



(51) International Patent Classification:

A61K 31/496 (2006.01) *A61P 1/08* (2006.01)
A61K 47/40 (2006.01) *A61P 25/20* (2006.01)
A61K 9/00 (2006.01) *A61K 47/48* (2006.01)

(21) International Application Number:

PCT/EP2012/061550

(22) International Filing Date:

18 June 2012 (18.06.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/498,722 20 June 2011 (20.06.2011) US

(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BEATO, Stefania** [IT/IT]; c/o GlaxoSmithKline, via Alessandro Fleming 2, I-37135 Verona (IT). **BRESCIANI, Massimo** [IT/IT]; GlaxoSmithKline, via Alessandro Fleming 2, I-37135 Verona (IT). **CROY, Scott, R** [US/US]; GlaxoSmithKline, 1250 S Collegeville Road, Collegeville, Pennsylvania 19426-0989 (US). **MULLER, Francis, Xavier** [US/US]; GlaxoSmithKline, 1250 S Collegeville Road, Collegeville, Pennsylvania 19426-0989 (US).

(74) Agent: **THORNLEY, Rachel, Mary**; GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))

(54) Title: PHARMACEUTICAL FORMULATIONS COMPRISING VESTIPITANT

(57) Abstract: A pharmaceutical formulation for intravenous (IV) administration comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and a process for its preparation and its use in medical therapy.



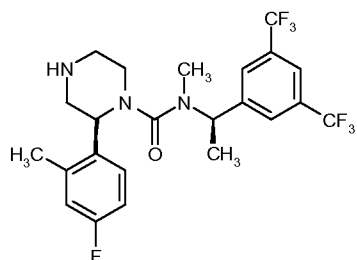
PHARMACEUTICAL FORMULATIONS COMPRISING VESTIPITANT

FIELD OF THE INVENTION

This invention relates to a pharmaceutical formulation for intravenous (IV) administration of the compound 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or salts thereof, a process for its preparation and its use in medical therapy.

BACKGROUND OF THE INVENTION

International patent application number WO2001/25219 describes piperazine derivatives. One such compound described therein is 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide (otherwise known as vestipitant) and it has the following chemical structure (I).



(I)

WO2001/25219 also describes the methanesulphonate salt of the compound (I).

The compound (I), pharmaceutically acceptable salts or solvates thereof are described in the aforementioned patent application as an antagonist of tachykinins, including substance P and other neurokinins, both in vitro and in vivo and thus is of potential use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

More particularly, the compound (I), and pharmaceutically acceptable salts or solvates thereof are described as useful in the treatment of central nervous system (CNS) disorders.

Thus, for example the compound (I), and pharmaceutically acceptable salts or solvates thereof are of particular use in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian rhythm disorders, sleep disorder due to a general medical condition, in particular sleep disturbances associated with such diseases as neurological disorders; neuropathic pain, restless leg syndrome, heart and lung diseases; and substance-induced sleep disorder including the subtypes insomnia type, hypersomnia type, parasomnia type and mixed type; sleep apnea and jet-lag syndrome.

Furthermore the compound (I), and pharmaceutically acceptable salts or solvates thereof are of use in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compound (I) pharmaceutically acceptable salts or solvates are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g.

cytarabine, methotrexate and 5- fluorouracil; alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intracranial pressure; decreased intracranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

The clinical management of the above disorders with the compound (I), and pharmaceutically acceptable salts or solvates thereof would be assisted by the availability of intravenous (IV) formulations.

In particular, an intravenous (IV) formulation of compound (I) or a pharmaceutically acceptable salt thereof would be of advantage in initiating treatment intravenously so as to obtain the required plasma concentrations and bioavailability as rapidly as possible. A rapidly administered intravenous (IV) formulation would also find utility in the treatment of those diseases, such as for example emesis including post-operative nausea and vomiting wherein patients experience difficulties in taking oral formulations and rapid administration is required to prevent further emetic episodes.

Therefore there is a need for an intravenous (IV) formulation for the compound (I) or a pharmaceutically acceptable salt thereof.

While an intravenous (IV) infusion formulation of vestipitant was previously developed, the formulation could not be rapidly administered due to the haemolytic properties of vestipitant. However, it was found that compound (I) and pharmaceutically acceptable salts thereof causes a degree of haemolysis when infused or injected at doses ranging between 1 to 5 mg/ml or greater as a simple sodium acetate buffer solution (Table 1).

