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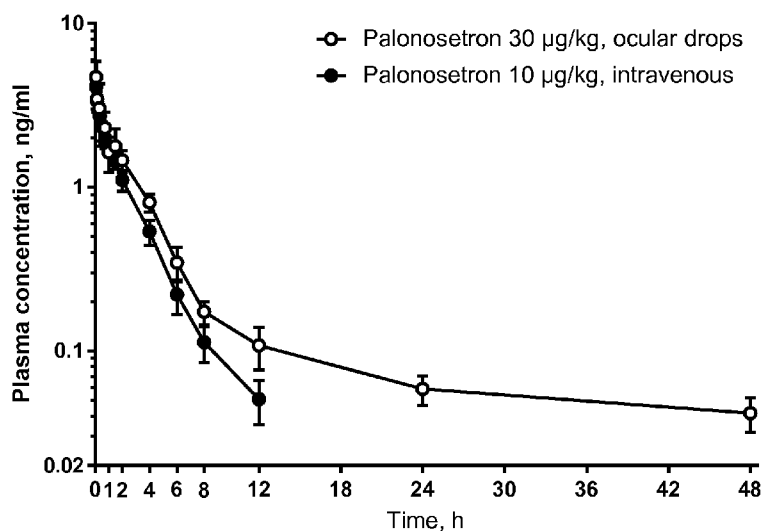


FIG. 1.

(57) Abstract: The invention relates to a method for treating or preventing nausea and vomiting. The method comprises administering an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof to the eye of the subject. The ocular administration results in fast systemic absorption, improved bioavailability compared to oral route and extended elimination time.



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PALONOSETRON FOR THE TREATMENT OR PREVENTION OF NAUSEA AND VOMITING

5 Technical field

The present invention relates to a method for treating or preventing nausea and vomiting in a subject. The method comprises administering to the eye of the subject an effective amount of an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof. The present invention also relates to the eye drop
10 compositions useful in the method.

Background of the invention

15 Nausea and vomiting are very common symptoms and can be caused by wide range of factors. Nausea and vomiting are common side effects of radiotherapy and chemotherapy of malignant tumors thereby seriously affecting the quality of life of patients. Therefore, the prevention or treatment of chemotherapy-induced nausea and vomiting (CINV) and radiotherapy-induced nausea and vomiting (RINV) have become an
20 important part of the comprehensive treatment of cancer. Other conditions involving nausea and vomiting include, for example, post-operative nausea and vomiting (POVN) and motion sickness (e.g. travel sickness, car sickness and seasickness). Several 5-HT₃ antagonists have been developed for use in inhibiting nausea and vomiting. Drugs within this class include, for example, granisetron, ondansetron, dolasetron, tropisetron and
25 palonosetron. These 5-HT₃ antagonists are administered mainly intravenously or orally. Intravenous administration is inconvenient and needs to be given by a nurse with professional skills. Oral administration of 5-HT₃ antagonists is associated with drawbacks such as difficult dosing due to vomiting, low bioavailability and slow onset of action.

30 Thus, there is a need for more convenient and practical dosage form of 5-HT₃ antagonists for patients in need of quick and easy medication which still provide rapid onset of action, good bioavailability and reliable dosing accuracy.

Summary of the invention

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It has been found that palonosetron or a pharmaceutically acceptable salt thereof is particularly suitable for ocular administration resulting in rapid and long-term amelioration of nausea and vomiting due to fast systemic absorption, improved bioavailability compared to oral route and extended elimination time. The eye drop compositions according to the invention provide therapeutic effect by non-invasive route of administration without the need for hospital setting thereby increasing patient compliance to the treatment. Eye drops are easy to administer by the patient at home and do not cause ocular discomfort. Therefore, the present invention provides a significant improvement in the treatment and prevention of nausea and vomiting.

Thus, according to one embodiment of the invention, the present invention provides a method for the treatment or prevention of nausea and vomiting in a subject comprising administering to the eye of the subject in need thereof an effective amount of an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof.

According to another embodiment of the invention, the present invention provides an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof as an active ingredient.

According to another embodiment of the invention, the present invention provides an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof as an active ingredient for use in the treatment or prevention of nausea and vomiting.

According to another embodiment of the invention, the present invention provides the use of an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof as an active ingredient in the manufacture of a medicament for the treatment or prevention of nausea and vomiting.

According to one embodiment of the invention the subject to be treated is human. According to other embodiment of the invention the subject to be treated is animal, particularly a companion animal such as a dog or a cat.

