דצמבר 2022

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 בעלון לרופא של התכשיר בנדון.

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).

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:

4.5 Interaction with other medicinal products and other forms of interaction

~~No clinical interaction studies have been performed with remdesivir. The overall potential for interactions is currently unknown; patients should remain under close observation during the days of remdesivir administration.~~

Pharmacodynamic interactions
Due to antagonism observed *in vitro*, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

Pharmacokinetic interactions
Effects of other medicinal products on remdesivir
In vitro, remdesivir is a substrate for esterases in plasma and tissue, drug metabolizing ~~enzymes CYP2C8, CYP2D6, and~~ enzyme CYP3A4~~,~~ and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. GS-704277 (a metabolite of remdesivir) is a substrate for OATP1B1 and OATP1B3.

~~The potential of interaction of remdesivir with inhibitors/inducers of the hydrolytic pathway (esterase) or CYP2C8, 2D6 or 3A4 has not been studied. The risk of clinically relevant interaction is unknown. Strong inhibitors may result in increased remdesivir exposure. The use of strong inducers (e.g. rifampicin) may decrease plasma concentrations of remdesivir and is not recommended.~~

~~Dexamethasone is reported to be a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after multiple doses. Dexamethasone is unlikely to have a clinically significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.~~

A drug-drug interaction study was conducted with remdesivir. Table 2 summarises the pharmacokinetic effects of studied drugs on remdesivir and metabolites GS-704277 and GS-441524.

Table 2: Effect of other drugs on remdesivir and metabolites GS-704277 and GS-441524

Co-administered Drug Dose (mg)	**Interaction Geometric mean change (%)**	**Recommendation concerning co-administration**
Cyclosporin 400 single dose	remdesivir: C_{max} ↑49% AUC_{inf} ↑89% GS-704277: C_{max} ↑151% AUC_{inf} ↑197% GS-441524: C_{max} ↑17% AUC_{inf} ↔ No interactions are expected when co-administering remdesivir with inhibitors of OATP1B1/1B3 and/or P-gp.	No dose adjustment of remdesivir is required when it is co-administered with inhibitors of OATP1B1 and OATP1B3.
Carbamazepine 300 twice daily	remdesivir: C_{max} ↓13% AUC_{inf} ↓8% GS-704277: C_{max} ↔ AUC_{inf} ↔ GS-441524: C_{max} ↔ AUC_{inf} ↓17% No interactions are expected when co-administering remdesivir with strong CYP3A4 inducers or CYP3A4 inhibitors.	No dose adjustment of remdesivir is required when it is co-administered with strong CYP3A4 and/or P-gp inducers.

NOTE: Interaction study conducted in healthy volunteers.

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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. ~~The~~ Until respective clinical ~~relevance~~ data become available, the coadministration of ~~these *in vitro* drug interactions has not been established. Remdesivir may transiently increase plasma concentrations of medicinal products that are~~ sensitive substrates of ~~CYP3A~~ these enzymes and/or ~~OATP 1B1/1B3. No data is available, however it can be suggested that medicinal products that are substrates of CYP3A4 or substrates of OATP 1B1/1B3~~ transporters should be ~~administered at least 2 hours after remdesivir~~. 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.
[…]

5.1 Pharmacodynamic properties

[…]

Antiviral activity

For the clinical isolates of the Delta (B.1.617.2) and Omicron (B.1.1.529~~sub-lineages~~, BA.1, BA.2, BA.2.12.1, BA.4 and BA.2~~5~~) variants, remdesivir also maintained antiviral activity (< 0.~~6~~7-fold change) relative to the lineage A SARS-CoV-2 isolates

[…]

5.2 Pharmacokinetic properties

[…]

Elimination
[…]

Pharmacokinetics of remdesivir and metabolites in adults with COVID-19

Pharmacokinetic exposures for remdesivir and its metabolites in adults with COVID-19 are provided in Table 6.

Table 6: Multiple dose PK parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) following IV administration of remdesivir 100 mg to adults with COVID-19

Parameters Mean[b] (95%CI)	Remdesivir	GS-441524	GS-704277
C_{max} (ng/mL)	2700 (2440, 2990)	143 (135, 152)	198 (180, 218)
AUC_{tau} (ng•h/mL)	1710 (1480, 1980)	2410 (2250, 2580)	392 (348, 442)
C_{tau}(ng/mL)	ND	61.5 (56.5, 66.8)	ND

CI=Confidence Interval; ND=Not detectable (at 24 hours post-dose)
a. Population PK estimates for 30-minute IV infusion of remdesivir for 3 days (Study GS-US-540-9012, n=147).
b. Geometric mean estimates

Other special populations

Gender, race and age
~~Pharmacokinetic differences for gender, race, and age have not been evaluated.~~
Based on gender, race and age, pharmacokinetic differences on the exposures of remdesivir were evaluated using population pharmacokinetic analysis. Gender and race did not affect the pharmacokinetics of remdesivir and its metabolites (GS-704277 and GS-441524). Pharmacokinetic

exposures of the GS-441524 metabolite were modestly increased in hospitalised COVID-19 patients ≥ 60 years of age, however no dose adjustment is needed in these patients.

[…]

Hospitalisation
Pharmacokinetic exposures for remdesivir in hospitalised patients with severe COVID-19 pneumonia were generally within the range of the exposures in non-hospitalised patients. The GS-704277 and GS-441524 metabolite levels were modestly increased.

Interactions
~~The potential of interaction of remdesivir as a victim was not studied with regards to the inhibition of the hydrolytic pathway (esterase). The risk of clinically relevant interaction is unknown.~~

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 ~~may however transiently inhibit CYP2B6, 2C8, 2C9 and 2D6 on the first day of administration. The clinical relevance of this inhibition was~~ is not ~~studied. The potential for~~ a time-dependent ~~inhibition~~ inhibitor of CYP450 enzymes ~~by remdesivir was not studied~~ *in vitro*.

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

In vitro data indicates no clinically relevant inhibition of ~~UGT1A1, 1A3~~ 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).
~~No data is available for OAT1, OAT3 or OCT2 inhibition by remdesivir.~~

[…]

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