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(54) Title: NOVEL TRIPLE COMBINATION FORMULATIONS FOR ANTIEMETIC THERAPY

(57) Abstract: The present invention relates to parenteral formulations comprising Palonosetron, NK_1 receptor antagonist and a corticosteroid. The present invention also relates to process of preparing such formulations.

NOVEL TRIPLE COMBINATION FORMULATIONS FOR ANTIEMETIC THERAPY

Background of the invention

Chemotherapy-induced nausea and vomiting (CINV) remains an important and common toxicity of cancer treatment. It presents many challenges for the continuation of treatment with the possibility of negatively affecting the outcome. Currently, antiemetic agents are used as prophylaxis against the development of CINV during the acute period (up to 24 hours after chemotherapy) and the delayed period. Newer agents like the second-generation 5-HT_3 receptor antagonist, Palonosetron and the NK_1 antagonists like Aprepitant, Fosaprepitant, Netupitant, and Rolapitant offer additional clinical benefit in highly and moderately emetogenic chemotherapy.

Palonosetron belongs to the class 5-HT_3 receptor antagonists. Palonosetron has improved antiemetic activity in the treatment of delayed chemotherapy-induced nausea and vomiting (CINV) compared to other agents in its class. Palonosetron hydrochloride Injection is marketed in the US as Aloxi® by Helsinn Healthcare. Each vial of Aloxi® contains Palonosetron hydrochloride, mannitol, and disodium edetate and citrate buffer in water for intravenous administration.

U.S Patent No. 5,202,333 to Jacob et al., discloses 5-HT_3 receptor antagonists such as Palonosetron, pharmaceutical compositions containing them and methods of preparing these compounds. Further the patent also discloses the use of the compounds for the treatment of emesis, gastrointestinal disorders, central nervous system disorders, cardiovascular disorders or pain.

U.S Patent No.s 7,947,724 and 7,947,725 to Giorgio et al. disclose stable liquid formulations comprising of Palonosetron at a pH from 4.0 to 6.0 and an aqueous pharmaceutically acceptable carrier including a chelating agent.

NK_1 receptor antagonists prevent both acute and delayed chemotherapy-induced nausea and vomiting (CINV). These agents act centrally at NK_1 receptors in vomiting centers within the central nervous system to block their activation by substance P released as an unwanted consequence of chemotherapy. They are effective for both moderately and highly emetogenic chemotherapy regimens. NK_1 receptor antagonists include drugs like Aprepitant, Fosaprepitant, Rolapitant and Netupitant.

Aprepitant is available in the form of oral suspension and capsule under the brand name Emend®. Fosaprepitant is a prodrug of Aprepitant. The meglumine salt of Fosaprepitant, Fosaprepitant dimeglumine, is available as Emend® in the form of a lyophilized powder for intravenous infusion. Netupitant is available in combination with Palonosetron in the form of oral capsules under the brand name Akynzeo®. Rolapitant is available in the form of a tablet as Varubi®.

U.S Pat No. 5,538,982 to Hagan et al., discloses use of NK, receptor antagonist for the treatment of emesis.

U.S Pat No 5,691,336 to Dorn et al, discloses the compound Fosaprepitant and further describe methods of synthesizing the said compound. U.S Pat No 5,716,942 also to Dorn et al., discloses the use of neurokinin 1 receptor antagonist such as Fosaprepitant for the treatment of inflammatory diseases, pain or migraine, asthma, emesis and nausea.

U.S. Pat No 6,297,375 to Michael et al., describes methods of synthesizing and formulating Netupitant and its prodrugs.

Dexamethasone is a synthetic corticosteroid which is functionally analogous to the endogenous hormones cortisol and cortisone, but characterized by more specific pharmacokinetic and therapeutic properties and lesser side effects. Dexamethasone and other glucocorticoids or corticosteroids are said to have antiemetic effects and may improve the efficacy of antiemetic regimens in some cancer patients.

Dexamethasone acetate and Dexamethasone sodium phosphate injectables are approved in the U.S under the brand names Decadron-LA, Decadron and Hexadrol.

Dexamethasone and its salts are described in U.S. Pat. No. 3,007,923 to Roland et al. The preparation of Dexamethasone acetate is also described.

Combinations of some of these actives are also disclosed in patents and applications. For instance, U.S patent application 2017/216205 to Thomas et al., discloses an injectable emulsion containing a two-drug combination of Netupitant or Aprepitant and dexamethasone sodium phosphate; U.S patent 9,446,052 to Seo et al., discloses several compositions comprising a 5-HT_3 receptor antagonist and a corticosteroid. U.S. Pat. No.s 9,186,357 and 8,623,826 to Fabio et al., describe an oral capsule formulation for treating CINV with a regimen of Palonosetron, NK_1 antagonist, particularly Netupitant in possible coadministration with Dexamethasone capsules.