According to one embodiment of the invention, the present invention provides a medicinal kit comprising a) an eye drop composition comprising palonosetron or a

pharmaceutically acceptable salt thereof as an active ingredient, b) a package for containing said composition, and c) instructions for administering said composition on the eye of a patient for the treatment or prevention of nausea and vomiting.

5 Brief description of the drawings

Figure 1 shows palonosetron plasma concentrations in systemic circulation after 30 $\mu\text{g}/\text{kg}$ palonosetron ocular drops compared to 10 $\mu\text{g}/\text{kg}$ intravenous palonosetron administration in Beagle dogs (n=6). Shown are mean \pm SD.

10 Figure 2 shows effects of palonosetron 30 and 120 $\mu\text{g}/\text{kg}$ eye drops on vomiting after cisplatin 18 mg/m^2 exposure in Beagle dogs (n=6). Shown are mean \pm SEM.

Figure 3 shows effects of palonosetron 30 and 120 $\mu\text{g}/\text{kg}$ eye drops on signs of nausea measured as area under curve (AUC) of visual analog scale (VAS) curve after cisplatin 18 mg/m^2 exposure in Beagle dogs (n=6). Shown are mean \pm SEM.

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Detailed description of the invention

The term “nausea”, as used herein, refers to a sensation of unease and discomfort in the upper stomach with an involuntary urge to vomit. The term “vomiting” refers to
20 expulsion of stomach contents including retching (vomiting movements without expulsion of matter).

The term “administration to the eye”, as used herein, refers to applying topically to the eye and surrounding tissues, particularly to the inner surface of the eye and the inner
25 surface of the eyelids (including e.g. cornea, conjunctiva and sclera). The term includes, for example, instillation administration, administration into conjunctival sac and conjunctival administration.

The term “eye drop composition”, as used herein, refers to a liquid or semisolid
30 pharmaceutical composition adapted to administration to the eye. Typical example of an eye drop composition is an ophthalmic aqueous solution to be administered dropwise to the eye.

The term “subject” refers to a mammal including human.

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The present invention relates to a method for the treatment or prevention of nausea and vomiting in a subject comprising administering to the eye of the subject in need thereof an effective amount of an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof as the active ingredient.

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According to one particular aspect of the invention, the present invention provides a method for the treatment or prevention of nausea and vomiting associated with cancer treatment in humans, including chemotherapy-induced nausea and vomiting (CINV) and radiotherapy-induced nausea and vomiting (RINV).

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According to another particular aspect of the invention, the present invention provides a method for the treatment or prevention of nausea and vomiting associated motion sickness such as travel sickness or car sickness in animals, particularly in companion animals such as a dog or a cat.

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The amount of palonosetron or a pharmaceutically acceptable salt thereof to be administered is suitably selected such as to provide sufficient nausea and vomiting inhibiting effect. Accordingly, for the treatment or prevention of nausea and vomiting in humans, for example associated with CINV, RINV or POVN, palonosetron or a pharmaceutically acceptable salt thereof, preferably hydrochloride salt, is administered to the eye generally in an amount of 0.3 – 300 µg/kg, preferably 0.5 – 200 µg/kg, more preferably 1 - 100 µg/kg, and typically 5 - 50 µg/kg. For the treatment or prevention of nausea and vomiting in animals, particularly companion animals such as dogs or cats, for example associated with motion sickness, palonosetron or a pharmaceutically acceptable salt thereof, preferably hydrochloride salt, is administered to the eye generally in an amount of 0.3 – 1000 µg/kg, preferably 0.5 – 500 µg/kg, more preferably 1 - 300 µg/kg, and typically 3 - 120 µg/kg.

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The actual amount of the drug to be administered may depend on numerous factors, such as the species, age and weight of the subject to be treated, the active ingredient used, and the type of the composition.

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According to one embodiment of the invention, the eye drop composition according to the invention comprises palonosetron or a pharmaceutically acceptable salt thereof as a sole active ingredient.

According to one other embodiment of the invention, the eye drop composition according to the invention may comprise in addition to palonosetron or a pharmaceutically acceptable salt thereof one or more other active ingredient(s) useful in the treatment or prevention of nausea and vomiting or related conditions and suitable for providing systemic effect by ocular administration.

Palonosetron or a pharmaceutically acceptable salt thereof can be formulated into a dosage form adapted for administration to the eye by combining the drug substance with conventional pharmaceutical diluents and carriers commonly used in eye drop compositions. The eye drop composition useful in the method of the invention may be, for example, in a liquid or semisolid form such as in the form of a solution, emulsion or suspension.

