OBJECTS OF THE INVENTION

Accordingly, it is an object of the invention to provide new methods for treating or preventing nausea and vomiting using an NK_1 antagonist, particularly netupitant.

It is another object of the invention to provide methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

Still another object of the invention is to augment existing treatments for CINV, RINV or PONV by steroids and 5-HT_3 antagonists, and thereby provide additional protection against both nausea and vomiting, especially during the acute and delayed phases.

Another object of the invention is to provide a single combined dose of netupitant and a 5-HT_3 antagonist and to the use of that single dose without further dosing, for the treatment of nausea and vomiting during the acute and delayed phases of CINV, RINV or PONV.

It is another object to provide novel methods to treat nausea, vomiting, and other undesirable effects from moderately emetogenic and highly emetogenic chemotherapy ("MEC and HEC"), especially HEC, during the acute and delayed phases following such treatments.

It is another object to provide novel dosage forms to reduce drug-drug interaction, improve stability, enhance bioavailability and potentiate therapeutic effect of each component of the combined dosage forms comprising netupitant and/or 5-HT_3 antagonist and/or dexamethasone, in treating or preventing nausea and vomiting.

SUMMARY ~~OF THE INVENTION~~

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

These discoveries have led to the development of a unique dosing regimen to treat nausea during the first day after an emesis-inducing event, in addition to the second, third, fourth and fifth days after such induction. Therefore, in one embodiment the ~~invention~~disclosure provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT_3 antagonist such as palonosetron and a corticosteroid such as dexamethasone, in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when palonosetron is in combination with netupitant as opposed to palonosetron in single dose administration. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant or another NK1 antagonist and palonosetron for the treatment of acute and delayed emesis.

It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself). Therefore, in another embodiment the ~~invention~~disclosure provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, consisting essentially of:

- Day 1 netupitant -- administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;
- Day 1 palonosetron -- administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;

- Day 1 dexamethasone -- administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and
- Days 2-5 dexamethasone – when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

In one aspect, there is provided a combination of (i) netupitant or a pharmaceutically acceptable salt thereof, (ii) a 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof, (iii) dexamethasone, for use in treating nausea and vomiting for five consecutive days in a patient in need thereof, wherein:

a) said netupitant or a pharmaceutically acceptable salt thereof is administered to said patient on day one, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

b) the 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof is administered to said patient on day one, in a therapeutically effective amount, which is effective to treat nausea and vomiting during the acute and delayed phases; and

c) dexamethasone is administered to said patient on day one in a first dose which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone.

In one aspect, there is provided a netupitant or a pharmaceutically acceptable salt thereof, for use in treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, said netupitant

being administered in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration, wherein the following are administered:

a) on day one, a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

b) if said patient is subject to highly emetogenic chemotherapy, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

In one aspect, there is provided a combination of a therapeutically effective amount of netupitant or pharmaceutically acceptable salt thereof, and a therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof, for use in treating nausea and vomiting in a human subject in need thereof, during the acute and/or delayed phases of CINV in response to moderately or highly emetogenic chemotherapy, wherein said combination is administered before said chemotherapy.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be

formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

Thus, in one embodiment the ~~invention~~disclosure provides an orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist (preferably netupitant), or a pharmaceutically acceptable salt or prodrug thereof.

In one aspect, there is provided an orally administrable dosage form comprising a combination of palonosetron and netupitant, or a pharmaceutically acceptable salt thereof, comprising:

a) an outer shell;

b) one or more netupitant units housed within said outer shell, each comprising said netupitant or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients; and

c) one or more palonosetron units housed within said outer shell, each comprising said palonosetron and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

In another embodiment the ~~invention~~disclosure provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist (preferably netupitant) or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically

acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

In one aspect, there is provided an orally administerable capsule dosage form comprising:

a) an outer shell;

b) one or more tablets housed within said outer shell, each comprising netupitant or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients; and

c) one or more soft-gel capsules housed within said outer shell, each comprising palonosetron and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

In still other embodiments the ~~invention~~disclosure provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present ~~invention~~disclosure to a human in need thereof, preferably shortly before the emesis inducing event.

In one aspect, there is provided the dosage form or capsule as defined above for use in treating emesis.

Additional embodiments and advantages of the ~~invention~~disclosure will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the ~~invention~~disclosure. The embodiments and advantages of the ~~invention~~disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the ~~invention~~disclosure, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. 1 depicts a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. 2 is a two dimensional graph plotting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. 3 is a two dimensional graph plotting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

FIG. 4 is a two dimensional graph plotting mean plasma concentrations of dexamethasone over time following administration with and without netupitant.

FIG. 5 contains two bar graphs that depict the average NK_1 receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in striatum and occipital cortex, as measured using positron emission topography.