The prior art references teach various methods and formulations to treat CINV. But none of the references disclose a single parenteral formulation comprising all the three actives i.e Palonosetron, NK_1 antagonist and a corticosteroid. Accordingly, there exists a need to develop improved formulations for treating CINV with minimal discomfort to the patients. The present invention addresses this need.

Summary of the invention

The present invention relates to a parenteral formulation comprising Palonosetron, NK_1 receptor antagonist and a corticosteroid.

One aspect of the invention provides parenteral formulation comprising of Palonosetron, NK_1 receptor antagonist selected from Fosaprepitant, Aprepitant, Netupitant and Rolapitant; and a corticosteroid.

Another aspect of the invention provides parenteral formulation comprising Palonosetron, NK_1 receptor antagonist selected from Fosaprepitant, Aprepitant, Netupitant and Rolapitant; and a corticosteroid selected from Dexamethasone and Methylprednisolone.

Yet another aspect of the invention provides parenteral formulation comprising Palonosetron, NK_1 receptor antagonist selected from Fosaprepitant, Aprepitant, Netupitant and Rolapitant; and a corticosteroid selected from Dexamethasone and Methylprednisolone, wherein the total impurities are less than 10%.

Detailed description of the invention

In the context of this invention, pharmaceutically acceptable salts, solvates, polymorphs, hydrates and anhydrous forms of any of the drugs *i.e* Palonosetron, NK_1 receptor antagonist and corticosteroid may be used. The NK_1 receptor antagonists of the invention can be Fosaprepitant, Aprepitant, Rolapitant or Netupitant. The corticosteroid may be selected from Methylprednisolone and Dexamethasone.

In the context of the present invention, "parenteral formulation" is intended to cover (i) a ready to use formulation, (ii) a ready to dilute formulation, (iii) a lyophilized formulation, (iv) a kit, (v) a suspension and (vi) an emulsion.

As used herein "ready to use" formulation refers to liquid formulations that are intended to be used as such without further dilution.

As used herein "ready to dilute" formulation refers to liquid formulations that are intended to be used after dilution.

As used herein "lyophilized formulation" refers to formulations that are intended to be used upon reconstitution with a diluent with or without further dilution.

As used herein "kit" formulation comprises one or more actives provided as lyophilized powders and the remaining are provided in the form of a solution for admixing with the lyophilized active(s).

The term "about" is meant to encompass a pH range of ± 0.5 from the specified value or range.

CINV strongly affects the quality of life of cancer patients. Nausea and vomiting still rank among the most distressing side effects. Certain chemotherapy regimens have a high risk of CINV (> 90% frequency of emesis).

For this reason, the antiemetic guidelines suggest using a triple combination of NK_1 receptor antagonists, 5 HT3 receptor antagonists and Dexamethasone. *(Roila et al; Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Annals Oncol 2010; 21 (Suppl 5): v232-243; Basch E et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2011; 29(31): 4189-98).*

Longo et al studied the efficacy of triple combination of Aprepitant, Palonosetron and Dexamethasone in cancer patients receiving highly emetogenic chemotherapy and reported high control of CINV during the first chemotherapy cycle and found

that the antiemetic protection was maintained over multiple cycles of chemotherapy. *(F. Longo et al., Combination of Aprepitant, Palonosetron and Dexamethasone as antiemetic prophylaxis in lung cancer patients receiving multiple cycles of cisplatin-based chemotherapy, Int J Clin Pract, August 2012, 66, 8, 753-757)* The administration was carried out using the individually available formulations which requires multiple injections thereby causing further discomfort to the patient.

Hence there is an unmet need for administering the antiemetic agents in a single formulation which would aid in minimizing the discomfort to the patients. However, formulations that have more than one active are difficult to stabilize when compared to single active formulations. This may be because of many reasons including the incompatibility of the active with the excipients and/or interaction between the two actives.

Sun et al studied the compatibility of intravenous Fosaprepitant with intravenous 5HT3 antagonists and corticosteroids and found that the combination of Palonosetron, Fosaprepitant and corticosteroid (Dexamethasone sodium phosphate or Methylprednisolone sodium succinate) is incompatible (Sun S, Schaller J et al., *Compatibility of intravenous Fosaprepitant with intravenous 5HT3 antagonists and corticosteroids. Cancer Chemother Pharmacol.* 2013 Sep;72(3):509-13).

Studies on admixtures of Rolapitant and Dexamethasone showed stability being maintained for atleast 6 hours when stored at 20°C to 25°C irrespective of the container. (Wu G1, Yeung S et al., *Compatibility and Stability of Rolapitant Injectable Emulsion Admixed with Dexamethasone Sodium Phosphate. Int J Pharm Compd. 2017 Jan-Feb;21(1):66-75*). Similar studies with Rolapitant in combination with Palonosetron showed that the solution is stable only for 48 hours at room temperature.

All the above studies teach that a combination of Palonosetron, NK_1 receptor antagonist with a corticosteroid show stability only for few hours.

