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Veklury® (remdesivir) Use in Pregnancy

This document is in response to your request for information regarding the use of Veklury® (remdesivir [RDV]) for the treatment of COVID-19 in women who are pregnant. This response was developed according to principles of evidence-based medicine and contains data from phase 4 studies and retrospective studies (N≥80) published in peer review journals.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Summary

Product Labeling[1]

Available data from a clinical trial (IMPAACT 2032), published reports, the COVID-PR pregnancy exposure registry, and compassionate use of RDV in pregnant individuals have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes following exposure in the second and third trimester. However, there are insufficient pregnancy data available to evaluate the risk of RDV exposure during the first trimester.

Inform patients to notify their healthcare provider in the event of a pregnancy.

Phase 4 Data on RDV Use in Pregnancy

In the IMPAACT 2032 study, exposures to RDV and its metabolites were comparable between pregnant (n=25) and non-pregnant (n=28) participants with confirmed or suspected COVID-19. RDV was safe and well tolerated in both arms. No dose adjustments were required for IV RDV during pregnancy.[2]

Retrospective Data on RDV Use in Pregnancy

An analysis of ADEs related to RDV reported to the FAERS pharmacovigilance database identified 6 potential safety signals related to pregnancies, fetuses, and neonates: maternal exposure during pregnancy, premature delivery, fetal death, premature labor, abortion, and maternal drugs affecting fetus.[3]

In a compassionate use program that provided RDV to pregnant (n=67) or postpartum (n=19) female patients, after RDV treatment initiation, most patients from both populations recovered from COVID-19 by Day 28, no RDV-related deaths were reported, and SAEs were reported in 18% and 11% of pregnant and postpartum patients, respectively.[4]

A cohort study in Kazakhstan included pregnant patients with confirmed or probable severe COVID-19 treated with RDV (main group; n=60) or without RDV (control group; n=60).

Patients at 28 to 40 weeks of pregnancy comprised the largest group by gestational age, accounting for 63.3% of the main group and 65% of the control group. The total number of bed-days spent in the hospital was higher in the main group than in the control group (*P*=0.001). After 3 days, 66.6% of patients in the main group reported cessation of subjective dyspnea, and 41.6% reported improved respiration rate.[5]

A cohort study in Iran among pregnant patients with moderate to severe COVID-19 compared the maternal and fetal outcomes of those in the RDV group (n=57) and the non-RDV group (n=24). There was a significant association between receiving RDV and reduced length of hospital stay. There were no maternal deaths in either cohort, and emergency termination was required in 13 pregnancies in the RDV group and in 6 pregnancies in the non-RDV group.[6]

Product Labeling[1]

Use in Specific Populations

Pregnancy

Risk summary

Available data from a clinical trial (IMPAACT 2032), published reports, the COVID-PR pregnancy exposure registry, and compassionate use of RDV in pregnant individuals have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes following exposure in the second and third trimester. However, there are insufficient pregnancy data available to evaluate the risk of RDV exposure during the first trimester. A study evaluating the PKs of RDV during pregnancy demonstrated no clinically relevant differences between pregnant and non-pregnant individuals. No dose adjustments are recommended in patients who receive RDV during pregnancy. In nonclinical reproductive toxicity studies, RDV demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals at systemic exposures (area under the concentration-time curve) of the predominant circulating metabolite of RDV (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical considerations: disease-associated maternal and/or embryo-fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Please refer to the US FDA-approved prescribing information for additional information regarding pregnancy in Section 8.1 Pregnancy.

Phase 4 Data on RDV Use in Pregnancy

IMPAACT 2032 Study: Pregnant and Non-Pregnant Females

Study design and demographics[2]

A phase 4, prospective, open-label, non-randomized opportunistic study evaluated the PK and safety profiles of RDV in hospitalized pregnant (Arm 1) and non-pregnant (Arm 2) females aged 18 to 45 years old with confirmed or suspected COVID-19. Exclusion criteria included starting or receiving a fourth RDV dose, contraindications to RDV treatment, and any disallowed medications within 48 hours prior to study entry. Participants were treated with RDV 200 mg on Day 1, followed by RDV 100 mg IV once daily up to 10 days total. The primary outcomes included PK parameters, maternal safety, infant safety, and gestational outcomes for Arm 1. The secondary outcomes included PK and safety assessments for Arm 2. Participants were enrolled between March 2021 and December 2021.