Preferably, the eye drop composition is in the form of an aqueous solution adapted for administration to the eye of the subject. The concentration of palonosetron or a pharmaceutically acceptable salt thereof in the eye drop composition, e.g. in the aqueous solution composition, is generally within the range of about 0.001 to about 10 % (w/w), typically from about 0.01 to about 5 % (w/w), preferably from about 0.05 – 3 % (w/w), more preferably from about 0.1 to about 2 % (w/w), per weight of the composition.

According to one further embodiment, the concentration of palonosetron or a pharmaceutically acceptable salt thereof in the eye drop composition, e.g. in the aqueous solution composition, is within the range of from about 0.01 to about 1 % (w/w), from about 0.05 – 0.5 % (w/w), or from about 0.1 to about 0.4 % (w/w), per weight of the composition.

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The preferred salt of palonosetron is hydrochloride salt.

According to one embodiment, the eye drop composition comprises about 0.01 – 5 %, preferably about 0.05 – 3 %, more preferably from about 0.1 to about 2 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof, and about 70 – 99 %, preferably about 75 – 98 %, for example about 80 – 97 %, per weight of the composition, of sterile water. According to one further embodiment, the eye drop composition comprises 0.01 – 1 %, 0.05 – 0.5 %, or from about 0.1 to about 0.4 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof, and at least 90 %, preferably at least 95 %, per weight of the composition, of sterile water.

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The composition may additionally comprise a tonicity adjusting agent such as sodium chloride or mannitol, pH adjusting agents or buffering agents such as sodium hydroxide, hydrochloric acid, citric acid/sodium citrate, tartaric acid, fumaric acid, antioxidants such as butylated hydroxyanisole (BHA) or butylated hydroxytoluene (BHT),
5 chelating agents such as edetate disodium, thickening agents such as polyvinylpyrrolidone (povidone), polyvinyl alcohol, polyethylene glycol, polyacrylic acid or a cellulose derivative such as sodium carboxymethylcellulose, chelating agents such as disodium edetate and other ingredients commonly used in the preparation of eye drop compositions.

10 Suitably, the eye drop composition may comprise about 0.1 – 10 %, preferably about 0.5 – 5 %, per weight of the composition, of a tonicity adjusting agent such as sodium chloride or mannitol. Sodium chloride can be suitably used in an amount of about 0.1 – 2 %, preferably about 0.1 – 1 %, per weight of the composition. Mannitol can be
15 suitably used in an amount of about 1 – 10 %, preferably about 2 – 5 %, per weight of the composition. The osmolality of the eye drop composition is suitably adjusted to 200 – 600 mOsm/kg, preferably to about 300 mOsm/kg. In some embodiments, the eye drop composition comprises 0.5 – 2 %, per weight of the composition, of a tonicity adjusting agent such as sodium chloride.

20 The eye drop composition may also suitably comprise about 0.1 – 5 %, preferably about 0.5 – 3 %, per weight of the composition, of a thickening agent such as polyvinylpyrrolidone.

The eye drop composition may also suitably comprise about 0.05 – 5 %, preferably
25 about 0.1 – 2 %, for example about 0.2 – 1 %, per weight of the composition, of buffering agent such as citric acid/sodium citrate.

The pH of the eye drop composition is generally within the range of from about 3
30 to about 8.5, preferably from about 3.5 to about 7.0, more preferably from about 4.0 to about 6.0.

According to one embodiment, the eye drop composition comprises ion-pairing agents such as hyaluronic acid or glucuronic acid. The eye drop composition may
35 comprise about 0.1 – 5 %, preferably about 0.5 – 10 %, per weight of the composition, of ion-pairing agents such as hyaluronic acid or glucuronic acid.

According to an particularly preferred embodiment, the eye drop composition comprises complexing agents such as cyclodextrins. The term "cyclodextrin" refers to a cyclic dextrin molecule that is formed by enzyme conversion of starch. Various cyclodextrins are commercially available including hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, sulfobutylether- β -cyclodextrin and γ -cyclodextrin.

It was found that cyclodextrins, particularly hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin and sulfobutylether- β -cyclodextrin, were able to significantly improve local tolerance of the eye drop composition, in particular in decreasing signs of milder discomfort of the eye such as blepharospasm and itching. The eye drop composition suitably comprises about 0.5 – 25 %, preferably about 1 – 20 %, more preferably about 2 – 15 %, for example about 3 – 12 %, per weight of the composition, of cyclodextrin. Hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin and sulfobutylether- β -cyclodextrin are particularly preferred.

