Drug interactions

Daclatasvir is a substrate of CYP3A. Moderate or strong inducers of CYP3A markedly decrease the plasma levels and therapeutic effect of daclatasvir; consequently co-administration of daclatasvir with strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort) is contraindicated. The dose of daclatasvir should be increased to 90 mg once daily when co-administered with moderate CYP3A inducers (e.g. efavirenz, etravirine, modafinil, nafcillin). Strong inhibitors of CYP3A (e.g. clarithromycin, azole antifungals, ritonavir) increase the plasma levels of daclatasvir. As such, when co-administered the dose of daclatasvir should be reduced to 30 mg once daily. Daclatasvir is an inhibitor of PGP, OATP1B1 and 1B3, and BCRP. Daclatasvir may increase systemic exposure to drugs that are substrates of PGP, OATP1B1 or 1B3, or BCRP, which could increase or prolong their therapeutic effect or adverse reactions.

Postmarketing, life-threatening bradyarrhythmias have been documented in individuals taking amiodarone in combination with sofosbuvir-containing regimens, including 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.

Up-to-date drug–drug interaction information can be accessed via hep-druginteractions.org.

LEDIPASVIR

Bioavailability

After oral administration of ledipasvir–sofosbuvir in healthy subjects, ledipasvir median C_{max} values were observed at t_{max} of 4–4.5 hours post dose. Relative to healthy subjects, ledipasvir AUC and C_{max} were lower (24% and 32%, respectively) in HCV-infected subjects. Relative to fasting conditions, food with did not significantly affect sofosbuvir, GS-331007 and ledipasvir exposure.

Drug distribution

See Table 261.10.

Clinically important pharmacokinetic and pharmacodynamic features

Ledipasvir plasma exposure (AUC) after a single 90-mg dose was similar in HCV-negative adults with severe hepatic impairment (Child-Pugh class C) as compared with adults with normal hepatic function. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis had no clinically relevant effect on the exposure of ledipasvir.

No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy adults and adults with severe renal impairment (eGFR < 30 ml/minute).

Excretion

Evidence of slow oxidative metabolism via an unknown mechanism has been observed. After a single dose of 90 mg ^{14}C-ledipasvir, systemic exposure was almost exclusively to the parent drug (> 98%). Unchanged ledipasvir is the major species present in feces.

After a single 90-mg oral dose of ^{14}C-ledipasvir, mean total recovery of the ^{14}C in feces and urine was approximately 87% (feces 86%). Unchanged ledipasvir excreted in feces accounted for a mean of 70% of the administered dose and the oxidative metabolite M19 accounted for 2.2% of the dose. Biliary excretion of unchanged ledipasvir is a major route of elimination, with renal excretion being a minor pathway (1%).

Drug interactions

Ledipasvir and sofosbuvir are substrates of drug transporters PGP and BCRP, whereas GS-331007 is not. PGP inducers (e.g. rifampicin, St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations, leading to reduced therapeutic effect. Co-administration with drugs that inhibit PGP and/or BCRP may increase ledipasvir and sofosbuvir plasma concentrations without increasing GS-331007 plasma concentration.

Postmarketing, life-threatening bradyarrhythmias have been documented in individuals taking amiodarone in combination with sofosbuvir-containing regimens, including sofosbuvir–ledipasvir (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.

ELBASVIR

Bioavailability

Based on population pharmacokinetic modeling in HCV-infected adults, geometric mean AUC_{0-24} and C_{max} values were 1920 ng/hr/ml (90% CI: 1880, 1960) and 121 (90% CI: 118, 123), respectively, with t_{max} occurring at 3 hours (range: 3–6 hours) (Merck, 2016; see Table 261.10).

Drug distribution

See Table 261.10.

Clinically important pharmacokinetic and pharmacodynamic features

In HCV-uninfected adults with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, single 50-mg oral doses of elbasvir resulted in reductions in AUC (24%) and C_{max} (42%) in mild hepatic impairment and reductions in AUC (14%) and C_{max} (31%) in moderate hepatic impairment compared with healthy controls (Marshall *et al.*, 2014; Merck, 2017). These results support the administration of elbasvir to adults with mild and moderate hepatic dysfunction without dose alteration.

Hemodialysis does not significantly affect elbasvir pharmacokinetics in adults with ESRD. The removal of elbasvir