# FORMULATIONS CONTAINING DEUTERATED DOMPERIDONE

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims priority to U.S. Provisional Patent Application No. 62/750,491, filed October 25, 2018, which is incorporated by reference herein.

## TECHNICAL FIELD

**[0002]** This disclosure relates to pharmaceutical formulations containing $d_4$-domperidone.

## BACKGROUND

**[0003]** Gastroparesis is a condition where motility of the stomach does not function or does not function properly, which prevents the stomach from emptying and interferes with digestion. Treatment of gastroparesis requires medications, *e.g.*, metoclopramide, erythromycin, or cisapride, to stimulate the stomach muscles. Metoclopramide poses serious side effects, such as development of movement disorders or adverse interactions with other medications; erythromycin is susceptible to loss of efficacy as patient drug tolerance increases; and cisapride has limited accessibility.

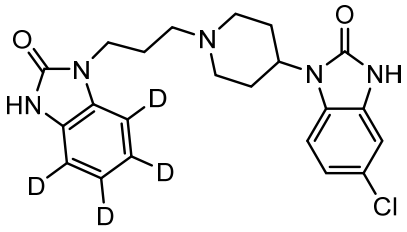
**[0004]** Medications to control nausea and vomiting, *e.g.*, prochlorperazine, thiethylperazine, diphenhydramine, or ondansetron, may also be administered to treat gastroparesis. The symptoms of gastroparesis also may be treated surgically, such as installing jejunostomy tubes, gastric venting tubes, or feeding tubes.

**[0005]** Domperidone, in both deuterated and non-deuterated forms, is an effective dopamine antagonist that does not readily cross the blood-brain barrier and may be used to treat gastroparesis. Safe and efficacious formulations of domperidone are needed.

## SUMMARY

**[0005a]** In one aspect of the present disclosure, there is provided a pharmaceutical formulation comprising:

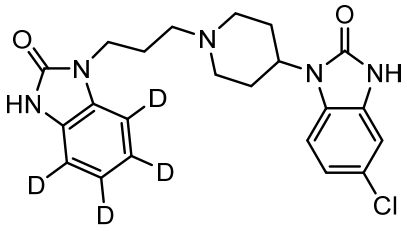
(i) deuterated $d_4$-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a glyceryl stearate, and a medium chain triglyceride;

or

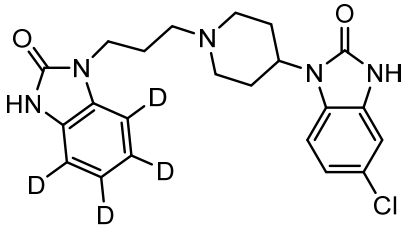
(ii) deuterated $d_4$-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a stearoyl polyoxyl glyceride, a nonionic poly(ethylene oxide) polymer, and a medium chain triglyceride;

or

(iii) deuterated $d_4$-domperidone of the formula (I):



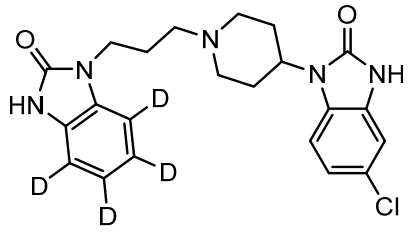
(I) or a pharmaceutically acceptable salt thereof; a nonionic poly(ethylene oxide) polymer, and a polyethylene glycol.

**[0005b]** In another aspect of the present disclosure, there is provided a pharmaceutical formulation disclosed herein for use in treating a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, or a combination thereof in a patient.

**[0005c]** In a further aspect of the present disclosure, there is provided a use of a pharmaceutical formulation disclosed herein in the manufacture of a medicament for treating

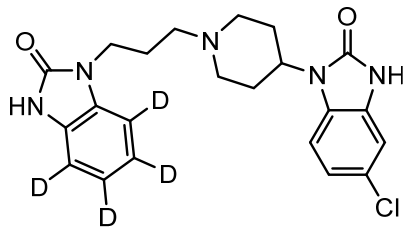
a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, or a combination thereof in a patient.

**[0006]** In some examples, the disclosure provides pharmaceutical formulation comprising $d_4$-domperidone of the formula (I):



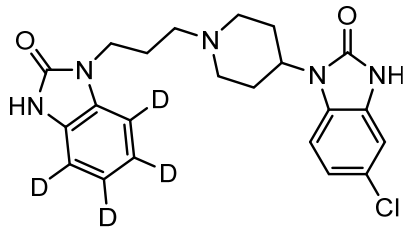
(I) or a pharmaceutically acceptable salt thereof; a glyceryl stearate, and a medium chain triglyceride.

**[0007]** In other examples, the disclosure provides pharmaceutical formulations comprising $d_4$-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a stearoyl polyoxyl glyceride, a nonionic poly(ethylene oxide) polymer, and a medium chain triglyceride.

**[0008]** In further examples, the disclosure provides pharmaceutical formulations comprising $d_4$-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a nonionic poly(ethylene oxide) polymer, and a polyethylene glycol.