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According to one embodiment, the eye drop composition comprises

- (a) 0.01 – 5 %, preferably about 0.05 – 3 %, more preferably from about 0.1 to about 2 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof;
- (b) 0.5 – 25 %, preferably about 1 – 20 %, more preferably about 2 – 15 %, for example about 3 – 12 %, per weight of the composition, of cyclodextrin;
- (c) 0.1 - 10 %, preferably about 0.5 – 5 %, per weight of the composition, of a tonicity adjusting agent;
- (d) 0.05 – 5 %, preferably about 0.1 – 2 %, for example about 0.2 – 1 %, per weight of the composition, of buffering agent; and
- (e) 70 – 99 %, preferably about 75 – 98 %, for example about 80 – 97 %, per weight of the composition, of sterile water.

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According to another embodiment, the eye drop composition comprises

- (a) 0.01 – 5 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof;
- (b) 0.5 – 25 %, per weight of the composition, of cyclodextrin;
- (c) 0.1 – 10 %, per weight of the composition, of a tonicity adjusting agent;
- (d) 0.05 – 5 %, per weight of the composition, of buffering agent; and
- (e) 70 – 99 %, per weight of the composition, of sterile water.

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According to still another embodiment, the eye drop composition comprises

- (a) about 0.05 – 3 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof;
- (b) about 1 – 20 %, per weight of the composition, of cyclodextrin;
- 5 (c) about 0.5 – 5 %, per weight of the composition, of a tonicity adjusting agent;
- (d) about 0.1 – 2 %, per weight of the composition, of buffering agent; and
- (e) about 75 – 98 %, per weight of the composition, of sterile water.

According to still another embodiment, the eye drop composition comprises

- 10 (a) about 0.1 – 2 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof;
- (b) about 3 – 12 %, per weight of the composition, of cyclodextrin;
- (c) about 0.5 – 5 %, per weight of the composition, of a tonicity adjusting agent;
- (d) about 0.2 – 1 %, per weight of the composition, of buffering agent; and
- 15 (e) about 80 – 97 %, per weight of the composition, of sterile water.

According to still another embodiment of the invention, eye drop composition comprises

- 20 (a) about 0.1 – 2 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof;
- (b) about 2 – 15 %, per weight of the composition, of cyclodextrin selected from hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin and sulfobutylether- β -cyclodextrin;
- (c) about 1 – 10 %, per weight of the composition, of mannitol;
- 25 (d) about 0.2 – 1 %, per weight of the composition, of a buffering agent which is citric acid/sodium citrate; and
- (e) about 80 – 97 %, per weight of the composition, of sterile water.

30 The eye drop formulation can be prepared e.g. by dissolving the active ingredient and excipients to the vehicle, for example water, followed by pH adjustment, if necessary, and sterile filtering.

The eye drop composition is preferably given to the eye of the subject from a prefilled bottle, ampoule or pipette in a volume ranging typically from about 0.01 to about 35 0.3 ml, more preferably from about 0.015 to about 0.2 ml, for example from about 0.02 to about 0.15 ml, of the eye drop composition.

Preferably, said package is an applicator, e.g. a squeezable prefilled single-use bottle, ampoule or pipette capable of dosing fixed volumes of the eye drop composition. The squeezable bottle, ampoule or pipette is preferably prepared from polymer material, such as LDPE. Suitably, the volume of the suitable bottle, ampoule or pipette ranges from about 0.5 to 5 ml. For example, about 0.5 to about 2 ml of the eye drop composition can be filled into single use blow fill seal (BFS) LDPE ampoules having volume of 0.5 ml, 1 ml or 2 ml.

The composition can be provided in the form of medicinal kit comprising a) an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof as an active ingredient, b) a package for containing said composition, and c) instructions for administering said composition on the eye of a patient for the treatment or prevention of nausea and vomiting.

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In situations where treatment or prevention of nausea and vomiting is desired, suitable amount of the eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof is administered to one or both eyes of the subject. The composition is given according to the need of the subject, for example daily or several times a day.

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The invention is further illustrated by the following examples, which are not meant to limit the scope of the invention.

25

Formulation Example 1.

Palonosetron hydrochloride	3.38 mg (equivalent to 3 mg of palonosetron base)
Povidone K30	20 mg
Sodium hydroxide	to adjust to pH 4.8
Sodium chloride (0.9 %)	ad 1 ml

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Formulation Example 2.

Palonosetron hydrochloride	5.64 mg (equivalent to 5 mg of palonosetron base)
Povidone K30	10 mg
Sodium chloride (0.9 %)	ad 1 ml
	pH 6.1

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Formulation Example 3.

