to the biotransformation of approximately 70% of clinically used drugs. Generally, these enzymes provide a clearance mechanism for drugs and other xenobiotics and facilitate elimination from the body in urine and/or bile. CYP represents one of nature's most versatile enzymes with respect to its broad substrate profile and types of biotransformation reactions. The individual CYP enzymes exhibit distinct, but sometimes overlapping, substrate and inhibitor selectivities. Many drugs inhibit the activity of one or more CYP enzymes, and thus have the potential to cause a drug-drug interaction. Thus, a therapeutic dose of a first drug that is metabolized by a CYP enzyme may become a toxic dose when the first drug is administered with a second drug that inhibits that same CYP enzyme, since the CYP enzyme action on the first drug will be reduced by the presence of the second drug, leading to increased levels of the first drug (as compared to the levels obtained by the same dose of the first drug in the absence of the second drug).

[0004] Many therapeutically important drugs are metabolized by the CYP2C9 enzyme. CYP2C9 substrate drugs include, for example, tolbutamide, glimepiride, glipizide, warfarin, benzbromarone, celecoxib, ibuprofen, lornoxicam, meloxicam, and piroxicam. For example, the CYP2C9 substrate tolbutamide (used in treating diabetes) is metabolized by CYP2C9; administration of tolbutamide along with the CYP2C9 inhibitor sulfaphenazole to human subjects led to a more than 5-fold increase in the plasma level of tolbutamide (measured as area under the curve (AUC); Perkins et al., Eur J Drug Metab Pharmacokinet 43(3):355-367 (2018)). Citing similar data regarding tolbutamide, Miners et al. indicated that the current practice is to "individualise" the dose of tolbutamide when used with CYP2C9 substrates (Br J Pharmacol 45:525-538 (2998)).

[0005] Relacorilant (see Fig. 1; see also Hunt et al., J. Med. Chem. 60:3405-3421 (2017)) is a selective, non-steroidal modulator of the glucocorticoid receptor that is being investigated in clinical trials in patients with Cushing's syndrome and in patients with various types of cancer including, e.g., pancreatic cancer or ovarian cancer.

SUMMARY

[0005a] In one aspect of the present disclosure, there is provided a use of relacorilant in the manufacture of a medicament for treating a disorder in a patient, wherein said patient is to be administered:

a) an effective dose of relacorilant; and

b) an effective dose of a therapeutic agent, wherein said therapeutic agent is a substrate for CYP2C9 enzyme metabolism, said therapeutic agent having a single agent dose when it is to be administered without other pharmaceutical agents, wherein said therapeutic agent effective dose is substantially the same as said single agent dose;

wherein a) and b) are to be administered at times effective to provide the patient with an effective level of relacorilant and an effective level of the therapeutic agent at the same time,

whereby the disorder is treated.

[0005b] In another aspect of the present disclosure, there is provided a use of relacorilant and a CYP2C9 substrate in the manufacture of a medicament for the treatment of a disorder, wherein relacorilant and said CYP2C9 substrate is used concomitantly, wherein CYP2C9 substrate alone has been used in treating said disorder, and wherein the amount of said CYP2C9 substrate used in said concomitant treatment with relacorilant is the same amount of CYP2C9 substrate as used alone in treating said disorder.

[0006] Many therapeutic drugs are substrates of CYP2C9 enzymes; an otherwise safe dose of a first drug metabolized by CYP2C9 may be a toxic dose when concomitantly administered with a second drug that is a CYP2C9 inhibitor. *In vitro* studies are used to indicate drug combinations expected to suffer from such negative drug-drug interactions (DDIs).

