



Review Article

Pharmacokinetics and Pharmacodynamics of Sofosbuvir in Adults and Special Populations: A Systematic Review

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ABSTRACT

Hepatitis C virus (HCV) infection affects more than 70 million individuals globally and remains a leading cause of cirrhosis, hepatocellular carcinoma, and liver-related mortality. The advent of direct-acting antivirals (DAAs) has transformed therapy, with sofosbuvir, a uridine nucleotide prodrug, serving as a cornerstone of modern regimens. Following oral absorption, sofosbuvir undergoes hepatic activation to the active triphosphate metabolite GS-461203, which inhibits the NS5B RNA-dependent RNA polymerase, resulting in termination of viral RNA synthesis. The major circulating metabolite GS-331007, primarily renally excreted, accounts for most systemic exposure. Sofosbuvir exhibits rapid absorption (T_{max} 0.5–2 h), moderate plasma protein binding (61–65%), and elimination predominantly via the kidneys (~80% of dose), with half-lives of ~0.4 h (parent drug) and ~27 h (GS-331007). Pharmacokinetic studies show that renal impairment significantly increases GS-331007 exposure, particularly in dialysis patients, though sustained virologic response (SVR) rates remain high with careful monitoring. In contrast, hepatic impairment, advanced age, and HIV coinfection exert minimal effects on exposure, and dose adjustment is generally unnecessary. Sofosbuvir-based regimens are approved for adults, children ≥ 3 years, and are widely used in transplant settings, though pregnancy data remain limited. The drug is well tolerated, with headache, fatigue, and nausea being the most common adverse effects, while serious risks include HBV reactivation and rare bradycardia with amiodarone.

INTRODUCTION

Hepatitis C virus (HCV) infection affects over 70 million individuals globally and is a major cause

of liver disease. The advent of DAAs has revolutionized treatment, replacing interferon-based therapies. Sofosbuvir, a uridine nucleotide prodrug, is central to many DAA

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combinations. After intracellular activation to GS-461203, it inhibits the NS5B RNA polymerase, halting viral replication. A systematic review of PK/PD data across adult and special populations (renal/hepatic impairment, dialysis, HIV coinfection, elderly) is vital for guiding optimal dosing and understanding clinical implications.

Chronic hepatitis C virus (HCV) infection remains a major global health challenge, contributing substantially to cirrhosis, hepatocellular carcinoma, and liver-related mortality. The World Health Organization (WHO) estimated ~242,000 HCV-related deaths in 2022 and notes that, although direct-acting antivirals (DAAs) can cure >95% of infections, gaps in testing and treatment persist worldwide. These figures align with recent global surveillance indicating tens of millions of people are living with chronic HCV and underscoring the need for scalable antiviral strategies.

Sofosbuvir, a uridine nucleotide analog prodrug, is a cornerstone of modern DAA regimens and is approved either alone for combination use or as part of fixed-dose combinations (e.g., ledipasvir/sofosbuvir, sofosbuvir/velpatasvir; sofosbuvir/velpatasvir/voxilaprevir). Once absorbed, sofosbuvir undergoes intracellular activation to the active uridine analog triphosphate (GS-461203), which is incorporated by the HCV NS5B RNA-dependent RNA polymerase and terminates RNA synthesis. Systemic circulation is dominated by the inactive nucleoside metabolite GS-331007, reflecting extensive first-pass hepatic activation and subsequent dephosphorylation. In human mass-balance and clinical pharmacology studies, ~78–80% of the dose is recovered in urine primarily as GS-331007, ~14% in feces, and ~3–4% as unchanged sofosbuvir; median terminal

half-lives are ~0.4 hours for parent and ~27 hours for GS-331007.

