USE OF MARIBAVIR FOR THE TREATMENT OF AND TREATMENT REGIMENS THEREOF

CROSS REFERENCE TO RELATED APPLICATION

[0001] The present application claims priority to U.S. Provisional Application No. 63/281,206, filed November 19, 2021, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Cytomegalovirus (CMV) infection and disease are significant post-transplant complications and are associated with substantial morbidity and reduced long-term survival among transplant recipients. There are currently no approved therapies for the treatment of CMV infection in transplant recipients.

[0003] Transplant patients often receive numerous concomitant medications to manage their comorbidities. Characterization of drug-drug interaction properties and pharmacological properties of maribavir is useful to inform potential drug-drug interactions and dosing strategies when administering with co-medications.

SUMMARY

[0003a] In a first aspect of the present disclosure, there is provided a use of maribavir in the manufacture of a medicament for treating cytomegalovirus (CMV) infection in a patient suffering therefrom, wherein:

about 800 or about 1200 mg of maribavir is to be orally administered twice daily to the patient; and

wherein the patient is a transplant recipient concomitantly exposed to or receiving an anticonvulsant.

[0004] Maribavir is a benzimidazole riboside, and is an orally available antiviral medication against cytomegalovirus (CMV). Maribavir is also known under its trade name LIVTENCITY™. Typically, patients (e.g., adults and/or children over 12 years of age and weighing at least 35 kg) are administered 400 mg if maribavir orally, twice daily. However, in some examples, the present disclosure recognizes that, when co-administered with certain

drugs (e.g., a cytochrome P450 3A4 (CYP3A4) inducer such as carbamazepine, phenytoin, or phenobarbital, a p-glycoprotein inducer (P-gp), an immunosuppressant, an antiarrhythmic such as digoxin, ganciclovir, or valganciclovir), the dose of maribavir and/or the co-administered drug must be monitored, altered (e.g., increased or decreased), or discontinued.

[0005] In some examples, the present disclosure demonstrates, among other things, potential drug-drug interactions with maribavir and how exposure to maribavir and/or a CYP3A4 inducer is affected. In some examples, the present disclosure provides methods of treating CMV infection in a patient suffering therefrom comprising:

administering a therapeutically effective amount of maribavir to the patient, wherein the patient is receiving or has received a CYP3A4 inducer prior to administration of maribavir; and

discontinuing administration of the CYP3A4 inducer prior to administration of maribavir.

[0006] In some examples, the present disclosure provides methods of treating CMV infection in a patient suffering therefrom comprising:

administering an initial therapeutically effective amount of maribavir to the patient, wherein the patient is receiving a CYP3A4 inducer; and

increasing the amount of maribavir administered to the patient.

[0007] In some examples, the present disclosure provides methods of treating CMV infection in a patient suffering therefrom comprising:

administering a therapeutically effective amount of maribavir to the patient, wherein the patient has received a CYP3A4 inducer prior to administration of maribavir.

[0008] In some examples, a CYP3A4 inducer is selected from the group consisting of rifampin, avasimibe, carbamazepine, phenytoin, rifabutin, phenobarbital, and St. John's wort. In some examples a CYP3A4 inducer decreases maribavir exposure. In some examples, an initial therapeutically effective amount of maribavir is administered to the patient, and the amount of maribavir is increased when co-administering a CYP3A4 inducer. In some examples, an initial therapeutically effective amount of maribavir is about 400 mg, orally twice daily. In some examples, an amount of maribavir is increased to an amount between about 800 mg and about 1200 mg, orally twice daily. In some examples, the provided methods further comprising a step of monitoring patient blood (e.g., whole blood or plasma) concentration of maribavir and/or the CYP3A4 inducer.

[0009] In some examples, the present disclosure demonstrates, among other things, potential drug-drug interactions with maribavir and how exposure to maribavir and/or an immunosuppressant is affected. In some examples, the present disclosure provides methods of treating cytomegalovirus (CMV) infection in a patient suffering therefrom comprising administering a therapeutically effective amount of maribavir to the patient, wherein the patient is receiving or has received an immunosuppressant. In some examples, the immunosuppressant is selected from the group consisting of tacrolimus, cyclosporine, everolimus, sirolimus, prednisone, and mycophenolate. In some examples, the

immunosuppressant is selected from the group consisting of tacrolimus, cyclosporine, everolimus, and sirolimus. In some examples, an immunosuppressant is tacrolimus. In some examples, provided methods further comprising the step of monitoring the levels of immunosuppressant after discontinuing administration of maribavir (e.g., with comparison to a reference or standard level). In some examples, provided methods further comprising the step of increasing the amount of immunosuppressant administered to the patient (e.g., to the amount of immunosuppressant that was administered prior to commencing administration of maribavir).

