דצמבר 2024

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:

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בברכה,

מריה חורגין

רוקחת ממונה

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העדכונים המהותיים בעלון לרופא:

4.1 Therapeutic indications

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

(see section 5.1)

4.2 Posology and method of administration

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Posology

Table 1: Recommended dose in adults and paediatric patients

	Given by intravenous infusion		
	Adults	**Paediatric patients (weighing at least 40 kg)**	**Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Day 1 (single loading dose)	200 mg	200 mg	**5 mg/kg**
Day 2 and onwards (once daily)	100 mg	100 mg	**2.5 mg/kg**

Table 2: Treatment duration

	Adults	**Paediatric patients (weighing at least 40 kg)**	**Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Patients with **pneumonia and requiring supplemental oxygen**	The recommended duration of treatment is **5 days**	The recommended duration of treatment is **5 days**	**Daily for up to a total of 10 days**
Patients who **do not require supplemental oxygen and are at increased risk for progressing to severe COVID-19**	The total duration of treatment should be **3 days**, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms.	Daily for **3 days**, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms. ~~Not applicable.~~	Not applicable.

4.5 Interaction with other medicinal products and other forms of interaction

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Effects of remdesivir on other medicinal products

~~*In vitro*, remdesivir is an inhibitor of CYP3A4, UGT1A1, MATE1, OAT3, OCT1, OATP1B1 and OATP1B3. Until respective clinical data become available, the coadministration of sensitive substrates of these enzymes and/or transporters should be considered with caution. Remdesivir induced~~

~~CYP1A2 and potentially CYP3A *in vitro*. Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.~~

~~Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after IV administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure.~~ Remdesivir is not a clinically relevant inhibitor of CYP3A4, OATP1B1, and OATP1B3. *In vitro*, remdesivir is an inhibitor of UGT1A1, MATE1, OAT3, and OCT1; however no clinically significant drug interactions are expected with remdesivir and substrates of these enzymes or transporters.

Remdesivir is not a clinically relevant inducer of CYP3A4. Remdesivir induced CYP1A2 *in vitro*; however no clinically significant drug interaction is expected with remdesivir and CYP1A2 substrates.

Drug-drug interaction studies were conducted with remdesivir. Table 6 summarises the effect of remdesivir on the pharmacokinetics of studied drugs.

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Table 6: Effect of remdesivir on other drugs

Co-administered Drug Dose (mg)	**Remdesivir Dose (mg)**	**Interaction Geometric mean change (%)**	**Recommendation concerning co-administration**
Midazolam 2.5 single dose	200 single dose	C_{max} ↑29% [a] AUC_{inf} ↑20% [a] No inhibition is expected when co-administering remdesivir with substrate of CYP3A	No dose adjustment of remdesivir is required when it is co-administered with substrate of CYP3A
Midazolam 2.5 single dose	200 single dose followed by 100 once daily (10 doses)[b]	C_{max} ↑45%[c] AUC_{inf} ↑30%[c] No induction is expected when co-administering remdesivir with substrate of CYP3A	
Pitavastatin 2 single dose	200 single dose	C_{max} ↑5% [a] **AUC_{inf} ↑17% [a]** **No inhibition is expected when co-administering remdesivir with substrate of OATP1B1/OATP1B3**	No dose adjustment of remdesivir is required when it is co-administered with substrate of OATP1B1/OATP1B3

NOTE: Interaction study conducted in healthy volunteers.
a. No effect = 1.00 (0.80-1.25).
b. Midazolam administered with last dose of remdesivir.
c. No effect = 1.00 (0.70-1.43)

4.8 Undesirable effects

Description of selected adverse reactions

Transaminases ~~I~~increased

~~In healthy volunteer studies, increases in ALT, aspartate aminotransferase (AST) or both in subjects who received remdesivir were grade 1 (10%) or grade 2 (4%). In a randomised, double-blind, placebo-controlled clinical study of patients with COVID-19 (NIAID ACTT-1), any grade (≥ 1.25 × upper limit of normal (ULN)) laboratory abnormalities of increased AST and increased ALT occurred in 33% and 32% of patients, respectively, receiving remdesivir compared with 44% and 43% of patients, respectively, receiving placebo. Grade ≥ 3 (≥ 5.0 × ULN) laboratory abnormalities of increased AST and increased ALT occurred in 6% and 3% of patients, respectively, receiving remdesivir compared with 8% and 6% of patients, respectively, receiving placebo. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5773) in hospitalised patients with severe COVID-19 receiving remdesivir for 5 (n=200) or 10 days (n=197), any grade laboratory abnormalities of increased AST and~~

~~increased ALT occurred in 40% and 42% of patients, respectively, receiving remdesivir. Grade ≥ 3 laboratory abnormalities of increased AST and increased ALT both occurred in 7% of patients receiving remdesivir. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5774) in hospitalised patients with moderate COVID-19 receiving remdesivir for 5 (n=191) or 10 days (n=193) compared to standard of care (n=200), any grade laboratory abnormalities of increased AST and increased ALT occurred in 32% and 33% of patients, respectively, receiving remdesivir, and 33% and 39% of patients, respectively, receiving standard of care. Grade ≥ 3 laboratory abnormalities of increased AST and increased ALT occurred in 2% and 3% of patients, respectively, receiving remdesivir and 6% and 8%, respectively, receiving standard of care.~~
In healthy volunteer studies, increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or both in subjects who received remdesivir were 1.25 to 2.5 times the upper limit of normal (ULN) (10%) or 2.5 to 5 times ULN (4%). In clinical studies of patients with COVID-19, the incidence of increased transaminases was similar in patients treated with remdesivir compared to placebo or standard of care.