Table 1

Component	Quantity (mg/vial)	
	1 mg/mL	5 mg/mL
Active ingredient	5.98 ²	29.90 ³
Mannitol	225.00	225.00
Sodium acetate trihydrate	12.25	12.25
Glacial acetic acid	10.50	10.50
Water for Injection	qs to 5 ml ⁴	qs to 5 ml ⁴

The active ingredient was 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate

Haemolysis, which is the lysis of the erythrocytes resulting in a loss of haemoglobin, can cause anaemia and therefore it is generally undesired.

There exists a need for intravenous (IV) formulation containing the compound (I), or a pharmaceutically acceptable salt thereof which has a reduced tendency to cause drug induced haemolysis.

Several methods for reducing drug-induced haemolysis are known in the art, for example a longer infusion time for intravenous (IV) formulation is known. However, longer infusion times can delay the onset of therapeutic effect causing continued discomfort the patient.

Other approaches include for example the use of a complexation agent such as cyclodextrin. By virtue of the ability of cyclodextrin to complex with the free drug, resulting in less free drug that can disrupt erythrocyte cell membranes and therefore reduced haemolysis.

International patent application number WO1993/05791 discloses certain polyanionic β -cyclodextrin of use for protecting erythrocytes from the haemolytic effects of haemolysis inducing agents. However, this document does make it possible to conclude that the haemolytic protective effects are neither applicable to the specific ingredient of the present invention nor effective in vivo.

International patent application number WO2005/082419 discloses a pharmaceutical composition with an improved site toleration comprising an NK1 antagonist and a cyclodextrin.

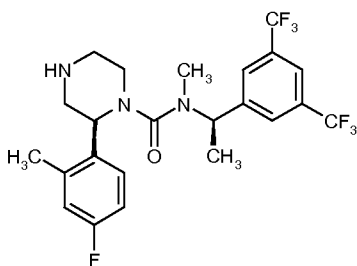
Nagase et al Journal of Pharmaceutical Sciences Vol. 91 N0 11, November 2002 and European patent application EP 1897542 describe the protective effects of cyclodextrin derivatives from the haemolytic effects of a specific anti-cancer drug.

However, there is neither teaching nor suggestion in the art that a complexation with a cyclodextrin would result in a reduction of the haemolytic effect of the specific active agent of the present invention.

SUMMARY OF THE INVENTION

The present invention provides an intravenous (IV) aqueous pharmaceutical formulation of compound (I) or a pharmaceutically acceptable salt thereof.

In particular it was found that adding a cyclodextrin to an intravenous (IV) formulation of 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide (otherwise known as vestipitant) of chemical structure (I), reduces drug-induced haemolysis without affecting the pharmacological activity of the drug.



(I)

The compound of formula (I) is also named as S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide according to The ChemBioDraw naming software package (ChemBioDraw Ultra Version 12.0).

In a first aspect thereof, the invention provides an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin.

In a further aspect, there is provided an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin for use in the treatment of diseases or conditions for which a NK1 antagonist is indicated.

In a further aspect, there is provided an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin for use in the treatment of emesis, such as post operative nausea and vomiting, or sleep disorders.

In a further aspect, there is provided the use of an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin in the manufacture of a medicament for the treatment of diseases or conditions for which a NK1 antagonist is indicated.

In a further aspect, there is provided the use of an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin in the manufacture of a medicament for the treatment of emesis, such as post operative nausea and vomiting, or sleep disorders.

In a further aspect, there is provided a method for the treatment of diseases or conditions for which a NK1 antagonist is indicated which method comprises intravenously administering to the human patient an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin.

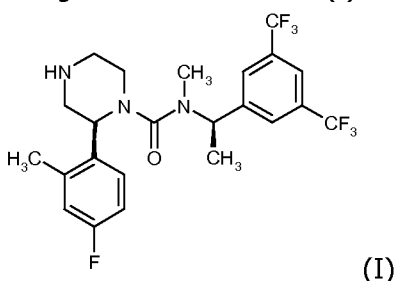
In a further aspect, there is provided a method of reducing haemolysis activity of 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof, comprising adding at least

one cyclodextrin to an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof.