The inventors of the present invention have developed a novel stable parenteral formulation that comprises Palonosetron, NK_1 receptor antagonist selected from Fosaprepitant, Aprepitant, Netupitant and Rolapitant and a corticosteroid to address the unmet need in the prior art.

An embodiment of the invention relates to parenteral formulation comprising:

i. Palonosetron
ii. NK_1 receptor antagonist
iii. Corticosteroid, and
iv. Pharmaceutically acceptable excipients

Another embodiment of the invention relates to parenteral formulation comprising:

i. Palonosetron Hydrochloride
ii. NK_1 receptor antagonist selected from the group comprising Fosaprepitant, Aprepitant, Rolapitant and Netupitant
iii. Corticosteroid selected from Dexamethasone and Methylprednisolone and
iv. Pharmaceutically acceptable excipients

Yet another embodiment of the invention provides parenteral formulation comprising:

i. Palonosetron Hydrochloride
ii. NK_1 receptor antagonists selected from the group comprising Fosaprepitant, Aprepitant, Rolapitant and Netupitant
iii. Corticosteroid selected from Dexamethasone and Methylprednisolone and
iv. Pharmaceutically acceptable excipients selected from the group comprising stabilizing agents, solubilizing agents, buffering agents, pH adjusting agents and solvents.

An embodiment of the invention provides parenteral formulation having a pH in the range of about 4-12. More specifically, the invention provides parenteral formulation having a pH in the range of 6-10.

Suitable stabilizing agents and solubilizing agents are selected from surfactants, chelating agents and cyclodextrins. Suitable cyclodextrins include the following, but not limited to α, β, and γ-cyclodextrin and cyclodextrins modified with alkyl-, hydroxyalkyl-, dialkyl-, and sulfoalkyl-ether modified cyclodextrins such as methyl or hydroxypropyl β-cyclodextrins (HPβCD), methyl-and-ethyl-β-cyclodextrin, sulfoalkylether-substituted beta-cyclodextrin, sulfobutylether-β-cyclodextrin (SBECD) and the like. Suitable surfactants include amphoteric, non-ionic, cationic or anionic surfactants such as sodium lauryl sulfate, polyoxyethylene alkyl aryl ethers, polyethylene glycol fatty acid esters, polyoxyethylene- polyoxypropylene block co-polymers, polyoxyethylene sorbitan fatty acid ester such as polysorbate, sorbitan fatty acid mono esters, polyoxyethylene castor oil derivatives such as polyoxyl castor oil, polyoxyl hydrogenated castor oil, monooleate, monolaurate, monopalmitate, monostearate, dioctyl sulfosuccinate, lecithin, polyoxyethylene fatty acid glycerides, poloxamer, cremophor, cetrimide, polyethylene glycols and the like. Chelating agents can be selected from, but not limited to DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DTPA (diethylene triamine-N,N,N',N",N"-penta acetate), EDTA (Ethylenediaminetetraacetic acid) or its salts. Meglumine can also be used as a solubilizing agent.

Suitable buffering agents include the following, but not limited to buffers such as aconitic, citrate buffer, sodium carbonate, sodium bicarbonate, tartarate, benzoate, lactate, acetate buffer, phosphate buffer, metabolic acids, glutaric, malic, succinic, aspartic acid and carbonic acid, alkali or alkaline earth salt of one of these acids, Tris buffer and amino acid buffers such as arginine, histidine, glycine, lysine and glutamic acid.

pH adjusting agents may be selected from acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate and sodium lactate.

Suitable solvents can be selected from glycerine, ethanol, propylene glycol, PEG, dimethylacetamide, N-methylpyrrolidone, transcutol, glycofurol, water and mixtures thereof.

The parenteral formulation of the present invention may contain anti-oxidants and preservatives such as butylated hydroxyanisole (BHA), butylated hydroxyl toluene (BHT), citric acid, tocopherol, sorbic acid, monothioglycerol, ascorbic acid, boric acid, propyl gallate, aminoacids and mixtures thereof; tonicity modifiers such as dextrose, mannitol, potassium chloride, sodium chloride; bulking agents such as mannitol, lactose, trehalose, inositol, glucose, sucrose, maltose, xylitol, starches, sorbitol, dextrose and sodium chloride; oils such as soybean oil, sesame oil, cotton seed oil, safflower oil, sunflower oil, arachis oil, corn oil, castor oil and olive oil.

Evaluation of buffer system

The inventors of this formulation have surprisingly developed a stable parenteral formulation containing all the three actives, wherein the formulation has less than 10% impurities.

This is particularly challenging because Fosaprepitant rapidly gets converted to Aprepitant in aqueous solution which often precipitates out due to low aqueous solubility. The inventors carried out experiments with various buffering agents to determine suitable buffer system for Fosaprepitant. The formulations were stressed at 60°C for 12hours.The samples obtained were filtered and analysis was carried out to determine the solubility of Aprepitant in the buffer system.