CLAIMS

1) Use of netupitant or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating nausea and vomiting for five consecutive days in a patient in need thereof, wherein:

a) said patient is to be administered on day one, netupinant or a pharmaceutically acceptable salt thereof in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

b) said patient is to be administered, on day one, a therapeutically effective amount of a 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof, which is effective to treat nausea and vomiting during the acute and delayed phases; and

c) said patient is to be administered, on day one, a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone.

2) The use of claim 1, wherein said patient is to be administered, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

3) The use of claim 1 or 2, wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum seventy-two hours after said administration.

4) The use of any one of claims 1 to 3, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is to be administered during said five days.

5) The use of any one of claims 1 to 4, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is to be administered during said five days, and said one dose is to be administered orally.

6) The use of any one of claims 1 to 5, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof.

7) The use of any one of claims 1 to 6, wherein said therapeutically effective amount of netupitant comprises about 300 mg. of netupitant as a free base.

8) The use of any one of claims 1 to 7, wherein said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

9) The use of any one of claims 1 to 8, wherein only one dose of 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof is to be administered during said five days.

10) The use of any one of claims 1 to 9, wherein the 5-HT_3 antagonist is ondansetron or palonosetron.

11) The use of any one of claims 1 to 10, wherein said therapeutically effective amount of 5-HT_3 antagonist comprises from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof.

12) The use of any one of claims 1 to 11, wherein said therapeutically effective amount of 5-HT_3 antagonist comprises about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

13) The use of any one of claims 1 to 12, wherein said palonosetron is to be administered orally.

14) The use of any one of claims 1 to 13, wherein:

a) about 300 mg. of netupitant as a free base is to be orally administered on day one;

b) about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, is to be orally administered on day one; and

c) about 12 mg. of dexamethasone is to be orally administered on day one.

15) The use of any one of claims 1 to 14, wherein:

a) about 300 mg. of netupitant as a free base on is to be orally administered day one;

b) about 0.56 mg. of palonosetron hydrochloride (corresponding to about 0.5 mg of palonosetron as a free base) is to be orally administered on day one;

c) about 12 mg. of dexamethasone is to be orally administered on day one; and

about 8 mg. of dexamethasone is to be orally administered on days two, three and four.

16) The use of netupitant or a pharmaceutically acceptable salt thereof in the manufacture of medicament for treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, wherein the netupitant or the pharmaceutically acceptable salt thereof is in a therapeutically effective amount which is

effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

17) The use of claim 16, wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum seventy-two hours after said administration.

18) The use of claim 16 or 17, wherein:

a) said patient is to be administered, on day one, a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

b) if said patient is subject to highly emetogenic chemotherapy, said patient is to be administered, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

19) The use of any one of claims 16 to 18, wherein a therapeutically effective amount of a 5-HT_3 antagonist is to be further administered.

20) The use of any one of claims 16-19, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof, said therapeutically effective amount of 5-HT_3 antagonist comprises from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof, and said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

21) The use of any one of claims 16-20, wherein:

a) only one dose of netupitant is to be administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and

b) about 12 mg. of dexamethasone is to be administered on day one; and

c) if said patient is undergoing highly emetogenic chemotherapy, about 8 mg. of dexamethasone is to be administered on days two, three and four.

22) The use of claim 21, wherein only one dose of a 5-HT_3 antagonist is to be administered during said five days on day one, comprising about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

23) The use of any one of claims 1-22, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

24) The use of any one of claims 1-22, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

25) The use of any one of claims 1-24, wherein moderately or highly emetogenic chemotherapy is to be administered within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

26) The use of any one of claims 1-25,wherein the nausea and vomiting to be treated is in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

27) Use of netupitant or a pharmaceutically acceptable salt thereof in the manufacture of medicament for treating nausea and vomiting in a human subject in need thereof, during the acute and/or delayed phases of CINV in response to moderately or highly emetogenic chemotherapy, wherein the medicament is to be administered with a therapeutically effective amount of palonosetron, or a pharmaceutically acceptable salt thereof, before said chemotherapy.

28) The use of claim 27, wherein from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof, and from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof is to be orally administered.

29) The use of claim 27 or 28, wherein about 300 mg. of netupitant as the free base, and about 0.56 mg. of palonosetron hydrochloride is to be orally administered.

30) The use of any one of claims 27-29, wherein, if said subject is subject to highly emetogenic chemotherapy, a sub-therapeutic dose of dexamethasone is to be administered on days one, two, three and four.

31) The use of any one of claims 27-30, wherein if said subject is undergoing highly emetogenic chemotherapy, 12 mg. of dexamethasone is to be orally administered on day one, and 8 mg. of dexamethasone is to be orally administered on days two, three and four.

32) The use of any one of claims 1-31, wherein netupitant potentiates the therapeutic effect of dexamethasone.

