of remdesivir. In this same study, the incidence of increased prothrombin time or INR was higher in patients treated with remdesivir compared to placebo, with no difference observed in the incidence of bleeding events between the two groups (see section 5.1).

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5.1 Pharmacodynamic properties

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In Study GS-US-540-5912, among 60 patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase emerged in 8 patients treated with remdesivir. In 4 patients treated with remdesivir, substitutions in the RNA-dependent RNA polymerase (M794I, C799F, or E136V) emerged and were associated with reduced susceptibility to remdesivir *in vitro* (≤3.5-fold). No other substitutions in the RNA-dependent RNA polymerase detected in patients treated with remdesivir were associated with resistance to remdesivir.

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Study GS-US-540-5912 in patients with COVID-19 and renal impairment

A randomised, double-blind, placebo-controlled clinical study (Study GS-US-540-5912) evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 4 days (for a total of up to 5 days of intravenously administered therapy) in 243 hospitalised adult patients with confirmed COVID-19 and renal impairment. The trial included 90 patients (37%) with AKI (defined as a 50% increase in serum creatinine within a 48-hour period that was sustained for ≥6 hours despite supportive care), 64 patients (26%) with CKD (eGFR <30 mL/minute), and 89 patients (37%) with ESRD (eGFR <15 mL/minute) requiring haemodialysis. Patients were randomised in a 2:1 manner, stratified by ESRD, high-flow oxygen requirement, and region (US vs ex-US) to receive remdesivir (n=163) or placebo (n=80), plus standard of care.

At baseline, mean age was 69 years (with 62% of patients aged 65 or older); 57% of patients were male, 67% were White, 26% were Black, and 3% were Asian. The most common baseline risk factors were hypertension (89%), diabetes mellitus (79%), and cardiovascular or cerebrovascular disease (51%); the distribution of risk factors was similar between the two treatment groups. A total of 45 patients (19%) were on high-flow oxygen, 144 (59%) were on low-flow oxygen, and 54 (22%) were on room air at baseline; no patients were on invasive mechanical ventilation (IMV). A total of 182 patients (75%) were not on renal replacement therapy, and 31 patients (13%) had received a COVID-19 vaccine.

The study closed prematurely due to feasibility issues and was underpowered to assess primary (all-cause death or IMV by Day 29) and secondary efficacy endpoints because of lower than expected enrolment.

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5.2 Pharmacokinetic properties

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Renal impairment

~~The pharmacokinetics of remdesivir and GS-441524 in renal impairment have not been evaluated. Remdesivir is not cleared unchanged in urine to any substantial extent, but its main metabolite GS-441524 is renally cleared and the metabolite levels in plasma may theoretically increase in patients with impaired renal function. The excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function. Veklury should not be used in patients with eGFR < 30 mL/min.~~

The pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-704277) and the excipient SBECD were evaluated in healthy subjects, those with mild (eGFR 60-89 mL/minute), moderate (eGFR 30-59 mL/minute), severe (eGFR 15-29 mL/minute) renal impairment, or with ESRD (eGFR <15 mL/minute) on haemodialysis or not on haemodialysis following a single dose of up to 100 mg of remdesivir (Table 11); and in a Phase 3 study in COVID-19 patients with severely reduced kidney function (eGFR <30 mL/minute) receiving remdesivir 200 mg on Day 1 followed by 100 mg from Day 2 to Day 5 (Table 12).

Pharmacokinetic exposures of remdesivir were not affected by renal function or timing of remdesivir administration around dialysis. Exposures of GS-704277, GS-441524, and SBECD were up to 2.8-fold, 7.9-fold and 20-fold higher, respectively, in those with renal impairment than those with normal renal function which is not considered clinically significant based on limited available safety data. No dose adjustment of remdesivir is required for patients with renal impairment, including those on dialysis.

Table 11: Statistical comparison of single-dose pharmacokinetic parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) between adult subjects with decreased renal function[b] (mild, moderate, severe renal impairment and ESRD) and adult subjects[a] with normal renal function

GLSM Ratio[c] (90%CI)	60-89 mL per minute N=10	30-59 mL per minute N=10	15-29 mL per minute N=10	<15 mL per minute		
				Pre-haemodialysis N=6	Post-haemodialysis N=6	No dialysis N=3
Remdesivir						
C_{max} (ng/mL)	96.0 (70.5, 131)	120 (101, 142)	97.1 (83.3, 113)	89.1 (67.1, 118)	113 (79.4, 160)	93.9 (65.4, 135)
AUC_{inf} (h•ng/mL)	99.5 (75.3, 132)	122 (97.5, 152)	94 (83.0, 107)	79.6 (59.0, 108)	108 (71.5, 163)	88.9 (55.2, 143)
GS-441524						
C_{max} (ng/mL)	107 (90, 126)	144 (113, 185)	168 (128, 220)	227 (172, 299)	307 (221, 426)	300 (263, 342)
AUC_{inf}[d] (h•ng/mL)	119 (97, 147)	202 (157, 262)	326 (239, 446)	497 (365, 677)	622 (444, 871)	787 (649, 953)
GS-704277						
C_{max} (ng/mL)	225 (120, 420)	183 (134, 249)	127 (96.1, 168)	143 (100, 205)	123 (83.6, 180)	176 (119, 261)
AUC_{inf} (h•ng/mL)	139 (113, 171)	201 (148, 273)	178 (127, 249)	218 (161, 295)	206 (142, 297)	281 (179, 443)

CI=Confidence Interval; GLSM = geometric least-squares mean

a Exposures were estimated using noncompartmental analysis from a dedicated Phase 1 renal impairment study GS-US-540-9015; single doses up to 100 mg were administered; each subject with renal impairment had a matched adult subject enrolled with normal renal function (eGFR ≥90 mL/min/1.73m^2), same sex, and similar body mass index (BMI (± 20%)) and age (± 10 years)
Subjects with reduced renal function and matched adult subjects with normal renal function received the same remdesivir dose
b eGFR was calculated using Modification of Diet in Renal Disease equation and reported in mL/min/1.73 m^2
c Ratio calculated for the comparison of PK parameters of test (subjects with reduced renal function) to reference (subjects with normal renal function)
d $AUC_{0\text{-}72h}$ for subjects on haemodialysis

Table 12: Pharmacokinetic parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) following IV administration of remdesivir (200 mg on day 1 followed by 100 mg daily on days 2-5) to adults with COVID-19 and severely reduced kidney function (eGFR <30 mL/min /1.73 m^2)

Parameter Mean[b] (percentile, 5th, 95th)	Remdesivir	GS-441524	GS-704277
C_{max} (ng/mL)	2090 (953, 4120)	349 (80.2, 811)	232 (61.9, 594)
AUC_{tau} (h•ng/mL)	1700 (1040, 2970)	7580 (1790, 18600)	919 (519, 1600)

a Population PK estimates for 30-minute IV infusion of remdesivir for 5 days (Study GS-US-540-5912, n=90).
b Geometric mean estimates.