Table 1. IMPAACT 2032: Baseline Demographics and Disease Characteristics[2]

Key Demographics and Characteristics		Arm 1: Pregnant Participants (n=25)	Arm 2: Non-Pregnant Participants (n=28)
Age, median (IQR), years		33 (27–37)	37.5 (31.5–40.5)
Gestational age, median (IQR), weeks		27.6 (24.9–31)	–
Trimester, second/third,[a] n (%)		13 (52)/12 (48)	–
O_2 support at baseline,[b] n (%)	Low-flow O_2	12 (54.5)	18 (72)
	High-flow O_2	9 (40.9)	5 (20)
	NIPPV	0 (0)	2 (8)
Baseline laboratory parameters,[c] median (IQR)	ALT, U/L	25.1 (14.5–44.6)	26.1 (16–58.1)
	C-reactive protein, mg/L	62 (33.4–134)	63.9 (25.3–104)
	Hgb, g/dL	11.2 (10.4–12.1)	11.7 (10.5–12.4)

[a]Two participants in Arm 1 had missing data.
[b]These were defined as the highest level of respiratory support within the 48 hours before the first infusion of RDV and the first RDV infusion. Data were missing for 1 participant in Arm 1 and 8 participants in Arm 2.
[c]These were the laboratory parameters closest to, including prior to, the first infusion.

Safety results[2]

RDV was safe and well tolerated (Table 2). No dose adjustments were required for IV RDV during pregnancy. The following 3 TRAEs occurred, all in Arm 2: Grade 2 bradycardia occurred in 2 participants and caused discontinuation of treatment after Doses 2 and 4, and a Grade 3 decrease in eGFR occurred in 1 participant and resolved without intervention.

The most common reasons for premature RDV discontinuation were provider's discretion (n=9), TRAEs (n=2), lost to follow-up (n=1), and study withdrawal (n=2).

Table 2. IMPAACT 2032: Safety Outcomes Through Infusion and Through Week 4 After the Last RDV Infusion[2,7]

Safety Outcomes, n/N (%)	Arm 1: Pregnant Participants		Arm 2: Non-Pregnant Participants	
	Infusion	Week 4[a]	Infusion	Week 4[a]
Any-grade AE	15/24 (62.5)	16/24 (66.7)	15/26 (57.7)	15/25 (60)
Hematologic AE of any grade	6/23 (26.1)	7/22 (31.8)	5/25 (20)	6/23 (26.1)
Hepatic AE of any grade	0/23	1/19 (5.3)	1/26 (3.8)	1/24 (4.2)
Renal AE of any grade	0/23	0/19	1/25 (4)	1/23 (4.3)
Grade ≥3 AE	14/24 (58.3)	15/24 (62.5)	13/26 (50)	13/24 (54.2)
Grade ≥3 TRAE[b]	0/23	0/19	1/25 (4)	1/23 (4.3)

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Safety Outcomes, n/N (%)	Arm 1: Pregnant Participants		Arm 2: Non-Pregnant Participants	
	Infusion	Week 4[a]	Infusion	Week 4[a]
SAE	3/23 (13)	5/21 (23.8)	3/25 (12)	4/23 (17.4)

[a]Denominators are participants who had follow-up through Week 4 and those who experienced an event but discontinued prior to that time point.
[b]The Clinical Management Committee assessed causality of AEs.

Overall, 4 preterm births (<37 weeks) occurred, 2 neonates were small for gestational age, and 1 fetal death occurred during gestation Week 26 that was deemed to be unrelated to RDV treatment.

Retrospective Data on RDV Use in Pregnancy

FAERS Analysis: Safety Signals With RDV Treatment[3]

Study design

A quantitative and descriptive study of data reported to the FAERS pharmacovigilance database was performed to analyze the ADEs related to RDV that were reported between 2020 and 2022. Of 12,089 reports that involved RDV, 7147 reports listed RDV as the primary drug suspect for the reported ADE and were included in the analysis. Medicine-event pairs were formed and were used for ROR calculations; ADEs with a frequency ≥3 and whose ROR lower CI was >1 were categorized as safety signals. Signals were categorized according to MedDRA SOC classification.