5	Palonosetron hydrochloride	3.38 or 6.76 mg (equivalent to 3 or 6 mg of palonosetron base)
	Hydroxypropyl- β -cyclodextrin	100 mg
	Mannitol	25 mg
	Citrate buffer pH 4.8	ad 1 ml

10 Citrate buffer pH 4.8 was prepared in this and the following examples as follows:

	Citric acid monohydrate	168.0 mg
	Sodium citrate	353 mg
	Sterile water	ad 100 ml

15 Citric acid and sodium citrate is dissolved into the water. pH of solution is adjusted to pH 4.8 with 1 M NaOH or 1 M HCl, if needed.

Formulation Example 4.

	Palonosetron hydrochloride	3.38 mg (equivalent to 3 mg of palonosetron base)
20	Hydroxypropyl- β -cyclodextrin	50 mg
	Mannitol	35 mg
	Citrate buffer pH 4.8	ad 1 ml

Formulation Example 5.

25	Palonosetron hydrochloride	3.38 mg (equivalent to 3 mg of palonosetron base)
	Sulfobutylether- β -cyclodextrin	100 mg
	Mannitol	25 mg
	Citrate buffer pH 4.8	ad 1 ml
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Formulation Example 6.

35	Palonosetron hydrochloride	3.38 or 6.76 mg (equivalent to 3 or 6 mg of palonosetron base)
	Hydroxypropyl- γ -cyclodextrin	100 mg
	Mannitol	25 mg

Citrate buffer pH 4.8 ad 1 ml

Formulation Example 7.

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Palonosetron hydrochloride	3.38 mg (equivalent to 3 mg of palonosetron base)
γ -cyclodextrin	100 mg
Mannitol	25 mg
Citrate buffer pH 4.8	ad 1 ml

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Formulation Example 8.

Palonosetron hydrochloride	3.38 mg (equivalent to 3 mg of palonosetron base)
Hyaluronic acid 12kDa	10 mg
15 Mannitol	50 mg
Citrate buffer pH 4.8	ad 1 ml

Formulation Example 9.

20 Palonosetron hydrochloride	3.38 mg (equivalent to 3 mg of palonosetron base)
Glucuronic acid	30 mg
Citrate buffer pH 4.8	ad 1 ml

25 The above formulations can be prepared by dissolving the excipients and drug substance in the carrier solution followed by sterilized filtration.

Experiment 1. Bioavailability of palonosetron as ocular drops vs. intravenous administration

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Methods:

35 Bioavailability of palonosetron as ocular drops at the dose of 30 μ g/kg was compared to 10 μ g/kg intravenous (i.v.) palonosetron in Beagle dogs (n=6). The study was a crossover study with 7 days washout period between the treatment periods. The animals were fasted overnight before dosing by withdrawing the remaining feed (if any) at

least 12 h before dosing. On dosing days food was offered approximately at 4 h after dosing (after the 4 h blood sampling).

Palonosetron 30 µg/kg eye drops prepared according to Formulation Example 1
5 were administered in the eye using a micropipette in an amount of 10 µl/kg (approximately half volume in each eye).

Palonosetron 10 µg/kg intravenous dose was administered in cephalic vein in slow
10 i.v. bolus dosed within 30 seconds.

Blood samples were collected into K₂EDTA tubes over a 48 h period after each
treatment at the following time points: predose, 5 min, 10 min, 20 min, 30 min, 45 min, 1
h, 1.5 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h and 48 h post administration. Aliquots of plasma
were prepared and stored frozen until analysis. Palonosetron concentration in plasma was
15 determined using Liquid chromatography-triple quadrupole mass spectrometry. The lower
limit of quantification for palonosetron in dog plasma was 0.02 ng/ml.

Results:

The results are shown in Fig. 1. Palonosetron as ocular drops had a fast absorption
20 comparable to intravenous administration, good systemic exposure and extended
elimination phase. The bioavailability was 65.6 %. No significant eye irritation was seen.

Experiment 2. Local tolerance of palonosetron formulations in dog eye.

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Local tolerance of various eye drop formulations in Beagle dogs was evaluated by
observing clinical signs continuously during 30 min post dosing. Signs indicating milder
ocular discomfort e.g. blepharospasm, pawing the eye, rubbing the face to the floor were
recorded descriptively. Summary of the results is presented in the Table 1.

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Table 1. Signs of milder discomfort (blepharospasm and itching) in dog eye.
Number of signs/tested dog when dosing 35 μ l/eye.