[0007] Relacorilant is believed to be useful in treating many disorders, including cancer and hypercortisolism. Relacorilant is further believed to be useful in combination treatments for cancer and in treating hypercortisolism. *In vitro* tests demonstrated that relacorilant is a potent inhibitor of CYP2C9 (IC_{50} of 2.1 μM). Such potent inhibition of CYP2C9 would be expected to increase plasma exposure of CYP2C9 substrates by more than 5-fold when co-administered with relacorilant. Thus, it was expected that significant reductions in doses of CYP2C9 substrates (e.g., tolbutamide, glimepiride, glipizide, warfarin, benzbromarone, celecoxib, ibuprofen, and others) would be required when administered in combination with relacorilant.

[0008] Surprisingly, Applicant determined that it was safe to co-administer relacorilant and a CYP2C9 substrate to human subjects without modifying the dose of the CYP2C9 substrate. Applicant discloses herein that relacorilant may be safely administered along with unmodified doses of tolbutamide, glimepiride, glipizide, and other CYP2C9 substrates, such as, e.g., benzbromarone, celecoxib, ibuprofen, and others. Relacorilant and unmodified doses of tolbutamide, glimepiride or glipizide, and other CYP2C9 substrates may be administered for the treatment of hypercortisolism, or symptoms associated with hypercortisolism. For example, relacorilant and unmodified doses of tolbutamide, glimepiride or glipizide may be administered for the treatment of diabetes associated with hypercortisolism. Applicant's surprising discovery is further believed to apply to cancer patients receiving relacorilant as part of a combination therapy regimen including paclitaxel (e.g., nab-paclitaxel) for the treatment of cancer, such as, e.g., ovarian or pancreatic cancer, or a symptom associated with cancer in a cancer patient. These cancer patients being treated with paclitaxel (e.g., nab-paclitaxel) may benefit from concomitant treatment with relacorilant and tolbutamide, or glimepiride, or glipizide, or other CYP2C9 substrate, and may continue to receive tolbutamide, glimepiride or glipizide, or other CYP2C9 substrate at its therapeutic dose without need for reducing the dose of tolbutamide, glimeprimide, glipizide, or other CYP2C9 substrate concomitantly with relacorilant.

[0009] Accordingly, Applicant discloses herein that a CYP2C9 substrate may be concomitantly administered with the selective glucocorticoid receptor modulator relacorilant without reduction in the dose of the CYP2C9 substrate. Such concomitant administration of a CYP2C9 substrate and relacorilant is believed to be safe for the subject and to provide the therapeutic benefits of both drugs to the subject. In examples, the CYP2C9 substrate is tolbutamide. In examples the CYP2C9 substrate is glimepiride. In examples the

CYP2C substrate is glipizide. In examples, the CYP2C9 substrate may be selected from tolbutamide, glimepiride, or glipizide.

[0010] The methods disclosed herein surprisingly provide safe methods for administering drug combinations that were previously expected to be unsafe, allowing concomitant administration of drug combinations with relacorilant. Such drug combinations are believed to provide more effective treatments than treatment with only one of the drugs in the absence of the other. The surprising ability to safely administer these drug combinations provide advantages including more effective treatments, absence of previously expected side effects, and other advantages.

BRIEF DESCRIPTION OF THE DRAWING

[0011] Fig. 1 shows the chemical structure of relacorilant ((R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridine-2-yl)methanone).

DETAILED DESCRIPTION

[0012] Applicant discloses herein the surprising discovery that relacorilant may be safely co-administered with CYP2C9 substrate drugs without need for reducing the dosage of those CYP2C9 substrate drugs. Such CYP2C9 substrate drugs include tolbutamide, and others. Relacorilant and a CYP2C9 substrate may be co-administered to treat hypercortisolism, e.g., to treat Cushing's syndrome and Cushing's Disease without need for reducing the dosage of the CYP2C9 substrate. The CYP2C9 substrate drug administered with relacorilant to treat hypercortisolism, or a symptom associated with hypercortisolism, such as diabetes, may be, for example, tolbutamide, glimepiride, glipizide, or other CYP2C9 substrate. In embodiments, the CYP2C9 substrate drug is administered with relacorilant to treat hypercortisolism, or a symptom associated with hypercortisolism, is selected from tolbutamide, glimepiride and glipizide. In embodiments, the CYP2C9 substrate drug is administered with relacorilant to treat cancer, or a symptom associated with cancer, in a patient receiving paclitaxel (e.g., nab-paclitaxel) for the treatment of the cancer (e.g., ovarian or pancreatic cancer). The CYP2C9 substrate drug administered with relacorilant to treat cancer, or a symptom associated with cancer, in a patient receiving paclitaxel (e.g., nab-paclitaxel) treatment may be selected from tolbutamide, glimepiride and glipizide.