Results

The most common reporters of RDV-related ADEs were pharmacists (63.9%) and physicians (17.8%). Among the 7453 ADEs that listed RDV as the primary suspect, the following outcomes were reported: other serious outcomes (important medical events), n=3761 (50.5%); death, n=1840 (24.7%); initial or prolonged hospitalization, n=1203 (16.1%); life-threatening, n=420 (5.6%); required intervention to prevent permanent impairment/harm, n=124 (1.7%); disability, n=95 (1.3%); and congenital anomaly, n=10 (0.1%)

Of the 1484 types of RDV ADEs, 303 were considered possible safety signals; of these safety signals, 6 were related to pregnancies, fetuses, and neonates are shown in Table 3. Of the 27 reports that included premature delivery, fetal death, premature labor, and abortion as possible safety signals for RDV, 18 reports also noted an association with the use of medications other than RDV.

Table 3. FAERS Analysis: RDV Safety Signals Potentially Related to Pregnancies, Fetuses, and Neonates[3]

SOC	Signal	Frequency of Medicine-Event Pair	ROR (95% CI)
Pregnancy, puerperium, and perinatal conditions[a]	Premature delivery	11	2 (1.1–3.6)
	Fetal death	7	6.3 (3–13.3)
	Premature labor	4	4.2 (1.6–11.1)
	Abortion	3	5.2 (1.7–16.1)

SOC	Signal	Frequency of Medicine-Event Pair	ROR (95% CI)
Injury, poisoning, and procedural complications	Maternal exposure during pregnancy	70	2.3 (1.8–2.9)
	Maternal drugs affecting fetus	3	10.8 (3.4–33.7)

[a]Of the 27 reports within this SOC, the ages of the pregnant female patients at the time of the ADE were as follows: <18 years, n=1; 18 to 29 years, n=5; 30 to 39 years, n=14; 40 to 50 years, n=3. Age data were missing from 4 reports.

Compassionate Use Cohort: Patients With Severe COVID-19

Study design and demographics[4]

RDV was provided through a compassionate use, multicenter, open-label program for hospitalized pregnant women with severe SARS-CoV-2 infection (O_2 saturation ≤94% on room air or need for supplemental O_2). Exclusion criteria included CrCl (estimated by Cockcroft-Gault) <30 mL/min, serum ALT levels >5 × the upper limit of normal, or evidence of multiorgan failure. Patients were treated with RDV 200 mg IV on Day 1, followed by RDV 100 mg IV for 9 days, for a total of up to 10 days of therapy.

Data from 86 pregnant or postpartum patients from March 21 to June 16, 2020, were analyzed. Pregnant (n=67) and postpartum (n=19) patients received a median (IQR) of 8 (5–10) and 10 (9–10) RDV doses, respectively.

Table 4. Compassionate Use Cohort: Baseline Demographics and Disease Characteristics[4]

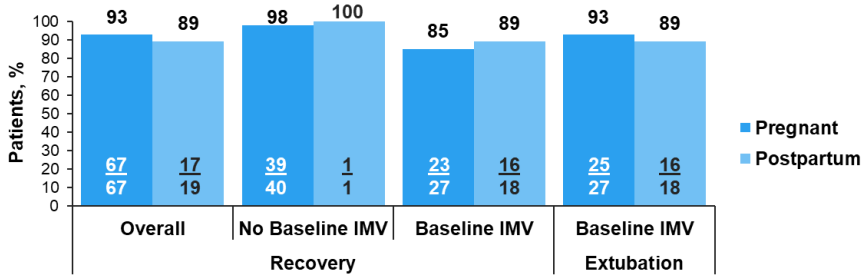
Key Demographics and Characteristics		All Patients (N=86)	Pregnant Patients (n=67)	Postpartum Patients (n=19)
Age, median (range), years		33 (20–43)	33 (21–43)	34 (20–41)
Gestational age, median (range), weeks		29 (14–39)	28 (14–39)	30 (27–36)
Any medical condition history, n (%)		55 (64)	45 (67)	10 (53)
Comorbid conditions with increased pregnancy or COVID-19 risks, n (%)	Obesity[a]	15 (17)	11 (16)	4 (21)
	Asthma	10 (12)	9 (13)	1 (5)
	Gestational diabetes	9 (10)	7 (10)	2 (11)
	Chronic hypertension[b]	7 (8)	6 (9)	1 (5)
	Diabetes mellitus[c]	7 (8)	7 (10)	0
O_2 support categories, n (%)	Room air	3 (3)	3 (4)	0
	Low-flow O_2	25 (29)	25 (37)	0
	High-flow O_2	11 (13)	10 (15)	1 (5)
	NIPPV	2 (2)	2 (3)	0
	IMV	44 (51)	27 (40)	17 (90)
	ECMO	1 (1)	0	1 (5)