Understanding the PK/PD of sofosbuvir across special populations is clinically important. Because GS-331007 is renally eliminated, exposure increases with declining kidney function and can be markedly elevated in patients with advanced chronic kidney disease (CKD) or on hemodialysis. Contemporary data—including prospective studies of sofosbuvir/velpatasvir in dialysis—suggest high efficacy with acceptable safety when regimens are selected and monitored appropriately, but they also highlight the need to account for altered metabolite handling in this group. In contrast, hepatic impairment has a limited impact on overall exposure, and dose adjustment is not generally required on the basis of liver function alone.

Pharmacology of sofosbuvir:

Pharmacokinetics:

Absorption: Sofosbuvir is rapidly absorbed, with peak plasma concentrations at 0.5–2 hours post-dose.

After a single oral 400 mg dose the median time to peak plasma concentration (T_{max}) for sofosbuvir is about 0.5–2 hours. The parent drug C_{max} (mean) observed in HCV-infected subjects is on the order of ~600 ng/mL, and GS-331007 C_{max} is typically lower but more persistent in plasma. Food does not have a clinically important effect on SVR when sofosbuvir is given with recommended combination regimens, so the drug may be taken with or without food in routine practice.

Distribution: Plasma protein binding ~61–65%.

Sofosbuvir is moderately plasma-protein bound (~61–65%), whereas GS-331007 is minimally protein-bound. Sofosbuvir distributes into the liver



where intracellular activation occurs; hepatic concentrations of the active metabolites have been shown to exceed plasma levels substantially in preclinical/human tissue studies

Metabolism: Extensively metabolized in hepatocytes to GS-461203 (active triphosphate) and GS-331007 (inactive metabolite).

Sofosbuvir is a phosphonamidites prodrug; after absorption it is sequentially metabolized in hepatocytes to the nucleoside monophosphate and then phosphorylated to the active triphosphate GS-461203 (the moiety that inhibits NS5B polymerase). The major circulating plasma species is the dephosphorylated nucleoside GS-331007, formed by intracellular dephosphorylation and subsequent efflux.

Elimination: GS-331007 is primarily renally excreted ($\approx 80\%$ of dose). Parent drug elimination half-life ≈ 0.4 hours; GS-331007 half-life ≈ 27 hours.

Mass-balance and clinical pharmacology studies report that $\sim 78\%$ of the administered dose is recovered in urine (predominantly as GS-331007), $\approx 14\%$ in feces, and $\approx 3-4\%$ as unchanged sofosbuvir. The median terminal elimination half-life is ~ 0.4 hours for sofosbuvir and ~ 27 hours for GS-331007. Reported mean AUC (single/steady-state depending on study) values in HCV patients are approximately AUC $\approx 1,010$ ng·h/mL for sofosbuvir and AUC $\approx 7,200$ ng·h/mL for GS-331007, illustrating the dominance of the metabolite in systemic exposure.

Special Populations:

Renal impairment:

Because GS-331007 is primarily renally cleared, its exposure increases markedly as renal function declines. Single- and multiple-dose studies show

progressive GS-331007 AUC increases with worsening eGFR (examples: mild $\sim 1.5\times$, moderate $\sim 2\times$, severe/ESRD substantially higher), and end-stage renal disease/hemodialysis patients may show $5-20\times$ higher GS-331007 concentrations compared with patients with normal renal function in some reports. Despite this accumulation, several clinical cohorts and recent studies of SOF-containing regimens in dialysis patients have reported high SVR rates and acceptable safety when regimens are used with appropriate monitoring — though product labels and guidelines urge caution and close observation.

Hepatic impairment: Minimal impact on PK

Population PK analyses and label summaries indicate no clinically meaningful change in sofosbuvir or GS-331007 exposures that would require hepatic dose adjustment across degrees of hepatic impairment; sofosbuvir may generally be used without dose modification in patients with mild, moderate, or severe hepatic impairment, according to regulatory labeling and clinical PK reviews.