Fosaprepitant (1.5mg/ml) and kleptose (73.6mg/ml) were dissolved in the buffer systems tabulated below to evaluate their suitability.

Table 1: Evaluation of buffer system

Buffer System	**After 12hours at 60°C**	
	pH	% Aprepitant
Arginine +Tartaric acid	7.60	2.73
Arginine + Isoleucine	7.93	3.23
Arginine + Glycine	8.57	4.66
Arginine+ Succinic Acid	9.06	4.50
Arginine + Aspartic acid	8.82	5.53
Tris + Tartaric acid	8.25	4.02
Tris + Isoleucine	8.22	3.51
Tris + Glycine	8.26	3.64
Tris + Aspartic acid	8.50	3.12
Tris + Succinic acid	8.35	4.23

From the above data it is observed that Aprepitant has best solubility in Aspartic Acid + Arginine buffer system.

To further improve the solubility of Fosaprepitant and Aprepitant in the formulation, inventors carried out stress studies using suitable solubilizer in the formulation. The formulations were prepared in the Arginine + Aspartic acid buffer system comprising different concentrations of meglumine. The samples were stressed at 60°C for 24 hours and were analyzed after filtration.

Table 2: Effect of Meglumine on solubility

Concentration of meglumine (mg/ml)	%Aprepitant
Nil	1.2
0.48	2.2
0.95	5.7
1.43	4.6
1.90	4.2

It was observed that meglumine improves the solubility of Aprepitant in the buffer system.

Concentration ranges of actives

In some aspects of the invention the fill volume of liquid formulations prepared according to the invention ranges from about 5 mL to 200mL. The concentration of NK_1 receptor antagonist, Palonosetron and corticosteroid varies accordingly. The concentration of Fosaprepitant ranges from about 0.5mg/ml to 10mg/ml, the concentration of Aprepitant ranges from about 0.5mg/ml to 100mg/ml, the concentration of Rolapitant ranges from about 0.5mg/ml to 20mg/ml, the concentration of Netupitant ranges from about 0.5mg/ml to 100mg/ml. The concentration of Palonosetron ranges from about 0.0005mg/ml to 5mg/ml. The concentration of dexamethasone ranges from about 0.01mg/ml to 50mg/ml. The concentration of Methylprednisolone ranges from about 1mg/ml to 100 mg/ml.

Effect of primary packing on stability

The formulations prepared according to the invention comprising all the three actives are filled in suitable containers selected from glass or polymer containers. The containers include vials, ampoules, syringes, bags and bottles with sizes ranging from 1 ml to 500 ml. Polymer material include cyclic olefin copolymer (COC), cyclic olefin polymer (COP), an olefin polymer, a polypropylene polymer,

a polyvinyl chloride polymer (PVC), polyethylene, modified propylene, copolyester, polycarbonate polymer and the like. Studies were carried out to check the stability of the formulation in various containers. The packing materials used were; type-I clear glass vial, COC vials, COP vials, and infusion bag.

Table 3: Stability of the formulation in different primary packs

Pack details	Initial	COC vials	COP vials	PVC Infusion bag	USP Type-I glass vial
Stability Condition	Initial	1Week, 40°C			
Description	CCS	CCS	CCS	CCS	CCS
pH	8.54	8.52	8.57	8.52	8.53
Palonosetron					
% Assay	104.9	104.8	104.7	104.2	104.4
Total Impurities	0.29	0.56	0.53	0.58	0.56
Dexamethasone					
% Assay	98.6	99.9	98.8	99.9	98.7
Total Impurities	1.32	1.38	1.29	1.24	1.26
Fosaprepitant					
% Assay	98.3	97.2	95.9	96.4	95.8
Aprepitant	0.5	2.63	2.60	2.64	2.60
Total Impurities	0.71	2.88	2.85	2.90	2.79

*CCS: Clear, colorless solution.

Stability studies

The formulations prepared according to the invention were studied for stability at 2-8^{0}C and 25^{0}C.

Table 4: Stability data of the products prepared according to examples 2 and 3

Stability data of the products prepared according to examples 2 and 3						
	Example 2			Example 3		
Condition	Initial	3M, 2-8°C	3M_25°C	Initial	3M, 2-8°C	3M, 25°C
Palonosetron						
Assay	103.7	105.5	105.4	105.5	106	105.3
Total Impurities	0.21	0.36	0.67	0.23	0.37	0.70
Dexamethasone						
Assay	102.1	103.2	102.9	100.1	100.8	101.1
Total Impurities	1.19	1.24	1.16	1.08	1.00	0.99
Fosaprepitant						
Assay	100.6	98.6	96.4	103.3	100.5	94.7
Aprepitant	0.41	0.75	2.98	0.42	0.58	4.32
Total Impurities	0.92	1.26	3.41	0.94	1.05	4.68

The above data shows excellent stability of the formulation.

Types of formulations

The formulations of the present invention can be administered as a ready to use solution; ready to dilute solution; lyophilized formulation; suspension, emulsion and the like. The formulations can be made by standard manufacturing techniques known in the art.

