GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Use in Pediatric Patients

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) for the treatment of chronic HCV infection in pediatric patients.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Summary

Product Labeling[1]

SOF/VEL is indicated for the treatment of adults and pediatric patients ≥3 years of age with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis, or with decompensated cirrhosis for use in combination with RBV.

Clinical Data on SOF/VEL Use in Pediatric Patients

A 5-year registry study examined the long-term outcomes of participants who received SOF-containing regimens (N=461). At a median follow-up of 3.7 years, SVR was maintained in all (100%) pediatric participants who had achieved SVR in a clinical trial. No effects on growth and development were observed.[2]

An open-label, phase 2 study evaluated the safety, tolerability, PK, and efficacy of SOF/VEL in 216 TN or IFN-experienced participants aged 3 to 17 years. Twelve weeks of SOF/VEL treatment resulted in high SVR12 rates (92% overall) and was generally well tolerated.[3]

In the PANDAA-PED study (N=50), which assessed 12 weeks of SOF/VEL treatment in children aged 6 to 18 years, the SVR12 rate was 100%. AEs were reported in 40% of participants; none were severe or led to SOF/VEL discontinuation.[4]

Product Labeling[1]

Dosage and Administration

Recommended treatment regimen and duration in patients ≥3 years of age

SOF/VEL for 12 weeks is the recommended treatment regimen in TN or TE patients without cirrhosis and with compensated cirrhosis (Child-Pugh A); and SOF/VEL + RBV for 12 weeks is the recommended treatment regimen in TN or TE patients with decompensated cirrhosis (Child-Pugh B or C).

Recommended dosage in patients ≥3 years of age

The recommended dosage of SOF/VEL in pediatric patients ≥3 years of age is based on weight and is provided in Table 1. Table 2 provides the weight-based dosage of RBV when used in combination with SOF/VEL for pediatric patients. Take SOF/VEL oral pellets or tablets taken once daily with or without food. In pediatric patients <6 years of age, administer the oral pellets with food to increase tolerability related to palatability.

Table 1. Dosing for Pediatric Patients ≥3 Years With HCV GT 1, 2, 3, 4, 5, or 6 Using SOF/VEL Oral Pellets or Tablets[1]

Body Weight	SOF/VEL Daily Dose	Dosing of SOF/VEL Oral Pellets	Dosing of SOF/VEL Tablet
<17 kg	150 mg/37.5 mg per day	One 150 mg/37.5 mg packet of pellets once daily	N/A
17 kg to <30 kg	200 mg/50 mg per day	One 200 mg/50 mg packet of pellets once daily	One 200 mg/50 mg tablet once daily
≥30 kg	400 mg/100 mg per day	Two 200 mg/50 mg packets of pellets once daily	One 400 mg/100 mg tablet once daily[a]

[a]Two 200 mg/50 mg tablets once daily can be used for patients who cannot swallow the 400 mg/100 mg tablet.

Table 2. Recommended Dosing for RBV in Combination Therapy With SOF/VEL for Pediatric Patients ≥3 Years[1]

Body Weight	Oral RBV Daily Dosage[a]
<47 kg	15 mg/kg/day (divided dose in am and pm)
47–49 kg	600 mg/day (1 × 200 mg in am; 2 × 200 mg in pm)
50–65 kg	800 mg/day (2 × 200 mg in am; 2 × 200 mg in pm)
66–80 kg	1000 mg/day (2 × 200 mg in am; 3 × 200 mg in pm)
>80 kg	1200 mg/day (3 × 200 mg in am; 3 × 200 mg in pm)

[a]The daily dosage of RBV is weight-based and is administered orally in 2 divided doses with food.

Preparation and administration of oral pellets

See the SOF/VEL oral pellets full Instructions for Use for details on the preparation and administration of SOF/VEL oral pellets.

Do not chew SOF/VEL oral pellets to avoid a bitter aftertaste. SOF/VEL oral pellets can be taken directly in the mouth or with food (see Instructions for Use). In pediatric patients <6 years of age, administer the oral pellets with food to increase tolerability related to palatability. Sprinkle the oral pellets on ≥1 spoonfuls of non-acidic soft food at or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, and ice cream. Take SOF/VEL oral pellets within 15 minutes of gently mixing with food and swallow the entire contents without chewing.