[0010] In some examples, tacrolimus is administered at an initial dose and whole blood trough concentrations are monitored. In some examples, an initial dose (e.g., prior to administration of maribavir or upon co-administration of maribavir) of tacrolimus administered is between about 0.075 mg/kg/day and about 0.3 mg/kg/day. In some examples, tacrolimus is administered orally in capsules of 0.5 mg, 1.0 mg, or 5.0 mg each. In some examples, tacrolimus is administered by injection in a concentration of 5.0 mg/mL. In some examples, tacrolimus is administered by oral suspension in 1 mg unit-dose granule packets. In some examples, observed whole blood trough concentration of tacrolimus is monitored over a period of time between about 0 months and about 12 months from initial administration of tacrolimus. In some examples, observed whole blood trough concentration of tacrolimus is monitored at initial administration, during co-administration, and at discontinuation of maribavir administration. In some examples, observed whole blood trough concentration of tacrolimus is between about 4 and about 20 ng/mL. In some examples, tacrolimus is administered at an initial dose of between about 0.03% and about 0.1% (w/w) per gram of ointment. In some examples, tacrolimus is administered topically in a base selected from the group consisting of mineral oil, paraffin, propylene carbonate, white petrolatum and white wax.

[0011] In some examples, a dose of tacrolimus is adjusted when co-administered with maribavir. In some examples, maribavir is co-administered at a concentration of 400 mg, 800 mg, or 1200 mg, administered twice daily. In some examples, co-administration of maribavir increases exposure to tacrolimus by about 50%.

[0012] In some examples, the present disclosure demonstrates, among other things, potential drug-drug interactions with maribavir and how exposure to maribavir and/or an antiarrhythmic (e.g., digoxin) is affected. In some examples, the present disclosure provides

methods of treating CMV infection in a patient suffering therefrom comprising administering a therapeutically effective amount of maribavir to the patient, wherein the patient is receiving or has received an antiarrhythmic (e.g., digoxin). In some examples, provided methods further comprise monitoring the levels of digoxin in patient serum. In some examples, provided methods further comprise the step of reducing the amount of digoxin administered to the patient (e.g., to the amount of antiarrhythmic that was administered prior to commencing administration of maribavir).

[0013] In some examples, the present disclosure demonstrates, among other things, potential drug-drug interactions with maribavir and how exposure to maribavir and/or ganciclovir or valganciclovir is affected. In some examples, the present disclosure provides methods of treating cytomegalovirus (CMV) infection in a patient suffering therefrom comprising:

administering a therapeutically effective amount of maribavir to the patient, wherein the patient is receiving or has received ganciclovir or valganciclovir prior to administration of maribavir; and

discontinuing administration of the ganciclovir or valganciclovir prior to administration of maribavir.

[0014] In some examples, concentration of maribavir and/or the other drug being co-administered (e.g., a CYP3A4 inducer such as carbamazepine, phenytoin, or phenobarbital, a p-glycoprotein inducer (P-gp), an immunosuppressant, an antiarrhythmic such as digoxin, ganciclovir, or valganciclovir) is monitored at initial administration, during co-administration, and at discontinuation of maribavir administration.

[0015] In some examples, the patient is refractory to treatment with one or more other drugs to treat CMV infection (e.g., ganciclovir, valganciclovir, cidofovir, or foscarnet). In some examples, maribavir is administered with or without food. In some examples, the patient is a transplant recipient (e.g., a hematopoietic stem cell transplant recipient or a solid organ transplant recipient). In some examples, the patient is an adult or a child over 12 years old and greater than 35 kg.

CLAIMS

1. Use of maribavir in the manufacture of a medicament for treating cytomegalovirus (CMV) infection in a patient suffering therefrom, wherein:

about 800 or about 1200 mg of maribavir is to be orally administered twice daily to the patient; and

wherein the patient is a transplant recipient concomitantly exposed to or receiving an anticonvulsant.

2. The use of claim 1, wherein the anticonvulsant is selected from the group consisting of carbamazepine, phenytoin, and phenobarbital.

3. The use of claim 1, wherein the anticonvulsant is carbamazepine, and the amount of maribavir to be administered is about 800 mg orally twice daily.

4. The use of claim 1, wherein the anticonvulsant is phenytoin, and the amount of maribavir to be administered is about 1200 mg orally twice daily.

5. The use of claim 1, wherein the anticonvulsant is phenobarbital, and the amount of maribavir to be administered is about 1200 mg orally twice daily.

6. The use of any one of claims 1-5, wherein the patient is refractory to treatment with one or more of ganciclovir, valganciclovir, cidofovir, or foscarnet.

7. The use of any one of claims 1-6, wherein the patient is a hematopoietic stem cell transplant recipient.

8. The use of any one of claims 1-6, wherein the patient is a solid organ transplant recipient.

9. The use of any one of claims 1-8, wherein the patient is an adult or wherein the patient is a child 12 years of age or older and weighing greater than 35 kg.

10. The use of any one of claims 1-9, wherein the patient is concomitantly exposed to or receiving an immunosuppressant.

11. The use of claim 10, wherein the immunosuppressant is selected from the group consisting of cyclosporine, everolimus, sirolimus, and tacrolimus.

12. The use of claim 11, wherein the immunosuppressant is cyclosporin.

13. The use of claim 11, wherein the immunosuppressant is everolimus.

14. The use of claim 11, wherein the immunosuppressant is sirolimus.

15. The use of claim 11, wherein the immunosuppressant is tacrolimus.