The following examples further describe certain specific aspects and embodiments of the present invention and also outline the quantitative proportions of the actives and excipients in the combination formulation. It is to be understood that the examples are given by way of illustration only and are not intended to limit the scope of the invention in any manner.

Example 1

Ready to use formulation

S.No	Ingredients	Quantity/mL (mg)
1.	Fosaprepitant dimeglumine	1.0
2.	Palonosetron hydrochloride	0.00167
3.	Dexamethasone sodium phosphate	0.08
4.	Hydroxy propyl beta cyclodextrin(Kleptose)	49.06
5.	Ethylenediamine tetraacetic acid	0.2507
6.	Sodium carbonate	0.16
7.	Sodium bicarbonate	1.3333
8.	Sodium chloride	7.0
9.	Sodium hydroxide	Qs to adjust pH 8.0-8.5
10.	Hydrochloric acid	Qs to adjust pH 8.0-8.5
11.	Water for injection	Qs to 1 mL

Manufacturing process:

Water for injection was taken in a compounding vessel and kleptose was added and stirred. The above solution was cooled to 2-8°C. Fosaprepitant dimeglumine was added to the above solution. Ethylenediamine tetraacetic acid was added followed by the addition of sodium carbonate and sodium bicarbonate. Palonosetron hydrochloride was added followed by the addition of Dexamethasone sodium and stirred. Sodium chloride was added to the above solution and pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filtered, followed by stoppering and sealing of the vials.

Example 2

Ready to use formulation

S.No	Ingredients	Quantity/mL (mg)
1.	Fosaprepitant dimeglumine	2.0
2.	Palonosetron hydrochloride	0.00333
3.	Dexamethasone sodium phosphate	0.16
4.	Kleptose (Hydroxy propyl Betadex)	98.12
5.	Ethylenediamine tetraacetic acid	0.5013
6.	Sodium carbonate	0.32
7.	Sodium bicarbonate	2.6667
8.	Sodium chloride	5.0
9.	Sodium hydroxide	Qs to adjust pH 8.0-8.5
10.	Hydrochloric acid	Qs to adjust pH 8.0-8.5
11.	Water for injection	Qs to 1 mL

Manufacturing process:

Water for injection was taken in a compounding vessel and kleptose was added and stirred. The above solution was cooled to 2-8°C. Fosaprepitant dimeglumine was added to the above solution. Ethylenediamine tetraacetic acid was added followed by the addition of sodium carbonate and sodium bicarbonate. Palonosetron hydrochloride was added followed by the addition of Dexamethasone sodium and stirred. Sodium chloride was added to the above solution and pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filtered, followed by stoppering and sealing of the vials.

Example 3

Ready to use formulation

S.No	Ingredients	Quantity/mL (mg)
1.	Fosaprepitant dimeglumine	1.5
2.	Palonosetron hydrochloride	0.0025
3.	Dexamethasone sodium phosphate	0.12
4.	Hydroxy propyl Beta cyclodextrin (Kleptose)	73.59
5.	Ethylenediamine tetraacetic acid	0.3760
6.	Sodium carbonate	0.24
7.	Sodium bicarbonate	2.0
8.	Sodium chloride	6.0
9.	Sodium hydroxide	Qs to adjust pH 8.0-8.5
10.	Hydrochloric acid	Qs to adjust pH 8.0-8.5
11.	Water for injection	Qs to 1 mL

Manufacturing process:

Water for injection was taken in a compounding vessel and kleptose was added and stirred. The above solution was cooled to 2-8°C. Fosaprepitant dimeglumine was added to the above solution. Ethylenediamine tetraacetic acid was added followed by the addition of sodium carbonate and sodium bicarbonate. Palonosetron hydrochloride was added followed by the addition of Dexamethasone sodium and stirred. Sodium chloride was added to the above solution and pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filtered, followed by stoppering and sealing of the vials.

Example 4

Ready to dilute formulation

S.No	Ingredients	Quantity/mL (mg)
1.	Fosaprepitant dimeglumine	3.0
2.	Palonosetron hydrochloride	0.005
3.	Dexamethasone sodium phosphate	0.24
4.	Kleptose (Hydroxy propyl Betadex)	147.18
5.	Ethylenediamine tetraacetic acid	0.752
6.	Sodium carbonate	0.48
7.	Sodium bicarbonate	4.0
8.	Sodium chloride	2.0
9.	Sodium hydroxide	Q.s to adjust pH
10.	Hydrochloric acid	Q.s to adjust pH
11.	Water for injection	Q.s to 1 mL

Manufacturing process:

Water for injection was taken in a compounding vessel and kleptose was added and stirred. The above solution was cooled to 2-8°C. Fosaprepitant dimeglumine was added to the above solution. Ethylenediamine tetraacetic acid was added followed by the addition of sodium carbonate and sodium bicarbonate. Palonosetron hydrochloride was added followed by the addition of Dexamethasone sodium and stirred. Sodium chloride was added to the above solution and pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filtered, followed by stoppering and sealing of the vials.