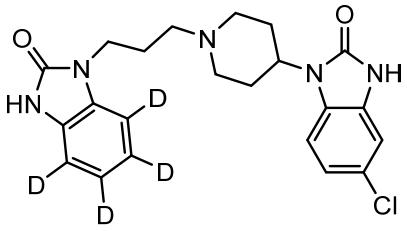
**[0009]** In still other examples, the disclosure provides methods for treating a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, or a combination thereof in a patient, comprising administering to the patient a formulation described herein. In some examples, the disorder is gastroparesis. In other examples, the disorder is gastroesophageal reflux disease. In further examples, the disorder is insufficient lactation.

**[00010]** Other examples of the present disclosure will be readily apparent from the following detailed description of the invention.

**What is Claimed is:**

1. A pharmaceutical formulation comprising:

   (i) deuterated $d_4$-domperidone of the formula (I):

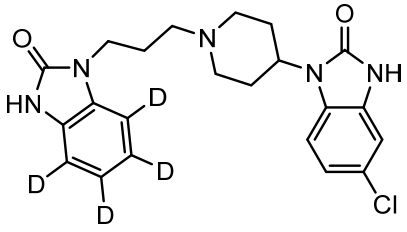


(I) or a pharmaceutically acceptable salt thereof;

a glyceryl stearate, and a medium chain triglyceride;

or

(ii) deuterated $d_4$-domperidone of the formula (I):

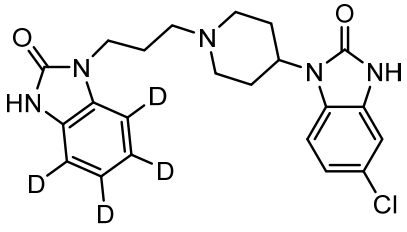


(I) or a pharmaceutically acceptable salt thereof;

a stearoyl polyoxyl glyceride, a nonionic poly(ethylene oxide) polymer, and a medium chain triglyceride;

or

(iii) deuterated $d_4$-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof;

a nonionic poly(ethylene oxide) polymer, and a polyethylene glycol.

2. The pharmaceutical formulation of claim 1, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, a glyceryl stearate, and a medium chain triglyceride.

3. The pharmaceutical formulation of claim 1 or 2, wherein the glyceryl stearate is a glyceryl palmitostearate, a glycerol distearate, a glyceryl distearate, or a combination thereof.

4. The pharmaceutical formulation of any one of the preceding claims, comprising about 2 to about 20% (w/w), based on the weight of the formulation, of the glyceryl stearate, preferably about 5 to about 15% (w/w), or more preferably about 10% (w/w).

5. The pharmaceutical formulation of any one of the preceding claims, comprising about 70 to about 90% (w/w), based on the weight of the formulation, of the medium chain triglyceride, or preferably about 80 to about 85% (w/w).

6. The pharmaceutical formulation of any one of the preceding claims, wherein the glyceryl stearate is Precirol® ATO 5.

7. The pharmaceutical formulation of claim 1, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, a stearoyl polyoxyl glyceride, a nonionic poly(ethylene oxide) polymer, and a medium chain triglyceride.

8. The pharmaceutical formulation of claim 1, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, a nonionic poly(ethylene oxide) polymer, and a polyethylene glycol.

9. The pharmaceutical formulation of any one of the preceding claims, further comprising an antioxidant.

10. The pharmaceutical formulation of claim 9, wherein the antioxidant is ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate, potassium metabisulfite, sodium metabisulfite, sodium thiosulfate, or vitamin E, or preferably butylated hydroxyanisole or butylated hydroxytoluene.

11. The pharmaceutical formulation of any one of the preceding claims, comprising about 1 to about 20% (w/w), based on the weight of the formulation, of $d_4$-domperidone, preferably about 5 to about 12% (w/w), or more preferably about 10% (w/w).

12. The pharmaceutical formulation of any one of the preceding claims, comprising about 1 to about 50 mg of $d_4$-domperidone.

13. A pharmaceutical formulation of any one of claims 1 to 12 for use in treating a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, or a combination thereof in a patient.

14. The pharmaceutical composition for use according to claim 13, wherein the formulation is in the form of a tablet, capsule, softgel, suspension, liquid, or combination thereof.

15. The pharmaceutical composition for use according to claim 13 or 14, wherein the disorder is gastroparesis.

16. The pharmaceutical composition for use according to claim 13 or 14, wherein the disorder is gastroesophageal reflux disease.

17. The pharmaceutical composition for use according to claim 13 or 14, wherein the disorder is insufficient lactation.

18. Use of a pharmaceutical formulation of any one of claims 1 to 12 in the manufacture of a medicament for treating a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, or a combination thereof in a patient.

19. The use according to claim 18, wherein the formulation is in the form of a tablet, capsule, softgel, suspension, liquid, or combination thereof.

20. The use according to claim 18 or 19, wherein the disorder is gastroparesis.

21. The use according to claim 18 or 19, wherein the disorder is gastroesophageal reflux disease.

22. The use according to claim 18 or 19, wherein the disorder is insufficient lactation.