33) The use of any one of claims 1-32, wherein netupitant promotes bioavailability of palonosetron.

34) An orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist, or a pharmaceutically acceptable salt or prodrug thereof, comprising:

a) an outer shell;

b) one or more NK1 antagonist units housed within said outer shell, each comprising said netupitant or pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and

c) one or more palonosetron units housed within said outer shell, each comprising said palonosetron or pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

35) The dosage form of claim 34, comprising about 0.56 mg. of palonosetron hydrochloride and from about 100 to about 500 mg, or from about 200 to about 400 mg, or about 300 mg of netupitant or a pharmaceutically acceptable salt thereof.

36) The dosage form of claim 34 or 35, wherein said one or more NK1 antagonist units are in the form of one or more orally administered tablets, and said palonosetron units are in the form of one or more orally administered soft-gel capsules.

37) The dosage form of any one of claims 34 to 36, wherein each of said tablets comprises from about 50 to about 200 mg, or from about 100 to about 150 mg, or about 100 mg of netupitant.

38) The capsule of any one of claims 34 to 37, wherein said outer shell of said capsule has an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

39) The capsule of any one of claims 34 to 38, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.

40) The capsule of any one of claims 34 to 39, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.

41) The capsule of any one of claims 34 to 40, wherein each of said soft-gel capsules comprises an outer shell having an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

42) An orally administered capsule dosage form comprising:

a) an outer shell;

b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and

c) one or more soft-gel capsules housed within said outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

43) The capsule of claim 42 comprising about 0.56 mg. of palonosetron hydrochloride and from about 100 to about 500 mg, or from about 200 to about 400 mg, or about 300 mg of netupitant.

44) The capsule of claim 42 or 43, wherein said outer shell of said capsule has an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

45) The capsule of any one of claims 42 to 44, wherein each of said tablets comprises from about 50 to about 200 mg, or from about 100 to about 150 mg, or about 100 mg of netupitant or a pharmaceutically acceptable salt thereof.

46) The capsule of any one of claims 42 to 45, wherein each of said soft-gel capsules comprises an outer shell having an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

47) The capsule of any one of claims 42 to 46, wherein said soft-gel capsule comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.

48) The capsule of any one of claims 42 to 47, wherein said soft-gel capsule comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.

49) The dosage form or capsule of any one of claims 34 to 48, wherein netupitant and palonosetron are formulated in separate form and then combined in one dosage.

50) The use of the dosage form of any one of claims 34-49 in the manufacture of a medicament for treating emesis.

51) The use of claim 50 wherein said emesis is delayed-onset emesis.

CLAIMS

1. A combination of (i) netupitant or a pharmaceutically acceptable salt thereof, (ii) a 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof, (iii) dexamethasone, for use in treating nausea and vomiting for five consecutive days in a patient in need thereof, wherein:

   a) said netupitant or a pharmaceutically acceptable salt thereof is administered to said patient on day one, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

   b) the 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof is administered to said patient on day one, in a therapeutically effective amount, which is effective to treat nausea and vomiting during the acute and delayed phases; and

   c) dexamethasone is administered to said patient on day one in a first dose which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone.

2. The combination for use according to claim 1, wherein, on days two, three and four, a second dose of dexamethasone, which is ineffective against nausea and vomiting when administered alone but effective against nausea and vomiting when administered in combination with said netupitant, is administered to said patient, said second dose comprising from 40 to 60% of a minimum effective dose when administered alone.
3. The combination for use according to claim 1 or 2, wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum seventy-two hours after said administration.

4. The combination for use according to any one of claims 1 to 3, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days.
5. The combination for use according to any one of claims 1 to 4, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days, and said one dose is administered orally.
6. The combination for use according to any one of claims 1 to 5, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof.
7. The combination for use according to any one of claims 1 to 6, wherein said therapeutically effective amount of netupitant comprises about 300 mg. of netupitant as a free base.
8. The combination for use according to any one of claims 1 to 7, wherein said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.
9. The combination for use according to any one of claims 1 to 8, wherein only one dose of 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof is administered during said five days.
10. The combination for use according to any one of claims 1 to 9, wherein the 5-HT_3 antagonist is ondansetron or palonosetron.
11. The combination for use according to any one of claims 1 to 10, wherein said therapeutically effective amount of 5-HT_3 antagonist comprises from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof.
12. The combination for use according to any one of claims 1 to 11, wherein said therapeutically effective amount of 5-HT_3 antagonist comprises about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.
13. The combination for use according to any one of claims 1 to 12, wherein said palonosetron is administered orally.

14. The combination for use according to any one of claims 1 to 13, wherein the following are orally administered:

a) about 300 mg. of netupitant as a free base on day one;

b) about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day one; and

c) about 12 mg. of dexamethasone on day one.

