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 disorder is selected from cancer, a symptom associated with cancer, hypercortisolism, and a symptom associated with hypercortisolism,

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 selected from tolbutamide, glimepiride, glipizide, paclitaxel, and nab-paclitaxel, 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 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,

wherein the combined administration of said relacorilant and said tolbutamide:

i) does not increase the AUC_{inf} of said therapeutic agent as compared to the AUC_{inf} of said therapeutic agent when administered in the absence of relacorilant, and

ii) reduces the C_{max} of said therapeutic agent by an amount that is 31% of the C_{max} of said therapeutic agent when it is administered in the absence of relacorilant

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 said disorder is selected from hypercortisolism, a symptom associated with hypercortisolism, cancer, and a symptom associated with cancer,

wherein relacorilant and said CYP2C9 substrate is used concomitantly, wherein CYP2C9 substrate alone has been used in treating said disorder, and

wherein the combined administration of said relacorilant and said CYP2C9 substrate:

i) does not increase the AUC_{inf} of said CYP2C9 substrate as compared to the AUC_{inf} of said CYP2C9 substrate when administered in the absence of relacorilant, and

ii) reduces the C_{max} of said CYP2C9 substrate by an amount that is 31% of the C_{max} of said CYP2C9 substrate when it is administered in the absence of relacorilant

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).

CLAIMS

1. Use of relacorilant in the manufacture of a medicament for treating a disorder in a patient, wherein said disorder is selected from cancer, a symptom associated with cancer, hypercortisolism, and a symptom associated with hypercortisolism,

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 selected from tolbutamide, glimepiride, glipizide, paclitaxel, and nab-paclitaxel, 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 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,

wherein the combined administration of said relacorilant and said tolbutamide:

i) does not increase the AUC_{inf} of said therapeutic agent as compared to the AUC_{inf} of said therapeutic agent when administered in the absence of relacorilant, and

ii) reduces the C_{max} of said therapeutic agent by an amount that is 31% of the C_{max} of said therapeutic agent when it is administered in the absence of relacorilant

whereby the disorder is treated.

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

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

4. The use of claim 3, wherein the relacorilant dose is to be administered at a time within 15 minutes of the time of administration of the therapeutic agent dose.

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

6. The use of claim 5, 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.

7. The use of claim 5, 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.

8. The use of claim 6, wherein said time interval is selected from one hour and one day.

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

10. 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.

11. The use of claim 10, wherein said symptom associated with hypercortisolism is selected from diabetes, hypertension, hyperglycemia, abnormal body fat, excessive body fat, moon-face, and abnormal blood clotting.

12. The use of claim 11, wherein said symptom associated with hypercortisolism is diabetes.

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

14. The use of claim 13, wherein the cancer is ovarian cancer or pancreatic cancer.

15. The use of claim 13, wherein said cancer patient is receiving paclitaxel or nab-paclitaxel.

16. Use of relacorilant and a CYP2C9 substrate in the manufacture of a medicament for the treatment of a disorder, wherein said disorder is selected from hypercortisolism, a symptom associated with hypercortisolism, cancer, and a symptom associated with cancer,

wherein relacorilant and said CYP2C9 substrate is used concomitantly, wherein CYP2C9 substrate alone has been used in treating said disorder, and

wherein the combined administration of said relacorilant and said CYP2C9 substrate:

i) does not increase the AUC_{inf} of said CYP2C9 substrate as compared to the AUC_{inf} of said CYP2C9 substrate when administered in the absence of relacorilant, and

ii) reduces the C_{max} of said CYP2C9 substrate by an amount that is 31% of the C_{max} of said CYP2C9 substrate when it is administered in the absence of relacorilant

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.

17. The use of claim 16, wherein the CYP2C9 substrate is selected from tolbutamide, glimepiride, and glipizide.

18. The use of claim 16, wherein said disorder is selected from hypercortisolism, and a symptom associated with hypercortisolism, and said therapeutic agent is selected from tolbutamide, glimepiride, and glipizide.

19. The use of claim 16, wherein said disorder is selected from cancer, and a symptom associated with cancer, and said therapeutic agent is paclitaxel or nab-pacltaxel.