Example 5

Emulsion formulation

S.No	Ingredients	Quantity/mL (mg)
1.	Aprepitant	15 mg
2.	Dexamethasone Sodium Phosphate	1.20 mg

3.	Palonosetron	0.025 mg
4.	Castor Oil	50.00 mg
5.	Polysorbate-80	40.00 mg
6.	Glycerine	22.00 mg
7.	Sorbic acid	1.00 mg
8.	Sodium acetate	0.50 mg
9.	Boric acid	1.00 mg
10.	Sodium EDTA	0.20 mg
11.	Sodium Hydroxide / Hydrochloric acid	Q.S
12.	Water for Injection	Q.S to 1 ml

Manufacturing process

Aprepitant was dissolved in preheated castor oil at temperature maintained between 50°C to 75°C. The aqueous phase was prepared by dissolving polysorbate-80, glycerin, sodium acetate, boric acid, sorbic acid, and disodium EDTA in water for injection at about 70°C. The oil phase and aqueous phase were mixed by using high shear mixer (Polytron) at about 7500 rpm at a temperature of about 70°C for approximately 60 minutes to form a coarse emulsion. The emulsion was cooled to room temperature and passed through high pressure homogenizer at 70±5°C (Pressure: 17000 psi & No. of Passes: 05) to get a fine emulsion. Palonosetron hydrochloride and Dexamethasone sodium phosphate were dissolved in the remaining water for injection. The solution was added to the emulsion of Aprepitant and stirred to achieve uniformity. pH was adjusted to desired target between 3.0 and 11.0 using 0.1N sodium hydroxide or hydrochloric acid.

The emulsion was further processed aseptically by filtration and filled into suitable primary packaging containers. The emulsion was analyzed and the results are shown in table 5:

Table 5

PH	5.06
Osmolality	521
Globule Size Distribution	
d10 (nm)	133
d50 (nm)	230
d90 (nm)	360
Z-Average	230
PDI (%)	22.9

Example 6

Suspension formulation

S.No	Ingredients	Quantity (mg/ml)
1	Aprepitant	100
2	Dexamethasone Sodium Phosphate	8
3	Palonosetron	0.16
4	Polysorbate-20	8
5	Citric acid monohydrate	3.33
6	Disodium hydrogen phosphate anhydrous	3.33
7	Sodium dihydrogen phosphate monohydrate	1.6
8	PEG 4000	20
9	Sodium hydroxide or hydrochloric acid	1.89
10	Water for Injection	Q.S to 1 ml

Manufacturing process

The aqueous phase was prepared by dissolving polysorbate-20 in water for injection at room temperature. Aprepitant was dispersed into the solution under homogenization at about 10000 rpm for 30 minutes approximately so that a suspension containing about 25%w/w solid content is obtained. The suspension was then milled in a bead mill with 55% occupancy, using 0.8mm beads, at an rpm of

1000 and for a duration of about 2 hrs. Palonosetron hydrochloride and Dexamethasone sodium phosphate were dissolved separately in water for injection and added to the suspension under stirring. PEG4000, citric acid monohydrate, disodium hydrogen phosphate, sodium dihydrogen phosphate, and sodium hydroxide were dissolved into the suspension under stirring. The pH was adjusted to desired target between 3.0 and 11.0 using 0.1N sodium hydroxide or hydrochloric acid solution and final weight was made up using water for injection. The suspension was analyzed and the results are shown below:

Description	White to off white suspension
pH	6.01
Particle Size Distribution	
d10 (nm)	0.3
d50 (nm)	1.1

Example 7

Lyophilized formulation

S.No	Ingredients	Quantity (mg)/Vial
1.	Fosaprepitant dimeglumine	150
2	Dexamethasone phosphate	12
3	Palonosetron hydrochloride	0.25
4	Hydroxypropyl beta cyclodextrin (HPBCD)	1000
5	Disodium edetate	37.6
6	Sodium hydroxide	Qs to adjust pH 7.0
7	Hydrochloric acid	Qs to adjust pH 7.0
8	Water for injection	QS

Manufacturing process

Water for injection was taken in a compounding vessel and HPBCD was added and stirred. The above solution was cooled to 2-8°C. Fosaprepitant dimeglumine was added to the above solution. Disodium edetate was added followed by the addition of Palonosetron hydrochloride. Dexamethasone phosphate was added and stirred.

pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filled in vials and lyophilized.