5 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin.

2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide (otherwise known as vestipitant), has the following chemical structure (I).



The compound (I) and its pharmaceutically acceptable salts may be prepared by the processes described in International patent applications WO2001/25219 and WO2007/048642, which are incorporated herein by reference. Specifically, Examples 37 and 36 of WO2001/25219 describe the synthesis of the compound (I) as free base and as methanesulphonate salt respectively. Hydrochloride and acetate salts of the compound(I) are described in the Examples 38 and 18 respectively. Example 1 of WO2007/048642 discloses a process for preparing an intermediate in the synthesis of the compound(I).

It will be appreciated that for use in medicine, the salts of the compound (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with pharmaceutically acceptable organic or inorganic acids. Examples of salts include hydrochloride, hydrobromide, sulphate, alkyl- or arylsulphonate e.g. methanesulphonate otherwise known as mesylates or p-toluenesulphonate (otherwise known as tosylate), phosphate, acetates, citrate, succinate, tartrate, fumarate and maleate.

One such pharmaceutically acceptable salt of the compound of formula (I) for use according to the present invention is the methanesulphonate salt.

Certain salts of the compound (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the salts of compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that salts of compounds of formula (I) may exist in

tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The compound (I) may form acid addition salts with one or more equivalents of the acid. The present invention may employ all possible stoichiometric and non-stoichiometric forms thereof in the formulations of the invention.

The compound (I) or pharmaceutically acceptable salts thereof may exist in the form of a solvate.

It will be appreciated that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallised. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvents with high boiling points and/or solvents with a high propensity to form hydrogen bonds such as water, ethanol, *iso*-propyl alcohol, and *N*-methyl pyrrolidinone may be used to form solvates. Methods for the identification of solvated include, but are not limited to, NMR and microanalysis.

The compound (I) or pharmaceutically acceptable salts thereof may exist in a different polymorphic form.

Polymorphism is defined as the ability of an element or compound to crystallise in more than one distinct crystalline phase. Thus, polymorphs are distinct solids sharing the same molecular formula, however since the properties of any solid depends on its structure, different polymorphs may exhibit distinct physical properties such as different solubility profiles, different melting points, different dissolution profiles, different thermal and/or photostability, different shelf life, different suspension properties and different physiological absorption rate. Inclusion of a solvent in the crystalline solid leads to solvates, and in the case of water as a solvent, hydrates.

Included within the compound (I) are all solvates (including hydrates) and polymorphs of the compound (I) or pharmaceutically acceptable salts thereof.

As used herein, the term "treatment" may include treatment and/or prophylaxis.

As used herein, the "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

In one embodiment, there is provided an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate and at least one cyclodextrin.

Typically, the concentration of 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or one of its pharmaceutically acceptable salts in the intravenous (IV) aqueous pharmaceutical formulation, calculated as free base, is from 1 to 15 mg/ml, preferably from 1 to 10 mg/ml, more preferably from 1 to 3 mg/ml, for example 2 mg/ml.

The term "cyclodextrin" as used herein means a cyclic oligosaccharide having a hydrophobic interior cavity and hydrophilic exterior. There are three main types of cyclodextrins: α cyclodextrin; β cyclodextrin and γ cyclodextrin. The term "cyclodextrin" also includes various substituted cyclodextrins, including as side chains any organic moiety or heterorganic moiety.

Substituted cyclodextrins also include cyclodextrins that have been alkylated, hydroxyalkylated or reacted to form a sulfoalkyl ether.

Cyclodextrins which may be used according to the present invention may be chosen from α , β , or γ cyclodextrins.

5 A preferred class of cyclodextrins according to the invention is β cyclodextrins, which cyclodextrins may be in the form of derivatives such as sulfoalkylether cyclodextrin (e.g. sulfobutyl ether β -cyclodextrin), hydroxyalkyl cyclodextrins, (e.g. hydroxyethyl hydroxypropyl- β -cyclodextrin, hydroxyethyl- β -cyclodextrin), alkylcyclodextrins (e.g. methyl- β -cyclodextrin, dimethyl- β -cyclodextrin, trimethyl- β -cyclodextrin, diethyl- β -cyclodextrin), or
10 carboxyalkylcyclodextrins (e.g., carbomethyl- β -cyclodextrin), or combinations thereof.

