אוגוסט 2021

הודעה על עדכון העלון לרופא:

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 בהתוויה ובמשטר המינון של התכשיר שבנדון.

נוסח ההתוויה המאושרת :

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and in adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment).

בנוסף לעדכון ההתוויה ומשטר המינון חלו שינויים נוספים בעלון לרופא של התכשיר בנדון.

השינויים מסומנים בעמוד הבא 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://data.health.gov.il/drugs/index.html#/byDrug

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.

בברכה,

הדר אוליאר

רוקחת ממונה

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העדכונים המהותיים שבוצעו בעלון לרופא:

4.1 Therapeutic indications

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and in adolescents (aged 12 to less than 18 years and ~~older with body weight~~ weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment).

4.2 Posology and method of administration

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Posology

The recommended dosage of remdesivir in ~~patients~~ adults and adolescents (12 to less than 18 years of age and ~~older and~~ weighing at least 40 kg) is:

- Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion
- Day 2 onwards – 100 mg given once daily by intravenous infusion.

The ~~total duration of treatment should be~~ recommended duration of treatment is ~~at least~~ 5 days ~~and not more than 10 days~~.

4.4 Special warnings and precautions for use

Hypersensitivity including infusion-related and anaphylactic reactions

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Monitor patients for hypersensitivity reactions during and following administration of remdesivir.

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4.8 Undesirable effects

Summary of the safety profile

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Tabulated summary of adverse reactions

The adverse reactions in Table 2 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

Table 2: Tabulated list of adverse reactions

Frequency	**Adverse reaction**
Immune system disorders	
…	
Not known	anaphylactic reaction
Investigations	
Very common	prothrombin time prolonged
…	

Description of selected adverse reactions

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Prothrombin time prolonged

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In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of prolonged prothrombin time or INR (predominantly Grades 1-2) was higher in subjects who received remdesivir compared to placebo, with no difference observed in the incidence of bleeding events between the two groups. Prothrombin time should be monitored while receiving remdesivir as clinically appropriate.

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5.1 Pharmacodynamic properties

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Clinical efficacy and safety

Clinical trials in patients with COVID-19

NIAID ACTT-1 Study (CO-US-540-5776)

A randomised, double-blind, placebo-controlled clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for up to 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalised adult patients with COVID-19 with evidence of lower respiratory tract involvement. The trial enrolled 1,~~063~~ 062 hospitalised patients: ~~120 (11.3~~ 159 (15%) patients with mild/moderate disease (15% in both treatment groups) ~~(defined by SpO2 >94% and respiratory rate <24 breaths/min without supplemental oxygen)~~ and 903 (85%) patients with severe disease (85% in both treatment groups). Mild/moderate disease was defined as SpO2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen; severe disease ~~(~~was defined ~~by~~ as SpO2 ≤ 94% on room air, ~~or~~ a respiratory rate ≥ 24 breaths/min, and an oxygen requirement, or a requirement for mechanical ventilation ~~requiring supplemental or ventilatory support~~. A total of 285 patients (26.8%) (n=131 received remdesivir) were on mechanical ventilation/Extracorporeal Membrane Oxygenation (ECMO). Patients were randomised 1:1, stratified by disease severity at enrolment, to receive remdesivir (n=541) or placebo (n=~~522~~ 521), plus standard of care.

The baseline mean age was 59 years and 36% of patients were aged 65 or older. Sixty-four percent were male, 53% were White, 21% were Black, 13% were Asian. The most common comorbidities were hypertension (~~49.6~~ 51%), obesity (~~37.0%),~~ 45%) and type 2 diabetes mellitus (~~29.7%), and coronary artery disease (11.6%).~~ 31%); the distribution of comorbidities was similar between the two treatment groups.

Approximately ~~33% (180~~ 38.4% (208/541) of the patients received a 10-day treatment course with remdesivir.