Elderly and HIV coinfectd:

Elderly and HIV-coinfectd patients have shown PK profiles not substantially different from general adult HCV populations, and no routine dose adjustments are recommended on the basis of age or common antiretroviral co-therapy after accounting for known DDIs. Paediatric and pregnancy PK data are available for specific age/weight groups and should be referenced separately for dosing in those populations.

Pharmacodynamics:

Mechanism:

Sofosbuvir is a nucleotide prodrug that is intracellularly converted to the active uridine-

analogue triphosphate GS-461203. GS-461203 competes with natural nucleotides for incorporation by the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase, and after incorporation causes chain termination, blocking viral RNA synthesis. The active triphosphate is not measurable in plasma; systemic exposure is represented by the inactive dephosphorylated nucleoside GS-331007

Viral kinetics:

Sofosbuvir produces a rapid decline in plasma HCV RNA within days of treatment initiation. Viral-kinetic analyses with nucleotide-based regimens commonly demonstrate a rapid first-phase fall (hours–days), occasionally a slower “shoulder” phase, and then a later phase of continued decline — a pattern that can be captured by multiphasic viral-kinetic models (triphasic kinetics) depending on baseline hepatocyte infection and immune/replicative dynamics. These rapid declines underlie the drug’s potent antiviral

Exposure:

At the approved 400 mg once-daily dose, sofosbuvir achieves systemic and intracellular exposures well above in-vitro antiviral thresholds for most HCV genotypes; consequently, clinical exposure–response analyses indicate a relatively flat relationship between usual-range exposure and sustained virologic response (SVR) at the recommended dose. In practice, SOF-containing regimens produce high SVR12 rates (commonly >90%) across genotypes when combined with appropriate partner DAAs and for guideline-recommended durations. Regulatory reviews and population PD analyses support that the standard dosing provides a wide therapeutic margin, which helps explain consistent high cure rates across diverse patient groups

Resistance:

The primary NS5B substitution that reduces sofosbuvir susceptibility in vitro is S282T. However, S282T is infrequent in clinical practice because it typically confers a substantial replicative fitness cost and tends to disappear without drug pressure. Large clinical programs and sequencing analyses report rare emergence of clinically relevant S282T after SOF-based therapy, and overall, the drug is regarded as having a high barrier to resistance when used in appropriate combination regimens

Clinical use and special populations

Indications and usual dosing:

Sofosbuvir is approved as a component of combination regimens for the treatment of chronic hepatitis C virus (HCV) infection across genotypes when used with appropriate partner agents (e.g., ledipasvir, velpatasvir, or vexillaries) or ribavirin as indicated by genotype and disease stage. The recommended adult dose of sofosbuvir is 400 mg orally once daily, administered as monotherapy only in the context of combination regimens (Sovaldi®, Harvoni®, Epclusa®, Vosevi® labeling and regulatory guidance). Treatment duration and partner agents are selected according to genotype, presence/absence of cirrhosis, prior treatment history, and transplant status.

Renal impairment and haemodialysis:

Because the inactive circulating metabolite GS-331007 is primarily renally excreted, GS-331007 exposure increases as renal function declines. Studies and regulatory/clinical guidance document progressive increases in GS-331007 AUC with worsening eGFR, and patients with end-stage renal disease (ESRD) on hemodialysis can have markedly elevated metabolite levels (reports commonly cite ~5–10× accumulation in severe impairment in some cohorts). Despite concerns



about accumulation, contemporary clinical studies of sofosbuvir/velpatasvir and other SOF-based regimens in patients with severe CKD and on dialysis report high sustained virologic response (SVR) rates and generally acceptable safety when patients are monitored closely; many guidelines therefore permit SOF-based regimens in CKD/ESRD with clinician judgment and monitoring for coexisting risks and DDIs. Nevertheless, product labeling and expert guidance emphasize awareness of metabolite accumulation and careful monitoring

Dialysis timing:

Hemodialysis clears a portion of GS-331007; study reports provide dialysis clearance estimates and have evaluated once-daily and alternate-day dosing strategies in small cohorts, but standard practice frequently uses the licensed once-daily dosing with monitoring rather than routine dose changes — decisions should be individualized and guided by specialist advice and local practice

Hepatic impairment:

Population PK analyses and regulatory reviews indicate that mild, moderate, and severe hepatic impairment have limited impact on systemic exposure to sofosbuvir and GS-331007 that would necessitate routine dose adjustment; therefore, sofosbuvir-containing regimens may generally be used in patients with compensated or decompensated liver disease according to regimen-specific guidance (with addition of ribavirin for some decompensated regimens). Clinical selection should still consider the overall clinical status, drug interactions, and the need for adjunctive agents (e.g., ribavirin) which may require dose modification.

HIV coinfection and antiretroviral interactions:

Sofosbuvir-based regimens are effective in people with HIV/HCV coinfection when used with compatible antiretroviral therapy. Sofosbuvir itself has low CYP450 interaction potential but is a substrate of P-gp/BCRP, so DDIs with antiretrovirals mediated by these transporters should be assessed. Expert guidance (AASLD-IDSA) provides regimen-specific recommendations to avoid interactions and maintain antiretroviral efficacy and safety

Paediatrics and pregnancy:

Sofosbuvir (in combination formulations) is approved for children ≥ 3 years (age/weight-based dosing varies by product and indication); paediatric pharmacokinetic and clinical data support efficacy with appropriate dosing regimens. Data in pregnancy remain limited, and routine use in pregnancy should weigh maternal benefit against limited fatal safety data, following specialist consultation and updated guidance. Breastfeeding data are sparse and clinical decisions should be individualized.

Elderly patients:

Available PK and clinical efficacy data do not demonstrate clinically meaningful differences in sofosbuvir exposures between older and younger adult patients that would mandate dose adjustment; therapy selection should nevertheless account for comorbidities, polypharmacy, and renal function.

Post-transplant patients and special clinical settings:

Sofosbuvir-containing regimens are used in pre- and post-liver transplant settings to prevent or treat recurrent HCV infection; regimen choice, timing, and adjunctive agents (e.g., ribavirin) depend on urgency, graft function, and interacting



immunosuppressants. Clinical pharmacology reviews and labeling provide guidance for transplant scenarios, and specialist hepatology/transplant input is recommended for individualized plans.

Drug–drug interactions

Sofosbuvir is a substrate of P-glycoprotein (P-gp) and BCRP transporters. Strong intestinal P-gp inducers (e.g., rifampin, St. John's wort, certain anticonvulsants) can substantially reduce sofosbuvir exposure and are therefore contraindicated or not recommended with sofosbuvir-containing regimens. Clinically important DDIs have also been reported with amiodarone (severe bradycardia when co-administered with sofosbuvir-containing regimens) — a safety warning added by regulatory authorities. Overall, sofosbuvir has relatively low propensity for CYP-mediated interactions but transporter-mediated DDIs are the principal concern.

Adverse effects:

Sofosbuvir is generally well tolerated. The most common adverse effects (often attributable to combination regimens) include headache, fatigue, and nausea. Serious risks include HBV reactivation in coinfecting patients and rare cases of bradycardia with amiodarone co-use

CONCLUSION:

Sofosbuvir is a cornerstone of modern direct-acting antiviral therapy for hepatitis C virus (HCV) infection, offering high efficacy, broad genotype coverage, and favorable tolerability. Its pharmacology is well defined: rapid absorption, hepatic activation to the active triphosphate, and renal elimination of the major metabolite GS-331007. Clinical data demonstrate consistent

sustained virologic response rates across diverse populations, including those with renal or hepatic impairment, HIV coinfection, and post-transplant patients, provided monitoring and regimen adjustments are applied where necessary. With a high barrier to resistance, manageable drug–drug interactions, and wide clinical applicability, sofosbuvir remains a key agent in achieving HCV elimination goals.

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