β cyclodextrins are particularly suitable for use in the intravenous (IV) aqueous pharmaceutical formulation of the present invention.

In one embodiment, the β cyclodextrin is selected from sulfobutyl ether β cyclodextrin and/or hydroxy-propyl β -cyclodextrin.

15 In one embodiment, the β cyclodextrin is sulfobutyl ether β cyclodextrin.

The cyclodextrin is present in the formulation in an amount of from 5% to 30% (w/v), preferably from 5% to 15% (w/v), for example 10% (w/v).

It is preferred, however, that the cyclodextrin be present in an amount effective to substantially reduce haemolysis caused by 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or one of its
20 pharmaceutically acceptable salts.

By "substantially reduce" it is meant that the cyclodextrin is present in an amount effective to reduce the haemolysis activity of the compound (I) by at least 20 fold reduction relative to the amount of haemolysis caused by the compound (I) in the absence of the cyclodextrin.

25 Cyclodextrins for use in the invention are commercially available.

Sodium Sulfobutyl ether 7- β cyclodextrin (SBE7-beta-CD) is also known as Captisol™ and it is available from CyDex, LLC.

The pharmaceutical formulations may also contain a pharmaceutically acceptable pH adjusting agent and/or buffering agent capable of dissolving the compound (I) or
30 pharmaceutically acceptable salt thereof and/or maintaining the solution in a physiologically acceptable range. Such agents include citric acid, lactic acid, boric acid, acetic acid, phosphoric acid, hydrochloric acid, sulfuric acids, and sodium phosphate monobasic; and bases/basic agents, such as sodium hydroxide, sodium citrate, sodium borate, sodium acetate, sodium sulfate, sodium phosphate dibasic, sodium phosphate tribasic, sodium carbonate, sodium
35 bicarbonate, tris-hydroxymethylaminomethane, diethylamine, triethylamine, and ammonium hydroxide.

Generally, the buffering agent if present is capable both of dissolving the compound (I) or pharmaceutically acceptable salt thereof and of maintaining the pH of the formulation between about 3 and 6, preferably between about pH 4 and pH 5.

40 Preferred buffering agents for use in the invention include, for example, buffer systems chosen from succinic acid/alkali metal succinate, citric acid/alkali metal citrate, acetic acid/alkali metal acetate, tartaric acid/alkali metal tartrate, lactic acid/alkali metal lactate, maleic acid/alkali metal maleate, fumaric acid/alkali metal fumarate methanesulphonic acid/alkali metal

methanesulphonate otherwise known as mesylate, alkali metal sulfates, alkali metal hydrogen sulfates, phosphate acid/monoalkali metal phosphate, alkali metal dihydrogen phosphate/dialkali metal hydrogen phosphate, trialkali metal citrate, alkali metal phosphate, and alkali metal carbonate/alkali metal hydrogen carbonate.

5 In one embodiment the buffering agent is acetic acid/ alkali metal acetate, for example glacial acetic acid / sodium acetate trihydrate.

In one embodiment, buffer solutions include 0.01 to 0.3 molar, more preferably 0.05 to 0.2 molar, aqueous buffer solutions of acetic acid/ alkali metal acetate, for example glacial acetic acid / sodium acetate trihydrate buffer.

10 In one embodiment, the formulation comprises a cyclodextrin which is Captisol™ at a concentration from 5% to 15% (w/v), the compound (I) as a free base is at concentration from 1 to 3 mg/ml and a buffering agent which is glacial acetic acid / sodium acetate trihydrate buffer is at concentration from 0.05 to 0.2 molar.

15 In one embodiment of the invention, the molar ratio of Captisol™ and the compound of formula (I) from 6:1 to 18:1.

There is still further provided by the present invention a process for preparing the formulation described herein, which process comprises dissolving the compound (I) or a pharmaceutically acceptable salt thereof and at least one cyclodextrin in an aqueous solution for intravenous (IV) administration.

20 In one embodiment, the process comprises the addition of acetic acid/ alkali metal acetate buffer, for example glacial acetic acid / sodium acetate trihydrate buffer to an aqueous solution of the compound (I) in the form of a methanesulphonate salt, followed by the addition of Captisol™.