Use in Specific Populations

Pediatric use

The PK, safety, and effectiveness of SOF/VEL for treatment of HCV GT 1, 2, 3, 4, or 6 infection in TN and TE pediatric patients ≥3 years of age without cirrhosis or with compensated cirrhosis have been established in an open-label, multicenter clinical trial (Study 1143; N=216; 190 TN, 26 TE; summarized below). No clinically meaningful differences in PK were observed in comparison with those observed in adults.

The safety and effectiveness in pediatric patients were comparable to those observed in adults. However, among the 41 pediatric patients <6 years of age, vomiting and product use issue (spitting up the drug) were reported more frequently (15% and 10%, respectively; all Grade 1 or 2) compared to patients ≥6 years of age. Five patients (12%) discontinued treatment after vomiting or spitting up the drug.

The safety and effectiveness of SOF/VEL for the treatment of HCV GT 5 in pediatric patients ≥3 years of age without cirrhosis or with compensated cirrhosis are supported by SOF, GS-331007, and VEL exposures in adults and pediatric patients. Similar rationale is used to support dosing recommendations for pediatric patients with HCV GT 1, 2, 3, 4, 5, or 6 infection who have decompensated cirrhosis (Child-Pugh B or C).

In patients with severe renal impairment, including those requiring dialysis, exposures of GS-331007, the inactive metabolite of SOF, are increased. No data are available regarding the safety of SOF/VEL in pediatric patients with renal impairment.

The safety and effectiveness of SOF/VEL have not been established in pediatric patients <3 years of age.

Clinical Pharmacology

PK in specific populations: pediatric patients

The PK of SOF, GS-331007, and VEL were determined in HCV GT 1, 2, 3, 4, or 6 infected pediatric patients ≥3 years of age receiving a daily dose of SOF/VEL as described below in Table 3. SOF AUC_T and C_{max} and VEL C_{max} values were 67%, 69%, and 78% higher in pediatric patients ≥30 kg, and 68%, 70%, and 96% higher in pediatric patients 17 to <30 kg, and 103%, 135%, and 92% higher in pediatric patients <17 kg compared to those observed in adults. These differences were not considered clinically significant. GS-331007 exposures and VEL AUC_T and C_T values in pediatric patients were similar to those observed in adults.

Table 3. Exposures of SOF, GS-331007, and VEL at Steady-State in HCV-Infected Pediatric Patients ≥3 Years of Age[1a]

Weight Group	Dose	PK Parameter	Mean (%CV)		
			SOF	GS-331007	VEL
<17 kg[b]	150/37.5 mg	C_{max}, ng/mL	1550 (65.2)	1090 (17)	488 (46.6)
		AUC_T, ng·h/mL	2830 (63.7)	11,900 (19.7)	4480 (53.4)
		C_{trough}, ng/mL	N/A	–	57.4 (82.7)
17 to <30 kg[c]	200/50 mg	C_{max}, ng/mL	1200 (73.8)	1070 (27.2)	483 (39.5)
		AUC_T, ng·h/mL	2280 (55.6)	11,400 (43.3)	4090 (38.5)
		C_{trough}, ng/mL	N/A	–	43 (65.8)

Weight Group	Dose	PK Parameter	Mean (%CV)		
			SOF	GS-331007	VEL
≥30 kg[d]	400/100 mg	C_{max}, ng/mL	1310 (91.4)	1180 (24.6)	456 (56.4)
		AUC_T, ng·h/mL	2570 (82.8)	13,600 (27.6)	4240 (46.7)
		C_{trough}, ng/mL	N/A	–	42.2 (66.4)

Abbreviations: C_{trough}=trough concentration; CV=coefficient of variation.
[a]Population PK-derived parameters.
[b]SOF, n=11; GS-331007, n=11; VEL, n=11.
[c]SOF, n=62; GS-331007, n=64; VEL, n=64.
[d]SOF, n=90; GS-331007, n=101; VEL, n=101.