15. The combination for use according to any one of claims 1 to 14, wherein the following are orally administered:

a) about 300 mg. of netupitant as a free base on day one;

b) about 0.56 mg. of palonosetron hydrochloride (corresponding to about 0.5 mg of palonosetron as a free base) on day one;

c) about 12 mg. of dexamethasone on day one; and

d) about 8 mg. of dexamethasone on days two, three and four.

16. Netupitant or a pharmaceutically acceptable salt thereof, for use in treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, said netupitant being administered in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration, wherein the following are administered:

a) on day one, a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

b) if said patient is subject to highly emetogenic chemotherapy, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

17. Netupitant for use according to claim 16, wherein a therapeutically effective amount of a 5-HT_3 antagonist is further administered.
18. Netupitant for use according to claims 16-17, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof, said therapeutically effective amount of 5-HT_3 antagonist comprises from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof, and said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.
19. Netupitant for use according to claims 16-18, wherein:

    a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and

    b) about 12 mg. of dexamethasone are administered on day one; and

    c) if said patient is undergoing highly emetogenic chemotherapy, about 8 mg of dexamethasone are administered on days two, three and four.

20. Netupitant for use according to claim 19, wherein only one dose of a 5-HT_3 antagonist is administered during said five days on day one, comprising about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.
21. Netupitant for use according to claims 1-20, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

22. Netupitant for use according to claims 1-21, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.
23. Netupitant for use according to claims 1-22, wherein moderately or highly emetogenic chemotherapy is administered within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.
24. Netupitant for use according to claims 1-23, said use comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

25. A combination of a therapeutically effective amount of netupitant or pharmaceutically acceptable salt thereof, and a therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof, for use in treating nausea and vomiting in a human subject in need thereof, during the acute and/or delayed phases of CINV in response to moderately or highly emetogenic chemotherapy, wherein said combination is administered before said chemotherapy.
26. The combination for use according to claim 25, wherein from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof, and from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof are orally administered.
27. The combination for use according to claim 25 or 26, wherein about 300 mg. of netupitant as the free base, and about 0.56 mg. of palonosetron hydrochloride are orally administered.
28. The combination for use according to any one of claims 25-27, wherein, if subject to highly emetogenic chemotherapy, said patient is further administered a sub-therapeutic dose of dexamethasone on days one, two, three and four.
29. The combination for use according to any one of claims 25-28, wherein, if undergoing highly emetogenic chemotherapy, said patient is further orally

administered 12 mg. of dexamethasone on day one, and 8 mg. of dexamethasone on days two, three and four.

30. The combination for use according to any one of claims 1-29, wherein netupitant potentiates the therapeutic effect of dexamethasone.
31. The combination of netupitant for use according to any one of claims 1-30, wherein netupitant promotes bioavailability of palonosetron.

32. An orally administrable dosage form comprising a combination of palonosetron and netupitant, or a pharmaceutically acceptable salt thereof, comprising:

a) an outer shell;

b) one or more netupitant units housed within said outer shell, each comprising said netupitant or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients; and

c) one or more palonosetron units housed within said outer shell, each comprising said palonosetron and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

33. The dosage form of claim 32, comprising about 0.56 mg. of palonosetron hydrochloride and from about 100 to about 500 mg, or from about 200 to about 400 mg, or about 300 mg of netupitant.
34. The dosage form of claim 32 or 33, wherein said one or more netupitant units are in the form of one or more orally administered tablets, and said palonosetron units are in the form of one or more orally administered soft-gel capsules.
35. The dosage form of any one of claims 32 to 34, wherein each of said tablets comprises from about 50 to about 200 mg, or from about 100 to about 150 mg, or about 100 mg of netupitant.

36. The capsule of any one of claims 32 to 35, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.
37. The capsule of any one of claims 32 to 36, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.

38. An orally administerable capsule dosage form comprising:

a) an outer shell;

b) one or more tablets housed within said outer shell, each comprising netupitant or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients; and

c) one or more soft-gel capsules housed within said outer shell, each comprising palonosetron and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

39. The capsule of claim 38 comprising about 0.56 mg. of palonosetron hydrochloride and from about 100 to about 500 mg, or from about 200 to about 400 mg, or about 300 mg of netupitant.
40. The capsule of any one of claims 38 to 39, wherein each of said tablets comprises from about 50 to about 200 mg, or from about 100 to about 150 mg, or about 100 mg of netupitant.
41. The capsule of any one of claims 38 to 40, wherein said soft-gel capsule comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.
42. The capsule of any one of claims 38 to 41, wherein said soft-gel capsule comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.

43. The dosage form or capsule of any one of claims 32 to 42, wherein netupitant and palonosetron are formulated in separate form and then combined in one dosage.
44. The dosage form or capsule according to any one of claims 32-43 for use in treating emesis.
45. The dosage form according to claim 44 wherein said emesis is delayed-onset emesis.