Formulation example	3 mg/ml		6 ml/mg	
	Blepharospasm	Itching	Blepharospasm	Itching
1	9/9	9/9	-	-
3	0/15	0/15	0/12	0/12
4	0/2	0/2	-	-
5	0/5	0/5	-	-
6	1/15	2/15	0/12	0/12
7	7/9	2/9	-	-
8	3/5	3/5	-	-
9	2/2	2/2	-	-

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The results show that cyclodextrin, in particular hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin and sulfobutylether- β -cyclodextrin, significantly improved local tolerance of the eye drop composition by decreasing signs of milder discomfort of the eye such as blepharospasm and itching.

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Experiment 3. Efficacy of palonosetron eye drops in cisplatin-induced nausea and vomiting model

15 Methods:

Six non-naive adult male Beagle dogs were intravenously administered (2 ml/min) cisplatin at 18 mg/m² body surface over 20 min. Then, 45 min after the end of the infusion, the dogs received eye drops prepared according to Formulation Example 1 at 30 or 120 μ g/kg of palonosetron or its vehicle (0.9% saline, 2% povidone) in a cross-over design. Then, the following parameters were recorded by blinded observers over 15 min periods from T0 (end of the infusion of cisplatin) to 420 min (T420) after the end of the infusion of cisplatin: vomiting episodes and nausea-like behaviours including salivation, exaggerated swallowing motions, lip licking, lethargy, restlessness, and turning behaviour signalling that vomiting is imminent. In addition, a visual analogue scale (VAS) from 0 to

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100 mm was used to assess the severity of the dogs' nausea-like behaviours (where a score of 0 mm = no nausea and a score of 100 mm = worst possible nausea).

Results:

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Effects on vomiting:

Cisplatin-treated dogs in vehicle eye drops group vomited 10.2 ± 2.1 times (range 5 and 17 times) during the observation period. In palonosetron 30 $\mu\text{g}/\text{kg}$ eye drops group, vomiting episodes decreased very strongly with only 1 vomiting episode in 2 dogs overall (p<0.0001 vs. vehicle). Palonosetron eye drops at the dose of 120 $\mu\text{g}/\text{kg}$ inhibited vomiting totally throughout the observation period (p<0.0001). The results are shown in Figure 2.

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Effects on nausea:

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In the vehicle-treated group the nausea-associated behaviour started between 2.5 and 2.75 hours after the end of the cisplatin infusion and peaked between 3.75 and 4.25 hours after the end of the cisplatin infusion. The area under the curve (AUC) of VAS was $7344 \pm 1050 \text{ mm} \cdot \text{min}$ in vehicle group. Ocular administration of palonosetron at 30 or 120 $\mu\text{g}/\text{kg}$ in cisplatin-treated dogs decreased the VAS score strongly. The VAS AUCs were 320 ± 268 (p<0.0001) and $0 \pm 0 \text{ mm} \cdot \text{m}$ (p<0.0001) in in 30 $\mu\text{g}/\text{kg}$ and 120 $\mu\text{g}/\text{kg}$ palonosetron groups, respectively. The results are shown in Figure 3.

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Claims

1. A method for the treatment or prevention of nausea and vomiting in a subject comprising administering to the eye of the subject in need thereof an effective amount of
5 an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof.
2. A method according to claim 1, wherein palonosetron or a pharmaceutically acceptable salt thereof is administered to the eye in an amount of 0.5 – 500 µg/kg.
3. A method according to claim 2, wherein palonosetron or a pharmaceutically
10 acceptable salt thereof is administered to the eye in an amount of 1 – 300 µg/kg.
4. A method according to any of claims 1-3 for the treatment or prevention of nausea and vomiting associated with chemotherapy-induced nausea and vomiting (CINV), radiotherapy-induced nausea and vomiting (RINV), post-operative nausea and vomiting (POVN) or motion sickness.
- 15 5. A method according to any of claims 1-4 wherein the subject to be treated is human.
6. A method according to any of claims 1-4 wherein the subject to be treated is animal, particularly a companion animal such as a dog or a cat.
7. An eye drop composition comprising palonosetron or a pharmaceutically
20 acceptable salt thereof as an active ingredient.
8. An eye drop composition according to claim 7 comprising 0.01 – 5 %, preferably 0.05 – 3 %, more preferably 0.1 – 2 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof.
9. An eye drop composition according to claim 8 comprising about 70 – 99 %, preferably about 75 – 98 %, for example about 80 – 97 %, per weight of the composition,
25 of sterile water.
10. An eye drop composition according to any one of claims 7 to 9 comprising about 0.1 - 10 %, preferably about 0.5 - 5 %, per weight of the composition, of a tonicity adjusting agent.
- 30 11. An eye drop composition according to claim 10 wherein the tonicity adjusting agent is sodium chloride or mannitol.
12. An eye drop composition according to any one of claims 7 to 11 comprising 0.5 – 25 %, preferably 1 – 20 %, more preferably 2 – 15 %, per weight of the composition, of cyclodextrin.