The primary clinical endpoint was time to recovery within ~~28~~29 days after randomisation, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care. ~~In an analysis performed after all patients had been followed up for 14 days, t~~The median time to recovery ~~in the overall population~~ was ~~11~~10 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.~~32~~29; [95% CI 1.12 to 1.~~55~~49], p < 0.001). ~~The outcome differed relevantly between the two strata. In the severe disease stratum time to recovery was 12 days in the remdesivir group and 18 days in the placebo group (recovery rate ratio 1.37 [95% CI: 1.15 to 1.63]; Table 3). For the mild/moderate disease stratum, time to recovery was not different between the two groups (5 days for both, remdesivir and placebo).~~

No difference in time to recovery was seen in the stratum of patients with mild-moderate disease at enrolment (n=159). The median time to recovery was 5 days in the remdesivir and 7 days in the placebo groups (recovery rate ratio 1.10; [95% CI 0.8 to 1.53]); the odds of improvement in the ordinal scale in the remdesivir group at Day 15 when compared to the placebo group were as follows: odds ratio, 1.2; [95% CI 0.7 to 2.2, p = 0.562].

Among patients with severe disease at enrolment (n=903), the median time to recovery was 12 days in the remdesivir group compared to 19 days in the placebo group (recovery rate ratio, 1.34; [95% CI 1.14 to 1.58]; p < 0.001); the odds of improvement in the ordinal scale in the remdesivir group at Day 15 when compared to the placebo group were as follows: odds ratio, 1.6; [95% CI 1.3 to 2.0].

Overall, the odds of improvement in the ordinal scale were higher in the remdesivir group at Day 15 when compared to the placebo group (odds ratio, 1.6; [95% CI 1.3 to 1.9], p < 0.001).

~~Table 3: Recovery outcomes in the severe disease stratum from NIAID ACTT-1~~

	~~Remdesivir (N=476)~~	~~Placebo (N=464)~~
~~Days to recovery~~		
~~Number of recoveries~~	~~282~~	~~227~~
~~Median (95 %CI)~~	~~12 (10; 14)~~	~~18 (15; 21)~~
~~Recovery rate ratio (95% CI)[a]~~	~~1.37 (1.15; 1.63)~~	

~~a Recovery rate ratio calculated from the stratified Cox model. Recovery rate ratios >1 indicate benefit for remdesivir~~

~~There was no difference in efficacy in patients randomized during the first 10 days after onset of symptoms as compared to those with symptoms for more than 10 days.~~

~~The clinical benefit of remdesivir was most apparent in patients receiving oxygen, however, not on ventilation, at Day 1 (rate recovery ratio 1.47 [95% CI 1.17–1.84]). For patients who were receiving mechanical ventilation or ECMO on Day 1 no difference in recovery rate was observed between the treatment groups (0.95 [95% CI 0.64 to 1.42]).~~

The 29-day mortality in the overall population was 11.6% for the remdesivir group vs 15.4% for the placebo group (hazard ratio, 0.73; [95% CI 0.52 to 1.03]; p=0.07). A post-hoc analysis of 29-day mortality by ordinal scale is reported in Table 3.

Table 3: 29-Day Mortality Outcomes by Ordinal Scale[a] at Baseline—NIAID ACTT-1 Trial

	Ordinal Score at Baseline			
	5		6	
	Requiring low-flow oxygen		Requiring high-flow oxygen or non-invasive mechanical ventilation	
	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)
29-day mortality	4.1	12.8	21.8	20.6
Hazard ratio[b] (95% CI)	0.30 (0.14, 0.64)		1.02 (0.54, 1.91)	

~~ECMO = Extracorporeal membrane oxygenation~~

a Not a pre-specified analysis.

b Hazard ratios for baseline ordinal score subgroups are from unstratified Cox proportional hazards models.

Study GS-US-540-5773 in Patients with Severe COVID-19

A randomised, open-label multi-centre clinical trial (Study 5773) of patients at least 12 years of age with confirmed SARS-CoV-2 infection, oxygen saturation of ≤ 94% on room air, and radiological evidence of pneumonia compared 200 patients who received remdesivir for 5 days

with 197 patients who received remdesivir for 10 days. All patients received 200 mg of remdesivir on Day 1 and 100 mg once daily on subsequent days, plus standard of care. The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death.

The odds of improvement at Day 14 for patients randomized to a 10-day course of remdesivir compared with those randomized to a 5-day course was 0.67 (odds ratio); [95% CI 0.46 to 0.98]. Statistically significant imbalances in baseline clinical status were observed in this study. After adjusting for between-group differences at baseline, the odds of improvement at Day 14 was 0.75 (odds ratio); [95% CI 0.51 to 1.12]. In addition, there were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups once adjusted for between group differences at baseline. All-cause 28-day mortality was 12% vs 14% in the 5- and 10-day treatment groups, respectively.

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