[0013] In embodiments, Applicant discloses a method of treating a disorder, comprising administering to a patient in need of treatment for said disorder:

CLAIMS

1. Use of relacorilant in the manufacture of a medicament for treating a disorder in a patient, wherein said patient is to be administered:

a) an effective dose of relacorilant; and

b) an effective dose of a therapeutic agent, wherein said therapeutic agent is a substrate for CYP2C9 enzyme metabolism, said therapeutic agent having a single agent dose when it is to be administered without other pharmaceutical agents, wherein said therapeutic agent effective dose is substantially the same as said single agent dose;

wherein a) and b) are to be administered at times effective to provide the patient with an effective level of relacorilant and an effective level of the therapeutic agent at the same time,

whereby the disorder is treated.

2. The use of claim 1, wherein said disorder is selected from cancer, a symptom associated with cancer, hypercortisolism, and a symptom associated with hypercortisolism.

3. The use of claim 1, wherein the relacorilant dose is between about 1 milligram per kilogram (mg/kg) and about 20 mg/kg.

4. The use of claim 1, wherein the relacorilant dose is between about 50 mg and about 500 mg.

5. The use of claim 4, wherein the relacorilant dose is to be administered at a time within about 15 minutes of the time of administration of the therapeutic agent dose.

6. The use of claim 1, wherein the relacorilant dose and therapeutic agent dose are to be administered sequentially.

7. The use of claim 6, wherein the relacorilant dose is to be administered to the patient, and then, after a time interval, the therapeutic agent dose is to be administered to the patient.

8. The use of claim 6, wherein the therapeutic agent dose is to be administered to the patient, and then, after a time interval, the relacorilant dose is to be administered to the patient.

9. The use of claim 7, wherein said time interval is selected from about one hour and about one day.

10. The use of claim 8, wherein said time interval is selected from about one hour and about one day.

11. The use of claim 1, wherein said disorder is hypercortisolism, or a symptom associated with hypercortisolism, and the therapeutic agent is selected from tolbutamide, glimepiride, and glipizide.

12. The use of claim 11, wherein said symptom associated with hypercortisolism is selected from diabetes, hypertension, hyperglycemia, abnormal body fat, excessive body fat, moon-face, and abnormal blood clotting.

13. The use of claim 12, wherein said symptom associated with hypercortisolism is diabetes.

14. The use of claim 1, wherein said disorder is cancer, or a symptom associated with cancer in a cancer patient.

15. The use of claim 14, wherein the cancer is ovarian cancer or pancreatic cancer.

16. The use of claim 14, wherein the therapeutic agent is selected from tolbutamide, glimepiride, and glipizide.

17. The use of claim 14, wherein said cancer patient is receiving paclitaxel or nab-paclitaxel.

18. Use of relacorilant and a CYP2C9 substrate in the manufacture of a medicament for the treatment of a disorder, wherein relacorilant and said CYP2C9 substrate is used concomitantly, wherein CYP2C9 substrate alone has been used in treating said disorder, and wherein the amount of said CYP2C9 substrate used in said concomitant treatment with relacorilant is the same amount of CYP2C9 substrate as used alone in treating said disorder.

19. The use of claim 18, wherein the CYP2C9 substrate is selected from tolbutamide, glimepiride, and glipizide.

20. The use of claim 18, wherein said disorder is selected from hypercortisolism, a symptom associated with hypercortisolism, cancer, and a symptom associated with cancer.