The PK of SOF, GS-331007, and VEL have not been established in pediatric patients <3 years of age.

Clinical Data on SOF/VEL Use in Pediatric Patients

Pediatric Patient Registry[2]

Study design and demographics

A 5-year registry study enrolled 461 adolescents and children aged ≥3 years who received a SOF-based regimen in a prior Gilead-sponsored HCV trial (parent study), including 158 who received SOF/VEL, to determine the long-term virologic outcomes of SOF-containing regimens and the effects on growth and development. Final results from the registry study have been reported. Of the 461 enrolled participants, 426 with ≥1 postbaseline assessment were included in the final analysis; baseline characteristics of these participants overall and according to treatment in the parent study are summarized in Table 4. A total of 173 participants completed 5 years of follow-up, and 253 participants discontinued due to being lost to follow-up (n=110), study discontinuation by sponsor (n=92), withdrawal of consent (n=43), investigator's decision (n=6), death (n=1; due to progressive cerebellar glioblastoma, unrelated to treatment), or protocol violation (n=1). Overall, the median (range) follow-up duration from registry baseline (date of the last visit in the parent study) was 3.7 (0.2–6.3) years.

Table 4. Pediatric Patient Registry: Baseline Demographics and Disease Characteristics[2a]

Key Demographics and Characteristics		Overall (N=426)	SOF/VEL (n=142)	LDV/SOF ± RBV (n=178)	SOF + RBV (n=88)	SOF/VEL/VOX (n=18)
Age, median (range), years		12 (3–18)	11 (3–18)	11 (3–18)	12 (3–18)	14 (12–18)
Male, n (%)		179 (42)	58 (41)	78 (44)	36 (41)	7 (39)
Race, n (%)	White	342 (80)	108 (76)	152 (85)	69 (78)	13 (72)
	Black	28 (7)	11 (8)	12 (7)	4 (5)	1 (6)
	Asian	26 (6)	9 (6)	7 (4)	8 (9)	2 (11)
	Other[b] or not reported	30 (7)	14 (10)	7 (4)	7 (8)	2 (11)
Duration of follow-up, median (range), weeks		193 (9–325)	169 (9–256)	239 (21–325)	239 (25–312)	143 (80–149)
BMI z-score, median (IQR)		0.4 (-0.3 to 1.2)	0.5 (-0.3 to 1.2)	-0.4 (-0.2 to 1.3)	0.2 (-0.4 to 1.1)	0.1 (-0.7 to 0.5)
Weight z-score, median (IQR)		0.3 (-0.5 to 1)	0.2 (-0.5 to 1)	0.3 (-0.5 to 1.1)	0.3 (-0.5 to 1)	0.1 (-0.7 to 0.5)

Key Demographics and Characteristics	Overall (N=426)	SOF/VEL (n=142)	LDV/SOF ± RBV (n=178)	SOF + RBV (n=88)	SOF/VEL/VOX (n=18)
Height z-score, median (IQR)	-0.2 (-0.9 to 0.5)	-0.2 (-0.8 to 0.5)	-0.2 (-1 to 0.5)	0 (-0.9 to 0.7)	0 (-0.5 to 0.4)
HCV GT, 1/2/3/4/ 5/6/unknown, %	66/9/21/3/ 0/1/<1	73/6/11/4/ 0/4/1	9/0/1/2/ 0/0/0	0/30/70/0/ 0/0/0	22/22/44/11/ 0/0/0

Abbreviation: VOX=voxilaprevir.
[a]Baseline was the date of the last visit in the parent study for each participant.
[b]Other races included American Indian/Alaska Native and Native Hawaiian/Pacific Islander.

Efficacy and safety

A total of 424 of the 426 participants (99.5%) achieved SVR in the parent study, and all of these participants (100%) maintained SVR during the registry study follow-up. The median (range) duration of SVR was 4 (0.6–6.5) years. The 2 participants who did not achieve SVR during the parent study both had NS5A RAVs. One of these participants received SOF/VEL and developed NS5A RAV L31V at Week 8 of treatment; this RAV was not detected at Weeks 24 or 48, was then detected at Week 72 as L31L/V, and was not detected thereafter through Week 192. The second participant received LDV/SOF and developed NS5A RAV Y93H 4 weeks after end of treatment, which was maintained through Week 144.