Abbreviation: ECMO=extracorporeal membrane oxygenation.
[a]Included abnormal BMI, defined as >35 kg/m^2, and obesity.
[b]No patients had preeclampsia.
[c]Included 2 patients with glucose intolerance.

Patient outcomes

At Day 28, 93% (62/67) of pregnant patients and 89% (17/19) of postpartum patients experienced recovery (main study outcome; defined as hospital discharge for patients on room air at baseline and discharge or an improvement to room air for patients who required supplemental O_2 at baseline; Figure 1). Recovery occurred more frequently in patients without baseline IMV than in those with IMV, regardless of pregnant or postpartum status.[4,8]

Figure 1. Compassionate Use Cohort in Pregnant or Postpartum Women: Clinical Outcomes at Day 28[8]



Forty-five deliveries occurred during the study, including 26 deliveries in patients who were pregnant when RDV was initiated and 19 deliveries prior to RDV initiation.[4]

Safety[4]

RDV treatment was well tolerated among pregnant and postpartum patients (Table 5). The following AEs occurred in pregnant patients: anemia, constipation, deep vein thrombosis, dysphagia, unspecified hypertension, hypoxia, nausea, and pleural effusion in 2 patients each and ARDS in 1 patient. One postpartum patient had an AE of ARDS. Most ALT and AST abnormalities and Cr elevations were Grade 1 or Grade 2.

One maternal death occurred in the postpartum group and was deemed unrelated to RDV treatment. One miscarriage occurred at 17 weeks of gestation in a female that also had *Staphylococcus aureus* bacteremia, endocarditis, and septic arthritis. No neonatal deaths occurred after any of the 45 deliveries.

Table 5. Compassionate Use Cohort: Safety Outcomes[4]

Safety Parameters, n (%) or n/N (%)	All Patients (N=86)	Pregnant Patients (n=67)	Postpartum Patients (n=19)
Any AE	25 (29)	22 (33)	3 (16)
Any SAE	14 (16)	12 (18)	2 (11)
AE that led to RDV discontinuation	7 (8)	7 (10)[a]	0
Any Grade 3–4 laboratory abnormality	15/84 (18)	12/67 (18)	3/18 (17)

[a]AEs included transaminase elevations (n=5), nausea (n=1), and hemoptysis (n=1).

Kazakh Study: Patients With Severe COVID-19[5]

Study design and demographics

A retrospective, non-interventional cohort study was conducted to assess the effectiveness of RDV use in pregnant patients who received RDV who were hospitalized with confirmed or probable severe COVID-19 between December 2021 and May 2022 in Kazakhstan; assessed outcomes included dynamics of temperature normalization, improvement in respiratory rate, and subjective reduction in dyspnea.

A total of 120 eligible pregnant patients were included in the analysis and either received RDV (main group; n=60) or did not receive RDV (control group; n=60). In both groups, patients at 28 to 40 weeks of pregnancy comprised the largest proportion by gestational age (63.3% in the main group and 65% in the control group). There were more patients aged 33 to 42 years in the main group than in the control group (*P*=0.019). Among patients in the main group, 25% had a history of ≥5 pregnancies and 18.3% had a history of

≥4 pregnancies. The total number of bed-days spent in the hospital was higher in the main group (median=9; IQR=8–11) than in the control group (median=8; IQR=7–10; *P*=0.001). Ultrasounds detected statistically significant differences (*P*=0.013) in changes in amniotic fluid between the groups.