13. An eye drop composition according to claim 12 wherein the cyclodextrin is hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin and sulfobutylether- β -cyclodextrin.

5 14. An eye drop composition according to any one of claims 7 to 13 having pH between 3.5 - 7.0.

15. An eye drop composition according to claim 14 having pH between 4.0 - 6.0.

16. An eye drop composition according to any one of claims 7 to 15 comprising about 0.05 – 5 %, per weight of the composition, of buffering agent.

10 17. An eye drop composition according to claim 16 wherein the buffering agent is citric acid/sodium citrate.

18. An eye drop composition according to any one of claims 7 to 17 comprising about 0.1 – 5 %, preferably 0.5 – 3 %, per weight of the composition, of a thickening agent.

15 19. An eye drop composition according to claim 18 wherein the thickening agent is polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol, polyacrylic acid or a cellulose derivative.

20. An eye drop composition according to any one of claims 7 to 17 comprising (a) 0.01 – 5 %, per weight of the composition, of palonosetron or a pharmaceutically acceptable salt thereof;

20 (b) 0.5 – 25 % per weight of the composition, of cyclodextrin;

(c) 0.1 - 10 %, per weight of the composition, of a tonicity adjusting agent;

(d) 0.05 – 5 %, per weight of the composition, of buffering agent; and

(e) 70 – 99 %, per weight of the composition, of sterile water.

25 21. An eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof as an active ingredient for use in the treatment or prevention of nausea and vomiting.

22. An eye drop composition according to any one of claims 7 to 20, for use in the treatment or prevention of nausea and vomiting.

30 23. Use of an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of nausea and vomiting.

24. Use of an eye drop composition according to any one of claims 7 to 20 in the manufacture of a medicament for use in the treatment or prevention of nausea and vomiting.

35 25. A medicinal kit comprising a) an eye drop composition comprising palonosetron or a pharmaceutically acceptable salt thereof as an active ingredient, b) a

package for containing said composition, and c) instructions for administering said composition on the eye of a patient for the treatment or prevention of nausea and vomiting.

- 5 26. A medicinal kit according to claim 25, wherein the eye drop composition is according to any of claims 7 to 20.

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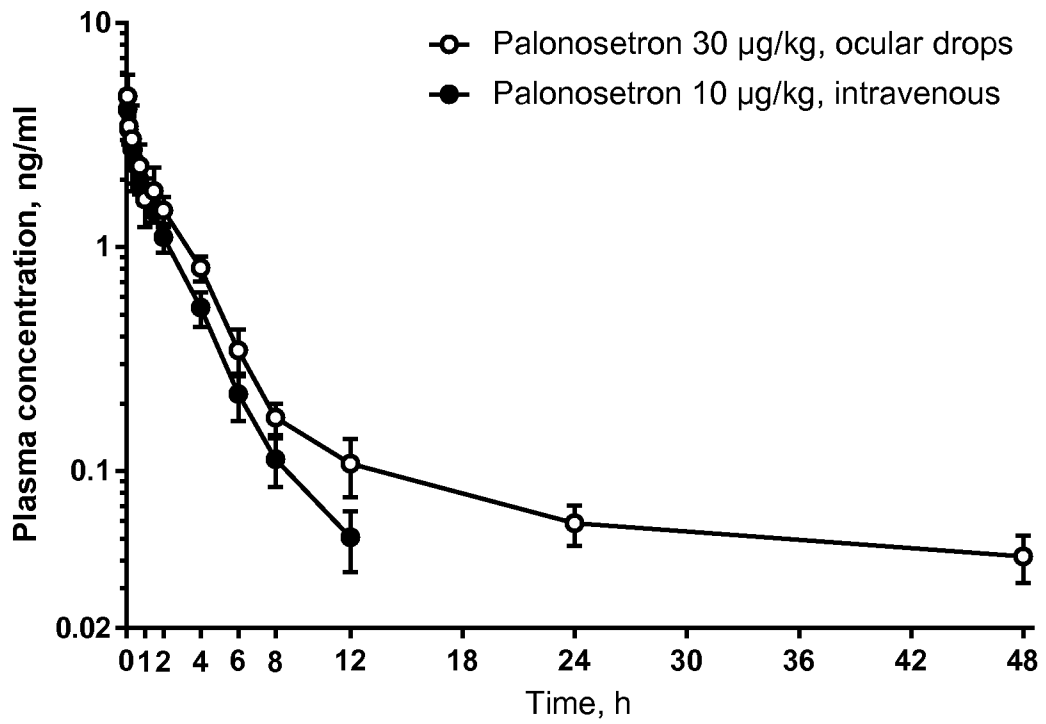


FIG. 1.