Prior SOF-based treatment was not associated with any long-term effect on growth. The median changes in z-scores for weight, height, and BMI were 0 at each time point except Week 192 (median change, +0.1) and Week 240 (median change, +0.2) for weight and at Week 240 for BMI (median change, +0.1). The development of secondary sexual characteristics was not affected by prior SOF-based treatment during the registry follow-up.

Open-Label, Phase 2 Study

Study design and demographics[3]

An open-label, multicenter (Belgium, Italy, UK, and US), phase 2 study evaluated 12 weeks of SOF/VEL therapy in 216 participants 3 to 17 years of age with chronic HCV of any GT who were TN or TE with an IFN-based regimen. The lead-in phase of the study evaluated steady-state exposures (AUC_T) of SOF, GS-331007, and VEL and confirmed the dose of SOF/VEL in three pediatric cohorts (3−5, 6−11, and 12−17 years of age). The primary safety and efficacy endpoints were AEs, with particular focus on those that led to discontinuation of SOF/VEL, and SVR12 (HCV RNA <LLOQ [15 IU/mL]).

The daily SOF/VEL doses and formulations given to those in the treatment phase were the following:

- Ages 3 to 5 years: 200/50 mg given as four 50/12.5 mg oral granule packets (≥17 kg), or 150/37.5 mg given as three 50/12.5 mg oral granule packets (<17 kg)
- Ages 6 to 11 years: 200/50 mg given as one 200/50 mg tablet or four 50/12.5 mg oral granule packets
- Ages 12 to 17 years: 400/100 mg given as a single tablet or two 200/50 mg tablets

Baseline characteristics are summarized in Table 5; although participants with cirrhosis were eligible to enroll in the study, no participants had findings consistent with cirrhosis.

Table 5. Baseline Demographics and Disease Characteristics (Jonas et al)[3]

Key Demographics and Characteristics		SOF/VEL		
		Age 3–5 Years (n=41)	Age 6–11 Years (n=73)	Age 12–17 Years (n=102)
Age, median (range), years		4 (3−5)	8 (6−11)	15 (12−17)
Female, n (%)		24 (59)	38 (52)	52 (51)
Race, n (%)	White	32 (78)	66 (90)	74 (73)
	Black or African American	3 (7)	4 (6)	9 (9)
	Asian	0	1 (1)	11 (11)
	American Indian or Alaska Native	0	0	2 (2)
	Other/not disclosed/not permitted	6 (15)	2 (3)	6 (6)
Weight, median (range), kg		19 (13−35)	27 (18−78)	57 (22−147)
HCV GT, 1/2/3/4/6, n (%)		32 (78)/6 (15)/ 2 (5)/1 (2)/0	56 (77)/2 (3)/ 11 (15)/4 (5)/0	77 (75)/5 (5)/ 12 (12)/2 (2)/6 (6)
HCV RNA, median (range), $\log_{10}$ IU/mL		5.9 (1.1−7.3)	5.9 (3.7−7.2)	6.1 (4.9−7.1)
HCV RNA ≥800,000 IU/mL, n (%)		20 (49)	35 (48)	59 (58)
TE, n (%)		0	4 (5)	22 (22)
Perinatal transmission, n (%)		40 (98)	69 (95)	91 (89)