Example 8

Kit with Fosaprepitant lyophilizate

S.No	Ingredient	Quantity (mg)/Vial
Fosaprepitant lyophilizate		
1.	Fosaprepitant	150
2.	Hydroxypropyl beta cyclodextrin (HPBCD)	1000
3.	Disodium edetate	18.8
4.	Sodium Hydroxide	Qs to adjust pH 7.0
5.	Hydrochloric acid	Qs to adjust pH 7.0
Liquid injection formulation with Palonosetron and Dexamethasone		
		Quantity (mg)/10 mL
1.	Dexamethasone Phosphate	12
2.	Palonosetron hydrochloride	0.25
3.	Dibasic sodium phosphate dihydrate	1323
4.	Monobasic sodium phosphate monohydrate	94
5.	Disodium edetate	18.8
6.	Sodium Hydroxide	Qs to adjust pH 7.0
7.	Hydrochloric acid	Qs to adjust pH 7.0
8.	Water	QS to 10 mL

Manufacturing process

Water for injection was taken in a compounding vessel and HPBCD was added and stirred. The above solution was cooled to 2-8°C. Fosaprepitant dimeglumine was added to the above solution. Disodium edetate was added. pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filled in vials and lyophilized.

Water for injection was taken in a compounding vessel and dibasic sodium phosphate dihydrate and monobasic sodium phosphate monohydrate were added Palonosetron hydrochloride was added followed by the addition of Dexamethasone phosphate and stirred. Disodium edetate was added. pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filtered, followed by stoppering and sealing of the vials.

Fosaprepitant lyophilizate and liquid injection formulation with Palonosetron and Dexamethasone are supplied together as a kit.

Example 9

Ready to dilute formulation

S.No	Ingredient	Quantity (mg)/20 mL
1.	Fosaprepitant	150
2.	Dexamethasone phosphate	12
3.	Palonosetron hydrochloride	0.25
4.	Polysorbate 80	100
5.	Disodium edetate	37.6
6.	Sodium Hydroxide	Qs to adjust pH 9.0
7.	Hydrochloric acid	Qs to adjust pH 9.0
8.	Water for injection	QS to 20 mL

Manufacturing process

Water for injection was taken in a compounding vessel and cooled to 2-8°C. Fosaprepitant dimeglumine was added to the above solution. Disodium edetate was added followed by the addition of Palonosetron hydrochloride and Dexamethasone phosphate and stirred. Polysorbate 80 was added. pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filtered, followed by stoppering and sealing of the vials.

Example 10

Kit with Fosaprepitant lyophilizate

S.No	Ingredients	Quantity (mg)/Vial
Fosaprepitant lyophilizate		
1.	Fosaprepitant	150
2.	Polysorbate 80	100
3.	Disodium edetate	18.8
4.	Sodium hydroxide	Qs to adjust pH 5.0
5.	Hydrochloric acid	Qs to adjust pH 5.0
Liquid injection formulation with Palonosetron and Dexamethasone		
		Qty. (mg)/10 mL
1.	Dexamethasone phosphate	12
2.	Palonosetron	0.25
3.	Sodium carbonate anhydrous	24
4.	Sodium bicarbonate	200
5.	Disodium edetate	18.8
6.	Sodium hydroxide	Qs to adjust pH 9.0
7.	Hydrochloric acid	Qs to adjust pH 9.0
8.	Water	QS to 10 mL

Manufacturing process

Water for injection was taken in a compounding vessel and cooled to 2-8°C. Fosaprepitant dimeglumine was added to the above solution. Disodium edetate was added followed by the addition of polysorbate 80. pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filled in vials and lyophilized.

Water for injection was taken in a compounding vessel and sodium carbonate anhydrous and sodium bicarbonate were added. Palonosetron hydrochloride was added followed by the addition of Dexamethasone phosphate and stirred. Disodium edetate was added. pH of the solution was adjusted with sodium hydroxide and

hydrochloric acid. The solution was filtered, followed by stoppering and sealing of the vials.

Fosaprepitant lyophilizate and liquid injection formulation with Palonosetron and Dexamethasone are supplied together as a kit.

Example 11

Ready to dilute formulation with Rolapitant

S.No	Ingredients	Quantity (mg/mL)
1.	Rolapitant	9
2.	Dexamethasone phosphate	1
3.	Palonosetron hydrochloride	0.0125
4.	Hydroxypropyl beta cyclodextrin	367.95
5.	Dibasic sodium phosphate dihydrate	13.23
6.	Monobasic sodium phosphate monohydrate	0.94
7.	Disodium edetate	1.88
8.	Sodium hydroxide	Qs to adjust pH 7.0
9.	Hydrochloric acid	Qs to adjust pH 7.0
10.	Water	QS to 1 mL

Manufacturing process

Water for injection was taken in a compounding vessel and hydroxypropyl beta cyclodextrin was added and stirred. Rolapitant was added to the above solution. Disodium edetate was added followed by the addition of dibasic sodium phosphate dihydrate and monobasic sodium phosphate monohydrate. Palonosetron hydrochloride was added followed by Dexamethasone phosphate and stirred. pH of the solution was adjusted with sodium hydroxide and hydrochloric acid. The solution was filtered, followed by stoppering and sealing of the vials.