25 The resultant solution may be diluted to the desired concentration with water for intravenous administration and then sterilised using conventional means such as filter sterilisation. It may then be dispensed into sterile plastic or glass containers, such as ampoules or vials, in volumes of, for example, from 7 to 17mL.

30 Thus, for example, in one embodiment of the invention, the resultant solution is aseptically filtered through two sterile filters (0.2 µm) and was filled under a nitrogen flush into pre-sterilized 17 mL USP Type 1 glass vials.

Generally, from 6 mg to 36 mg of compound (I) as a free base is intravenously administered to provide a therapeutically effective dose for the treatment of emesis. The rate of administration of the solution providing the required dose may vary.

35 Typically, compound (I) is intravenously administered once over a time period ranging from 30 seconds to 2 minutes.

In one embodiment, from 6 mg to 36 mg of compound (I) as a free base is intravenously rapidly administered once over a time period of 30 seconds.

The aqueous solution is suitable for intravenous administration either by injection or by infusion.

40 In a further embodiment there is provided the use of a aqueous pharmaceutical formulation for intravenous (IV) administration in the manufacture of a medicament for the treatment of emesis wherein the formulation delivers from 6 to 36 mg of 2-(S)-(4-Fluoro-2-methyl-phenyl)-

piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide as free base by intravenous administration over a period of time from 30 seconds to 2 minutes.

Also provided is the use of a formulation according to the invention in the manufacture of a medicament for the treatment of diseases or conditions for which a NK1 antagonist is indicated.

5 In one embodiment, there is provided the use of an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin in the manufacture of a medicament for the treatment of diseases or conditions for which a NK1 antagonist is indicated.

10 In one embodiment, there is provided the use of an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin in the manufacture of a medicament for the treatment of emesis, such as post operative nausea and vomiting, or sleep disorders.

15 In one embodiment, there is provided the use of an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate and at least one cyclodextrin in the manufacture of a medicament for the treatment of diseases or conditions for which a NK1 antagonist is indicated.

20 In one embodiment, there is provided the use of an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate and at least one cyclodextrin in the manufacture of a medicament for the treatment of emesis, such as post operative nausea and vomiting, or sleep disorders.

25 In one embodiment, there is provided an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin for use in the treatment of diseases or conditions for which a NK1 antagonist is indicated.

30 In a further embodiment there is provided an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate and at least one cyclodextrin for use in the treatment of diseases or conditions for which a NK1 antagonist is indicated.

35 In one embodiment, there is provided an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin for use in the treatment of emesis, such as post operative nausea and vomiting, or sleep disorders.

40 In a further embodiment there is provided an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate and at least one

cyclodextrin for use in the treatment of emesis, such as post operative nausea and vomiting, or sleep disorders.

Also provided is a method of treating diseases or conditions for which a NK1 antagonist is indicated, which method comprises intravenously administering to a human patient in need thereof an intravenous (IV) aqueous pharmaceutical formulation according to the invention.

In one embodiment there is provided a method of treating diseases or conditions for which a NK1 antagonist is indicated which method comprises intravenously administering to a human patient in need thereof an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin.

In one embodiment there is provided a method of treating diseases or conditions for which a NK1 antagonist is indicated which method comprises intravenously administering to a human patient in need thereof an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate and at least one cyclodextrin.

In one embodiment there is provided a method of treating emesis, such as post operative nausea and vomiting, or sleep disorders. which method comprises intravenously administering to a human patient in need thereof an intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate and at least one cyclodextrin.

It will be appreciated by those skilled in the art that the pharmaceutical formulations of the present invention can be administered, either sequentially or simultaneously with other therapeutic and/or prophylactic agents and /or medicament that are not medically incompatible therewith.

For example it may be used in conjunction with one or more other therapeutic agents, for instance, 5-HT uptake inhibitors (such as escitalopram, escitalopram oxalate, venlafaxine, sertraline, fluvoxamine or paroxetine), GABA receptor agonists (such as pregabalin) and antipsychotic such as for example risperidone and saripiprazole, 5HT3 antagonists such as for example ondansetron, granisetron, metoclopramide.

The compound (I) or its pharmaceutically acceptable salts or may be prepared by the processes described in International patent applications WO2001/25219 and WO2007/048642.

Specifically Compound (I) methanesulphonate salt in a crystalline Form 1 can be prepared according the following procedures.