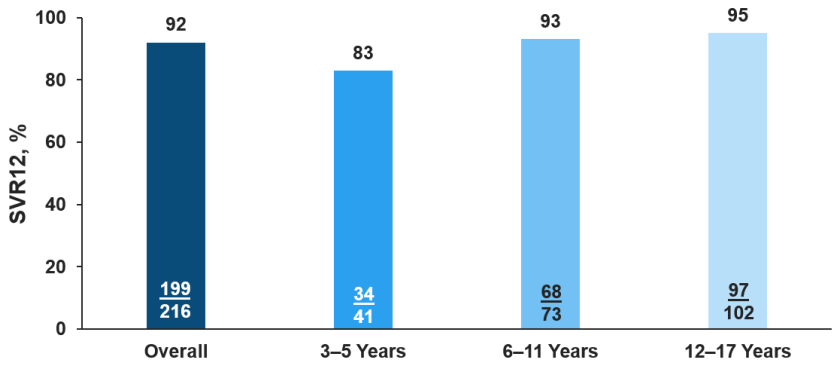
PK profile[3]

In general, exposure parameters for SOF, GS-331007, and VEL in the three pediatric age cohorts were all similar to those observed in adults based on historical data from phase 2 and 3 studies of SOF/VEL.

Efficacy[3]

Overall, SVR12 was achieved by 92% of participants (Figure 1). Virologic failure occurred in 2 participants (1%): a TN participant in the 6 to 11 years cohort with HCV GT 1a and emergent NS5A RAS (L31V) who had a non-response to SOF/VEL after 8 weeks of treatment with potential non-adherence based on drug levels; and a TN participant in the 12 to 17 years cohort with HCV GT 1a who achieved HCV RNA <LLOQ at Week 4 but discontinued SOF/VEL on Day 30 of treatment due to pregnancy and later experienced virologic relapse at post-treatment Week 4. No virologic failure occurred in the 3 to 5 years cohort. Non-virologic treatment failures (3−5 years of age, n=7; 6−11 years of age, n=4; and 12−17 years of age, n=4) occurred in participants who were lost to follow-up (n=7), discontinued treatment early (n=6), or experienced an AE (n=1) or whose parent/guardian withdrew consent (n=1).

Figure 1. SVR12 Rates (Jonas et al)[3]



All participants who had baseline RASs achieved SVR12. At baseline, among 3- to 5-year-old participants with available sequencing data, 18% (6/33) had NS5A RASs, and 3% (1/33) had NS5B RASs; among 6- to 11-year-old participants, 10% (7/68) had NS5A RASs and none had NS5B RASs; and among 12- to 17-year-old participants, 16% (16/98) had NS5A RASs and 5% (5/98) had NS5B RASs.

Safety[3]

Treatment with SOF/VEL was generally well tolerated (Table 6). There were no clinically significant effects observed on growth (weight, height, or BMI) or development (radiographic bone age or shifts in Tanner pubertal stages).

Table 6. Safety Results (Jonas et al)[3,5]

Safety Outcomes, n (%)		SOF/VEL		
		Age 3–5 Years (n=41)	Age 6–11 Years (n=73)	Age 12–17 Years (n=102)
Any AE		32 (78)	59 (81)	77 (76)
AEs reported in >10% in any age group	Vomiting	11 (27)	12 (16)	9 (9)
	Cough	6 (15)	11 (15)	10 (10)
	Pyrexia	6 (15)	8 (11)	10 (10)
	Rhinorrhea	6 (15)	4 (6)	4 (4)
	Fatigue	5 (12)	9 (12)	22 (22)
	Diarrhea	5 (12)	6 (8)	7 (7)
	Nasal congestion	5 (12)	4 (6)	6 (6)
	Headache	2 (5)	11 (15)	30 (29)
	Abdominal pain	2 (5)	9 (12)	6 (6)
	Nausea	0	5 (7)	17 (17)
Grade 3 or 4 AEs		0	1 (1)	2 (2)
Serious AEs		0	2 (3)[a]	2 (2)[b]
SOF/VEL discontinuation due to AEs		1 (2)[c]	2 (3)[d]	0
Grade 3 laboratory abnormalities		1 (2)	0	5 (5)

[a]Due to Grade 3 treatment-related auditory hallucinations (n=1) and Grade 2 constipation (n=1).
[b]Grade 3 suicidal ideation (n=1) and Grade 4 suicide attempt (2 events), Grade 3 exacerbated bipolar disorder, and Grade 3 suicidal ideation in a participant with a complex medical history that included bipolar disorder.
[c]Due to Grade 2 irritability, Grade 1 spitting up study drug, Grade 1 psychomotor hyperactivity, and Grade 1 decreased appetite.
[d]Due to Grade 1 spitting up study drug (n=1) and Grade 3 treatment-related SAE of auditory hallucinations (n=1).