Example 12

Ready to use formulation

S.No	Ingredients	mg/mL
1.	Fosaprepitant Dimeglumine	3
2.	Palonosetron Hydrochloride	0.005
3.	Dexamethasone Sodium phosphate	0.24
4.	Kleptose	100
5.	Meglumine	1.904
6.	L-Aspartic acid	2
7.	L-Arginine	2
8.	Disodium EDTA	0.05
9.	Ultra-pure Water	QS to 1mL

QS: Quantity sufficient

Manufacturing Process:

Required quantity of L- Aspartic acid and L- Arginine were added to water followed by kleptose and stirred. Required quantity of meglumine and disodium EDTA were added. The solution was cooled to 2-8°C. Fosaprepitant dimeglumine was added followed by Palonosetron hydrochloride and Dexamethasone sodium phosphate and stirred till a clear solution was obtained.

Table 6: Stability data of the product prepared according to example 12.

Stability Condition	Initial	1Month 2-8°C	2Months 2-8°C	3Months 2-8°C	6Months 2-8°C
pH	8.60	8.76	8.91	8.90	8.88
Description	Clear solution	Clear solution	Clear solution	Clear solution	Clear solution
Palonosetron					
% Assay	101.6	102.0	101.2	101.1	101.4
Total Impurities	0.08	0.20	0.15	0.20	0.22
Dexamethasone					
% Assay	99.5	99.6	99.4	97.6	98

Total Impurities	0.76	1.62	1.54	1.49	1.51
Fosaprepitant					
% Assay	98.6	98.9	99.8	98.0	98.1
Aprepitant	0.76	0.80	0.89	0.94	0.98
Total Impurities	1.19	1.24	1.29	1.33	1.38

Example 13

Ready to use formulation

S.No	Ingredients	mg/mL
1.	Fosaprepitant Dimeglumine	3
2.	Palonosetron Hydrochloride	0.005
3.	Dexamethasone Sodium phosphate	0.24
4.	Kleptose	100
5.	Meglumine	1.904
6.	L-Aspartic acid	2
7.	L-Arginine	2
8.	Disodium EDTA	0.05
9.	Sodium chloride	QS
10.	Ultra-pure Water	QS to 1mL

QS: Quantity sufficient

Manufacturing Process:

Required quantity of L- Aspartic acid and L- Arginine were added to water followed by kleptose and stirred. Required quantity of meglumine, disodium EDTA and sodium chloride were added. The solution was cooled to 2-8°C. Fosaprepitant dimeglumine was added followed by Palonosetron hydrochloride and Dexamethasone sodium phosphate and stirred till a clear solution was obtained. The solution was filtered and filled in polyvinyl chloride bags.

We Claim

1. A parenteral formulation comprising:
   i. Palonosetron
   ii. NK_1 receptor antagonist
   iii. Corticosteroid and
   iv. Pharmaceutically acceptable excipients.

2. The parenteral formulation of claim 1, wherein NK_1 receptor antagonist is selected from the group comprising Fosaprepitant, Aprepitant, Rolapitant and Netupitant and Corticosteroid is selected from Dexamethasone and Methylprednisolone.

3. The parenteral formulation of claim 1, wherein the pharmaceutically acceptable excipients are selected from stabilizing agents, solubilizing agents, buffering agents, pH adjusting agents and solvents.

4. The parenteral formulation of claim 1, wherein the total impurities are less than 10% when stored at 2-8°C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/056277

A. CLASSIFICATION OF SUBJECT MATTER
C07D451/04,A61K31/47,A61P1/08 Version=2018.01

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)

C07D, A61K, A61P

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)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US20170119800 A1, 04 May 2017 Abstract, paragraph 0003, 0047; claims	1-4
X	EP2722045 B1, 06 July 2016 Para 0048-0052; claims	1-4
Y	Wu G. Et al. "Compatibility and Stability of Rolapitant Injectable Emulsion Admixed with Intravenous Palonosetron Hydrochloride" Int J Pharm Compd. Jan, Feb 2017 Vol 21(1) pp: 76-82 Abstract	1-4
Y	Rojas C. Et al. "Mechanisms and latest clinical studies of new NK1 receptor antagonists for chemotherapy-induced nausea and vomiting: Rolapitant and NEPA (netupitant/palonosetron)" Cancer Treatment Reviews, 2015 Vol 41(10), pp: 904-913. http://dx.doi.org/10.1016/j.ctrv.2015.09.005 The whole document	1-4
Y	Koth SM et al. "New options and controversies in the management of chemotherapy-induced nausea and	

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31-10-2018	31-10-2018
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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.
	vomiting" Am J Health Syst Pharm. 01 June 2017 Vol 74(11), pp: 812-819. DOI: 10.2146/ajhp160227 The whole document	1-4
Y	US20120238596 A1, 20 September 2012 Abstract, para 0019, claims	1-4

International application No.
PCT/IB2018/056277

Citation	Pub.Date	Family	Pub.Date
EP 2722045 B1	06-07-2016	US 8623826 B2	07-01-2014