Abbreviations

The following abbreviations may be used in the preparations:

TBAB	tetrabutylammonium bromide
EtOAc	ethyl acetate
THF	tetrahydrofuran
IMS	Industrial Methylated Spirits

DMSO

Dimethyl sulfoxide

Preparation 1**(S)-2-(4-fluoro-2-methylphenyl)piperazine dihydrochloride**

5 A suspension of (S)-3-(4-fluoro-2-methylphenyl)piperazin-2-one (S)-2-hydroxy-2-phenylacetate (14.0Kg; contains 16%w/w EtOAc hence 11.8 kg corrected for solvent) and tetrabutylammonium bromide (TBAB, 236g) in THF (94L) was warmed to 40°C to obtain a clear solution that was cooled to 30°C and then added to a slurry of sodium borohydride (powder grade, 5.5kg) in THF (41L) at 20°C, followed by THF (5.6L). The mixture was warmed to 35°C and then
10 boron trifluoride-THF complex (36.6kg) was added over 90min, followed by THF (1L). The mixture was stirred for 6h and then IMS (47L) added over 3 hours. The mixture was distilled to ca. 94L, diluted with IMS (47L) and further distilled to 94L. The slurry was cooled to 25°C, filtered and the solids washed with IMS (2x35L). The combined filtrates were heated to 70°C and hydrogen chloride (5-6N in isopropanol, 15kg) added over 72min. The resulting slurry was heated at reflux for 3h,
15 cooled to 20°C over 2h and then held at this temperature for 2h. The suspension was filtered, washed with IMS (3x24L) and the solids dried under vacuum at 45-50°C to give the title compound (6.87kg) as a white powder.

¹H NMR NMR (D₂O) δ (ppm) 7.44 (dd, 1H), 7.03-7.00 (m, 2H), 4.89 (dd, 1H), 3.82-3.51 (m, 6H), 3.35 (s, 3H).

Preparation 2**(S)-tert-butyl 3-(4-fluoro-2-methylphenyl)piperazine-1-carboxylate hydrochloride**

Triethylamine (5.5kg) was added to a slurry of (S)-2-(4-fluoro-2-methylphenyl)piperazine dihydrochloride (6.60kg, 94.6% assay) in EtOAc (38L) and was rinsed in with EtOAc (1L). The slurry was stirred at 40°C for 120 minutes and was then cooled to 20°C. 79.2%w/w Di-*tert*-butyl dicarbonate in EtOAc solution (6.29kg) was added over 60 minutes and was rinsed in with EtOAc (1L). The slurry was stirred for 15 minutes. Further 79.2%w/w di-*tert*-butyl dicarbonate in EtOAc solution (0.19kg) and EtOAc (1L) was added and the slurry was stirred for 43 minutes. EtOAc (5L),
30 79.2%w/w di-*tert*-butyl dicarbonate in EtOAc solution (0.25kg) and EtOAc (1L) were added and the slurry was then stirred for 15 minutes to complete the reaction. Water (18.7L) was added to dissolve all solids present and the lower aqueous layer was separated. The organic layer was washed with water (18.7L). The solution was distilled under reduced pressure to a total volume of 25L. Fresh EtOAc (37L) was added and the solution was distilled under reduced pressure to a total volume of
35 25L. EtOAc (49L) was added and the temperature was adjusted to 15°C. A slurry of the title compound (31.2g) in EtOAc (310ml) was added followed by 5.5M hydrogen chloride in isopropanol solution (0.412kg) rinsed in with EtOAc (1L). The mixture was stirred for 60 minutes to give a slurry. 5.5M Hydrogen chloride in isopropanol solution (3.6kg) was added portionwise over 55 minutes and was rinsed in with EtOAc (1L). The resultant slurry was stirred for 30 minutes at 15°C. The slurry
40 was filtered and the solid was washed with EtOAc (2 x 16.8kg). The solid was dried under vacuum at 40°C to give the title compound (6.84kg) as a white solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.89 (brs, 2 H), 7.88 (dd, 1 H), 7.13 - 7.20 (m, 2 H), 4.43 (d, 1 H), 4.07 (d, 1 H), 3.96 (d, 1 H), 3.30 - 3.38 (m, 2 H), 3.21 (m, 2 H), 2.39 (s, 3 H), 1.42 (s, 9 H).