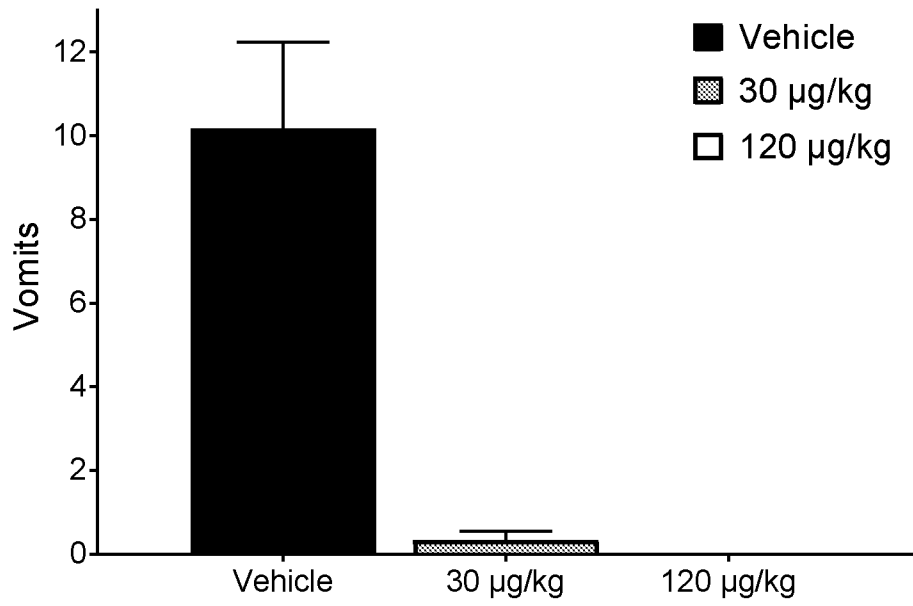


FIG. 2.

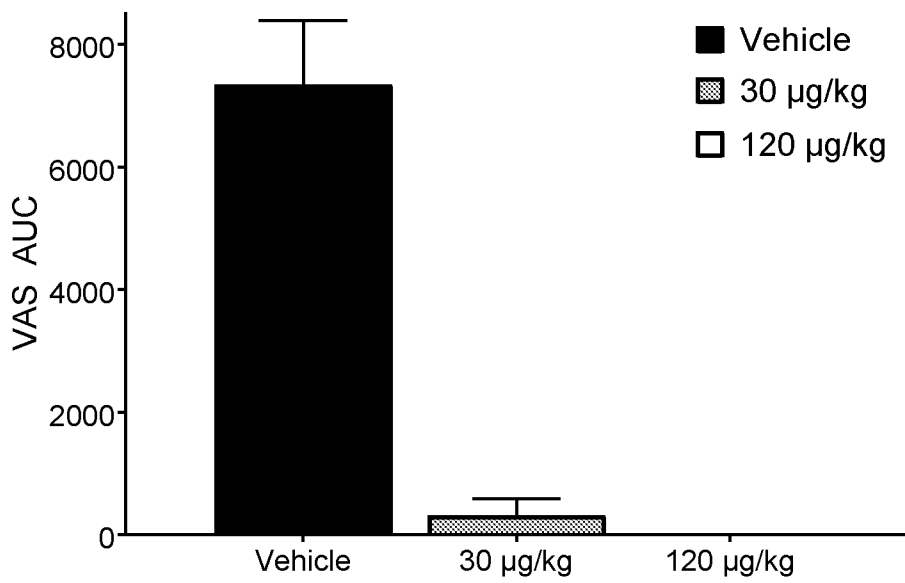


FIG. 3.

INTERNATIONAL SEARCH REPORT

International application No
PCT/FI2019/050017

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K31/473 A61K9/00 A61P1/08 A61P43/00
 ADD.
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 A61K
 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	WO 2004/073714 A1 (HELSINN HEALTHCARE SA [CH]; BARONI LUIGI [IT]; MACCIOCCHI ALBERTO [CH]) 2 September 2004 (2004-09-02) abstract claims 1-29 ----- -/--	1-26

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 20 March 2019	Date of mailing of the international search report 27/03/2019
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Taylor, Mark
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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