Prothrombin time prolonged
In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of prolonged prothrombin time or INR (predominantly less than 2 times ULN~~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.~~
In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in patients treated with remdesivir compared to placebo.

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4.9 Overdose

Treatment of overdose with remdesivir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with remdesivir. In one clinical pharmacology trial, remdesivir 600 mg as a single dose over 30 minutes, equivalent to 3 times the therapeutic loading dose of 200 mg, was administered to 60 healthy subjects. Nausea and/or vomiting (Grades 1-2) was reported for 33 (55%) subjects. One subject (2%) had increased AST and ALT (Grade 4) without elevation of bilirubin.

5.1 Pharmacodynamic properties

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Study GS-US-540-9012 in patients with confirmed COVID-19 at increased risk for disease progression
A randomised, double-blind, placebo-controlled, multi-centre clinical trial to evaluate treatment with remdesivir in an outpatient setting in 562 patients including 8 adolescents (12 years of age and older and weighing at least 40 kg) with confirmed COVID-19 and at least one risk factor for disease progression to hospitalisation. Risk factors for disease progression were: aged ≥ 60 years, chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease. Vaccinated patients were excluded from the study.

Patients treated with remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days for a total of 3 days of intravenously administered therapy. Patients were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (< 60 vs ≥ 60 years), and region (US vs ex-US) to receive remdesivir (n=279) or placebo (n=283), plus standard of care.

At baseline, mean age was 50 years (with 30% of patients aged 60 or older); 52% were male, 80% were White, 8% were Black, 2% were Asian, 44% were Hispanic or Latino; median body mass index was 30.7 kg/m^2. The most common comorbidities were diabetes mellitus (62%), obesity (56%), and

hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3,6) days; median viral load was 6.3 log_{10} copies/mL at baseline. The baseline demographics and disease characteristics were balanced across the remdesivir and placebo treatment groups. Post-hoc exploratory analysis of optional biomarker samples showed 14.8% of patients were serological positive at baseline and 37.7% were serological negative (47.5% did not consent to optional biomarker collection).

The primary endpoint was the proportion of patients with COVID-19 related hospitalisation (defined as at least 24 hours of acute care) or all-cause 28-day mortality. Events (COVID-19-related hospitalisation or all-cause 28-day mortality) occurred in 2 (0.7%) patients treated with remdesivir compared to 15 (5.3%) patients concurrently randomized to placebo, demonstrating an 87% reduction in COVID-19-related hospitalisation or all-cause mortality compared to placebo (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). The absolute risk reduction was 4.6% (95% CI, 1.8% to 7.5%). No deaths were observed at Day 28. Six of the 17 hospitalisation events occurred in participants with known baseline serostatus (serological positive: n=0 in remdesivir group and n=2 in placebo group; serological negative: n=2 in remdesivir group and n=2 in placebo group). Eleven of the 17 hospitalisation events occurred in participants with unknown baseline serostatus in placebo group and none in the remdesivir group. No conclusion can be made on efficacy in the subgroups stratified by serostatus due to the small number of patients with known serostatus and overall low event rates.

QT

In a thorough QT/QTc trial that dosed 60 healthy subjects with 600 mg of remdesivir as a single treatment, no effect was seen on the QTc interval.
~~Current non-clinical and clinical data do not suggest a risk of QT prolongation, but QT prolongation has not been fully evaluated in humans.~~

5.2 Pharmacokinetic properties

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Interactions
In vitro:
Remdesivir inhibited CYP3A4 ~~*in vitro* (see section 4.5)~~. At physiologically relevant concentrations (steady-state), remdesivir or its metabolites GS-441524 and GS-704277 did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 ~~*in vitro*~~. Remdesivir is not a time-dependent inhibitor of CYP450 enzymes ~~*in vitro*~~.

Remdesivir induced CYP1A2 and potentially CYP3A4, but not CYP2B6 ~~*in vitro* (see section 4.5)~~.

~~*In vitro*~~ The data indicate~~s~~ no clinically relevant inhibition of UGT1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277. Remdesivir, but not its metabolites, inhibited UGT1A1 ~~*in vitro*~~.

For GS-441524 and GS-704277, the only enzyme for which metabolism could be detected was UGT1A3.

Remdesivir inhibited OAT3, MATE1, OCT1, OATP1B1 and OATP1B3 ~~*in vitro* (see section 4.5)~~. At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit P-gp and BCRP ~~*in vitro*~~ (see section 4.5).

In vivo:
Based on clinical drug interaction studies with remdesivir, no clinically significant drug interactions are expected with substrates of CYP1A2, CYP3A4 (including dexamethasone), UGT1A1, MATE1, OAT3, OCT1, OATP1B1 and OATP1B3.