Patient outcomes

In the patients who received RDV, the subjective sensation of shortness of breath ended on Day 2 in 4 patients (6.6%), on Day 3 in 11 patients (18.3%), and after Day 3 in 40 patients (66.6%). A reduction in body temperature to normal values on Days 1 to 2 was observed in 17 patients (28%) in the main group and in 41 patients (68%) in the control group. The numbers of patients who demonstrated an increase in SpO_2 (>95%) leading to removal of O_2 therapy were 43 patients (71%) on Days 1 to 2 and 6 patients (10%) within 4 days after initiation of RDV, while 41 patients (68%) showed similar improvements on Days 7 to 8 after initiation of etiotropic treatment. In the control group, 26 patients (43%) withdrew from O_2 therapy on Day 1, 23 (38%) withdrew on Days 3 to 4, 9 (15%) withdrew on Days 5 to 6, and 2 (4%) withdrew after 7 to 8 days from treatment initiation. After 3 days, 66.6% of patients in the main group reported cessation of subjective dyspnea, and 41.6% reported improved respiration rate.

Iranian Study: Patients With Moderate to Severe COVID-19[6]

Study design

A retrospective cohort study was conducted among pregnant patients hospitalized with moderate to severe COVID-19 pneumonia in four hospitals in Iran between September 2020 and March 2022 to assess maternal and fetal outcomes of patients treated with RDV (n=57) and without RDV (n=24). Patients in the RDV group received IV RDV 200 mg on Day 1 (within 48 hours of hospitalization), followed by RDV 100 mg once daily for 5 days. Moderate COVID-19 was defined as having shortness of breath and/or chest pain and pressure, O_2 saturation ≥94%, or <50% lung involvement on imaging. Severe COVID-19 was defined as having tachypnea or O_2 saturation <94% on room air.

The primary outcome measures were the lengths of ICU and hospital stays, respiratory rate on Day 7, O_2 saturation on Day 7, level of O_2 support on Day 7, hospital discharges at Days 7 and 14, and the need for supplemental O_2 upon discharge to home. Secondary outcomes were maternal and neonatal outcomes.

None of the patients had received a COVID-19 vaccine. At baseline, the two cohorts were similar in terms of demographics, severity of symptoms, respiratory parameters, and laboratory measurements.

Patient outcomes

There was a significant association between receiving RDV and an overall reduced length of hospital stay (incidence rate ratio, 0.791; 95% CI: 0.655–0.955), being discharged by Day 7 (OR, 2.718; 95% CI: 1.105–7.398), and being discharged by Day 14 (OR, 4.953; 95% CI: 1.221–22.198). No significant relationship was found between receiving RDV and length of ICU stay, respiratory rate on Day 7, O_2 saturation on Day 7, or the need for supplemental O_2 upon discharge to home.

Safety

Three patients (12.5%) in the non-RDV group and no patients in the RDV group experienced preeclampsia; RDV use was associated with a reduction in the risk of developing preeclampsia (OR, 27.11; 95% CI: 3.67–221.41; *P*=0.024). There were no maternal deaths in either cohort, and there was 1 intrauterine fetal death in the RDV group. Emergency termination was required in 13 pregnancies in the RDV group and in 6 pregnancies in the non-RDV group (*P*=0.228). Among patients with moderate COVID-19, 11.1% of patients in the RDV group and 42.9% of patients in the non-RDV group had an emergency termination (*P*=0.042). One neonatal death occurred in each cohort (*P*=0.517).

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Abbreviations

ADE=adverse drug event
AE=adverse event
ARDS=acute respiratory distress syndrome
FAERS=FDA Adverse Event Reporting System
ICU=intensive care unit
IMPAACT=International Maternal Pediatric Adolescent AIDS Clinical Trial
IMV=invasive mechanical ventilation
MedDRA=Medical Dictionary for Regulatory Activities
NIPPV=noninvasive positive pressure ventilation
O_2=oxygen
OR=odds ratio
PK=pharmacokinetic(s)
RDV=remdesivir
ROR=reporting odds ratio
SAE=serious adverse event
SOC=System Organ Class
SpO_2=saturation of peripheral oxygen
TRAE=treatment-related adverse event

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Veklury US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Follow Up

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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