Across the age cohorts and time points (Day 1 and Week 12/early termination), 59% to 100% of participants or their caregivers reported the ease of taking study drug as acceptable, and 69% to 95% reported that they could not taste the study drug or that it tasted palatable.

PANDAA-PED Study[4]

A study assessed the efficacy and safety of 12 weeks of SOF/VEL treatment (fixed dose adjusted to the participant's weight) for chronic HCV infection in children aged 6 to 18 years and included those who were treated and had an SVR12 assessment between January 2022 and December 2023 (N=50). The primary endpoint was SVR12, and secondary endpoints included safety.

The baseline characteristics were as follows: male sex, n=23 (46%); median (IQR) age, 10 (8–12) years; HCV GT 1, 74%; vertical transmission, n=47 (94%); median (IQR) HCV viral load, 5.8 (5.4–6.2) log_{10} IU/mL; and F0/F1 liver fibrosis, n=49 (98%).

At Week 4 of treatment, 2 participants (4%) had detectable HCV RNA, but all participants (100%) achieved SVR12. AEs were reported in 20 participants (40%) and consisted of headache (n=9), abdominal pain (n=8), asthenia (n=6), fatigue (n=4), dizziness (n=3), diarrhea (n=2), nausea (n=2), somnolence (n=2), rash (n=1), and calf cramps (n=1). No AEs were severe, and none led to discontinuation of SOF/VEL.

References

1. EPCLUSA, Gilead Sciences Inc. EPCLUSA® (sofosbuvir and velpatasvir) Tablets, for Oral Use. U. S. Prescribing Information. Foster City, CA.
2. Leung DH, Whitworth S, Wen J, et al. Long-Term Safety and Efficacy of Sofosbuvir-Based Direct-Acting Antivirals in Pediatric Patients With Hepatitis C Virus [Poster 1881-A]. Paper presented at: AASLD: The Liver Meeting; November 10–14, 2023; Boston, MA.
3. Jonas MM, Romero R, Rosenthal P, et al. Sofosbuvir-velpatasvir in children 3-17 years old with hepatitis C virus infection. *J Pediatr Gastroenterol Nutr.* 2024;78(6):1342-1354.
4. Pokorska-Spiewak M, Talarek E, Dobrzeniecka A, Aniszewska M, Pluta M, Marczyńska M. Safety and efficacy of two pan- genotypic DAAs (sofosbuvir/velpatasvir and glecaprevir/ pibrentaswir) for treatment of hepatitis C in children.[Poster #THU-387]. Paper presented at: European Association for the Study of the Liver (EASL); June 5-8, 2024; Milan, Italy.
5. Sokal EM, Schwarz KB, Rosenthal P, et al. Safety and Efficacy of Sofosbuvir/Velpatasvir for the Treatment of Chronic Hepatitis C Infection in Children and Adolescents Aged 3 to 17 Years Old Through 24 Weeks Posttreatment [Poster 931]. Paper presented at: American Association for the Study of Liver Diseases (AASLD) Virtual; 13-16 November, 2020.

Abbreviations

AE=adverse event
AUC_T=area under the concentration curve for a dosing interval
C_T=plasma concentration at the end of a dosing interval
C_{max}=maximum plasma concentration
GS-331007=predominant circulating metabolite of sofosbuvir
GT=genotype
IFN=interferon
LDV=ledipasvir
LLOQ=lower level of quantitation
PK=pharmacokinetic(s)
RAS=resistance-associated substitution
RAV=resistance-associated variant
RBV=ribavirin
SOF=sofosbuvir
SVR=sustained virologic response
SVR12=sustained virologic response 12 weeks after end of treatment
TE=treatment experienced
TN=treatment naive
VEL=velpatasvir

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 https://www.gilead.com/utility/contact/report-an-adverse-event

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

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact gilead.privacy@gilead.com.