Preparation 3**(R)-1-(3,5-bis(trifluoromethyl)phenyl)-N-methylethanamine**

To a suspension of (R)-1-(3,5-bis(trifluoromethyl)phenyl)-N-methylethanamine (S)-2-hydroxysuccinate (9Kg) in EtOAc (27L), 13% w/w aqueous sodium carbonate solution (27L) was added. The mixture was stirred for 30 minutes at 25°C to ensure complete dissolution. The layers were separated and the organic phase was washed with water (27L). EtOAc (36L) was added and the solution concentrated *in vacuo* to 18L. Further EtOAc (49Kg) was added and the solution concentrated *in vacuo* to 18L to give a colourless 33.4% w/w solution of the title compound in EtOAc (17.9Kg).

¹H NMR for title compound (500 MHz, DMSO-*d*₆) δ ppm 8.01 (s, 2 H), 7.90 (s, 1 H), 3.79 (q, *J*=6.56 Hz, 1 H), 2.35 (br s, 1 H), 2.10 (s, 3 H), 1.25 (d, *J*=6.56 Hz, 3 H)

¹H NMR for EtOAc peaks (500 MHz, DMSO-*d*₆) δ ppm 4.02 (q, *J*=7.17 Hz, 2 H), 1.98 (s, 3 H), 1.17 (t, *J*=7.10 Hz, 3 H)

NMR shows a ratio of 1:6.1 the title compound:EtOAc.

Preparation 4**(S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide methanesulfonate (Crystalline Form 1)**

To a 33.4% w/w solution of (R)-1-(3,5-bis(trifluoromethyl)phenyl)-N-methylethanamine in EtOAc (14.70Kg) was added EtOAc (22L). The solution was vacuum purged three times with carbon dioxide gas and stirred under a flow of CO₂ at 20°C for 1 hour. Triethylamine (2.40Kg) was added followed by EtOAc (1.35Kg) and the solution stirred for 50 minutes under a flow of CO₂. Chlorotrimethylsilane (2.50Kg) was added over 30 minutes keeping the internal temperature below 25°C followed by EtOAc (1.35Kg) and the suspension stirred under a flow of CO₂ at 20°C for 30 minutes. Pyridine (2.85Kg) was added followed by EtOAc (2.70Kg). Thionyl chloride (3.25Kg) was added over 20 minutes followed by EtOAc (2.70Kg) and the suspension heated to 25°C for 6 hours. The reaction was cooled to 10°C and quenched with 28% w/w aqueous malic acid solution (14.30Kg). The layers were separated at 20°C and the organic phase washed with 14% w/w aqueous malic acid solution (13.50Kg), water (12.70Kg) and 20% w/w aqueous potassium phosphate dibasic solution (22.40Kg). EtOAc (4.50Kg) was added and the solution concentrated *in vacuo* to 15L. Further EtOAc (15L) was added and the solution concentrated *in vacuo* to 15L.

To the concentrated solution, EtOAc (5L) was added followed by (S)-tert-butyl 3-(4-fluoro-2-methylphenyl)piperazine-1-carboxylate hydrochloride (5.00Kg) and EtOAc (2.50Kg). Tributylamine (7.00Kg) was added and the suspension heated to reflux for 1 hour. The reaction was cooled to 30°C and EtOAc (27.20Kg) followed by water (15.00Kg) were added. The layers were separated, diethylamine (1.10Kg) was added to the organic phase and the solution heated to 40°C for 1 hour. The reaction was cooled to 30°C and washed with 0.5M sulfuric acid (25.90Kg), 0.5M sulfuric acid (15.45Kg) and water (15.00Kg).

To the organic phase, methanesulfonic acid (5.85Kg) was added and the solution heated to 40°C for 1 hour. The reaction was cooled to 10°C then 13%w/w aqueous ammonia solution

(23.75Kg) was added over 30 minutes keeping the internal temperature below 35°C. The layers were separated at 30°C and the organic phase was washed with 1% w/w aqueous ammonia solution (15.15Kg) and water (15.00Kg). EtOAc (4.50Kg) was added to the organic phase and the solution was concentrated *in vacuo* to 15L. EtOAc (40L) was added and the solution concentrated *in vacuo* to 15L.

