Glecaprevir and Pibrentasvir
Hepatitis C Therapy

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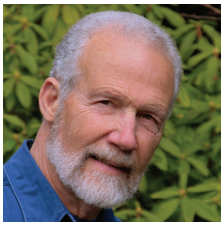
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THE TREATMENT OF THE HEPATITIS C VIRUS (HCV) has rapidly evolved over the past decade. Current therapy consists of combinations of antiviral drugs usually having unique antiviral activity. Mavyret contains 100 mg of the protease inhibitor glecaprevir and 40 mg of the NS5A inhibitor pibrentasvir. Recommended dosage is 3 tablets once daily. This product has been approved for 6 genotypes of HCV in patients with or without cirrhosis.[1]

INTERACTION POTENTIAL

Glecaprevir is minimally metabolized by CYP 3A4 but is a substrate for breast cancer resistance protein (BCRP), the hepatic uptake transporters organic anion transporting polypeptide (OATP1B1 and OATP1B3), and P-glycoprotein (P-gp). Glecaprevir is also an inhibitor of these transporters. Pibrentasvir does not appear to undergo any metabolism. It is a substrate of BCRP and P-gp and acts as an inhibitor of BCRP, OATP1B1, and P-gp. The combination shows weak inhibition of CYP 1A2 and CYP 3A4. When administered at the recommended dose, glecaprevir increased pibrentasvir area under the concentration time curve (AUC) by about 3-fold. Pibrentasvir did not significantly alter glecaprevir concentrations.[2] Taking glecaprevir/pibrentasvir with a meal is recommended because of a 1.5-to-3-fold increase in glecaprevir/pibrentasvir concentrations, compared with fasting administration.[1]

DRUGS AFFECTING ABSORPTION

The administration of 20 or 40 mg daily of omeprazole for 5 days before a morning dose of glecaprevir/pibrentasvir reduced the glecaprevir AUC by 30% and 50%, respectively.[1] Administration of omeprazole 40 mg daily in the evening produced a similar effect on glecaprevir administered the next morning. The solubility of glecaprevir is pH dependent. It is likely that other acid-reducing agents will cause similar reductions in glecaprevir concentrations and should be avoided. It is unknown whether acid suppressants with shorter duration of action (eg antacids and H2-receptor antagonists) could avoid a significant interaction with glecaprevir/pibrentasvir by separating the doses.

DRUGS REDUCING CONCENTRATION

Rifampin and carbamazepine reduced the AUC of both glecaprevir and pibrentasvir by 50% to 90%.[1] The mechanism for this interaction is induction of P-gp. The magnitude of the reduction in glecaprevir/pibrentasvir concentration may reduce its efficacy. Rifampin, carbamazepine, and other P-gp inducers (eg, barbiturates, phenytoin, and St John's wort) should be avoided.

DRUGS INCREASING CONCENTRATION

Drugs that inhibit P-gp have been reported to increase glecaprevir/pibrentasvir plasma concentrations. The coadministration of atazanavir or lopinavir when combined with ritonavir resulted in a 4-to-5-fold increase in glecaprevir and a 2-to-2.5-fold increase in pibrentasvir. The combination of darunavir plus ritonavir produced a 5-fold increase in glecaprevir, with minimal change in pibrentasvir. Cyclosporine 100 mg single dose increased glecaprevir AUC by 37% but had no effect on pibrentasvir. When the cyclosporine dose was increased to a 400-mg single dose, glecaprevir AUC increased by 5-fold and pibrentasvir AUC by 2-fold.[1] Drugs known to reduce P-gp activity (eg, amiodarone, clarithromycin, itraconazole, and verapamil) would be likely to increase glecaprevir/pibrentasvir concentrations. Be alert for glecaprevir/pibrentasvir adverse effects, including fatigue, headache, and nausea.

DRUGS AFFECTED

Based on the pharmacology of glecaprevir/pibrentasvir, drugs that are substrates for P-gp or OATP1B1 or OATP1B3 may act as object drugs when combined with glecaprevir/pibrentasvir. For example, statins that are substrates of P-gp and/or OATP have the following increases in their AUCs when administered with glecaprevir/pibrentasvir: atorvastatin, 8-fold; lovastatin acid, 4-fold; pravastatin, 2.3-fold; rosuvastatin, 2.15-fold; and simvastatin acid, 4.5-fold.[1] Concurrent administration of these statins with glecaprevir/pibrentasvir should be avoided. Following the coadministration of glecaprevir/pibrentasvir, digoxin and dabigatran, both substrates of P-gp, had 1.5- and 2.4-fold increases in AUC, respectively.[1] Betrixaban, colchicine, edoxaban, raltegravir, and other drugs that are substrates of P-gp may also demonstrate increased plasma concentrations if glecaprevir and pibrentasvir