were 28% and 1280% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after hemodialysis, respectively. A 4-hour hemodialysis session removed approximately 18% of the administered dose. Although no dose adjustment is required for patients with mild or moderate renal impairment, safety and efficacy have not been established in patients with severe renal impairment or ESRD.

Excretion

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis (by carboxylesterase 1, cathepsin A, and histidine triad nucleotide-binding protein) followed by diphosphorylation (mediated by UMP-CMP kinase) and triphosphorylation (mediated by nucleoside diphosphate kinase) to form GS-461203. Intrahepatic dephosphorylation of the monophosphate results in the formation of the nucleoside metabolite GS-331007, which cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*.

After a single 400 mg oral dose of ^{14}C-sofosbuvir, mean total recovery of the dose was> 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%). Renal clearance is the major elimination pathway for GS-331007.

Drug interactions

Drugs that are potent PGP inducers in the intestine (e.g. rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect. Co-administration with drugs that inhibit PGP and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration; accordingly, sofosbuvir may be co-administered with PGP and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of PGP and BCRP and thus are not expected to increase exposures of drugs that are substrates of these transporters. The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low-affinity and high-capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant drugs.

Postmarketing, life-threatening bradyarrhythmias have been documented in individuals taking amiodarone in combination with sofosbuvir-containing regimens, including sofosbuvir plus ledipasvir, sofosbuvir plus simeprevir and sofosbuvir plus daclatasvir (Brainard *et al.*, 2015; US Food and Drug Administration, 2015). The mechanism for this effect is unknown. See section 6, Adverse reactions and toxicity for further details.

See Table 261.14 for potentially significant drug interactions with ledipasvir–sofosbuvir. See Table 261.15 for potentially significant drug interactions with sofosbuvir–velpatasvir. Up-to-date drug–drug interaction information can be accessed via hep-druginteractions.org.

5c. NS5A inhibitors

DACLATASVIR

Bioavailability

In dose-ranging studies in HCV-infected subjects, geometric mean (coefficient of variation [CV], %) daclatasvir C_{max} was 1,534 (58) ng/ml and AUC_{0-24} was 14,122 (70) ng/h/ml, with a t_{max} at 1–2 hours post dose. The absolute bioavailability of the tablet formulation is 67%. A food effect was not observed with administration of daclatasvir 60-mg tablet after a low-fat, low-caloric meal compared with fasted conditions.

Drug distribution

See Table 261.10.

Clinically important pharmacokinetic and pharmacodynamic features

The pharmacokinetics of daclatasvir after a single 60-mg oral dose was studied in non–HCV-infected individuals with renal impairment. The predicted AUC of daclatasvir was estimated to be 26%, 60%, and 80% higher in individuals with CrCl values of 60, 30, and 15 ml/minute, respectively, relative to individuals with normal renal function (CrCl ≥ 90 ml/minute). Individuals with ESRD requiring hemodialysis had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to individuals with normal renal function. Daclatasvir is highly bound to plasma proteins and is unlikely to be removed by dialysis.

The pharmacokinetics of daclatasvir after a single 30-mg oral dose was studied in non-HCV-infected adults with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment and a corresponding matched control group. The C_{max} and AUC of total daclatasvir (free and protein-bound drug) were lower by 46% and 43%, respectively, in individuals with Child-Pugh class A impairment; by 45% and 38%, respectively, with Child-Pugh class B impairment; and by 55% and 36%, respectively, with Child-Pugh class C. The C_{max} and AUC of unbound daclatasvir were lower by 43% and 40%, respectively, in Child-Pugh class A impairment; by 14% and 2%, respectively, in Child-Pugh class B; and by 33% and 5%, respectively, in Child-Pugh class C. Consequently, no dose adjustment is required for hepatic impairment.

Excretion

Daclatasvir is a substrate of CYP3A, with CYP3A4 being the primary isoform responsible for metabolism. After single-dose oral administration of 25 mg ^{14}C-daclatasvir in healthy subjects, the majority of radioactivity in plasma was predominately attributed to parent drug (≥ 97%).

After a single-dose oral administration of 25 mg ^{14}C-daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% unchanged) and 6.6% of the dose was excreted in the urine (primarily unchanged).