Further EtOAc (10L) was added followed by methanesulfonic acid (1.20Kg) and (S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide methansulfonate (25g) in isooctane (0.25Kg) and the suspension was stirred at 20°C for 70 minutes. Isooctane (50L) was added over 90 minutes and the reaction stirred for 1 hour. The suspension was filtered and washed with 2:1 isooctane/EtOAc (12.5L) three times. The solid was co-milled to give the title compound (6.31Kg) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.96 (br. s., 2 H), 8.00 (s, 1 H), 7.71 (s, 2 H), 7.29 (dd, *J*=8.56, 6.11 Hz, 1 H), 6.99 (dd, *J*=10.27, 2.69 Hz, 1 H), 6.83 (td, *J*=8.56, 2.45 Hz, 1 H), 5.35 (q, *J*=6.60 Hz, 1 H), 4.52 (dd, *J*=11.74, 3.18 Hz, 1 H), 3.52-3.22 (m, 4 H), 3.12-2.92 (m, 2 H), 2.74 (s, 3 H), 2.39 (s, 3 H), 2.37 (s, 3 H), 1.49 (d, *J*=7.09 Hz, 3 H)

ES⁺: m/z 492 [MH – CH₃SO₃H]⁺

Melt onset is 171°C obtained by Differential Scanning Calorimetry (DSC).

The DSC thermogram of the product was obtained using a TA Q2000 calorimeter. The sample was weighed into an aluminium pan, a pan lid placed on top and lightly crimped without sealing the pan.

The experiment was conducted using a heating rate of 10°C /min.

Crystalline Form 1 is characterized by an X-ray powder diffraction pattern which at least substantially includes the peaks of Table I.

Table I	
2 theta angle (°) ¹	d-spacings/Å
3.6	24.8
7.1	12.5
9.4	9.4
10.6	8.3
10.9	8.1
12.5	7.1
13.2	6.7
14.2	6.3
15.9	5.6
16.7	5.3
17.0	5.2
17.7	5.0
18.0	4.9
23.1	3.9

¹ Margin of error = approximately. $\pm 0.1 \ 2\theta$ for each of the peak assignments.

The data were acquired on a Panalytical X'Pert Pro powder diffractometer, model PW3040/60 using an X'Celerator detector. The acquisition conditions were: radiation $\text{CuK}\alpha$, generator tension: 40Kv, generator current: 45mA, start angle: $2.0^\circ 2\theta$, end angle: $40.0^\circ 2\theta$, step size: $0.0167^\circ 2\theta$, time per step: 31.75 seconds. The sample was prepared by mounting a few milligrams of sample on a silicon wafer (zero background) plate, resulting in a thin layer of powder.

The Compound (I) as succinate or hemisulphate salt can be obtained according the following procedures.

Preparation 5 (seed used for preparation 6)

(S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide

(S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide methanesulfonate (10 g) was dissolved in ethyl acetate (100 mL) in a beaker with stirring. To this solution, aqueous sodium carbonate (9.02 g in 100 mL water) was gradually added whilst stirring. The mixture was transferred to a separating funnel and shaken with venting. The lower aqueous layer was collected. Anhydrous magnesium sulphate was added to the organic solution to absorb any residual moisture. The flask was shaken and then filtered into a round bottomed flask. Further ethyl acetate (20 mL) was used to rinse and this solution was filtered through and combined with the extract in the round bottomed flask.

The ethyl acetate was removed by distillation using rotary evaporation yielding a thick sticky oil. The stopper was removed allowing any free residual ethyl acetate to evaporate, over time a soft and waxy solid precipitated (8.7 g product).

¹H NMR (400 MHz, DMSO- D_6) δ ppm 1.49 (d, $J=6.85$ Hz, 3 H) 2.33 (s, 3 H) 2.37 (s, 1 H) 2.52 - 2.56 (m, $J=9.54$ Hz, 1 H) 2.70 (s, 3 H) 2.74 - 2.91 (m, 4 H) 3.18 - 3.27 (m, 1 H) 4.24 (dd, $J=9.54$, 3.42 Hz, 1 H) 5.29 (q, $J=6.85$ Hz, 1 H) 6.78 (td, $J=8.56$, 2.69 Hz, 1 H) 6.92 (dd, $J=10.15$, 2.57 Hz, 1 H) 7.29 (dd, $J=8.56$, 6.36 Hz, 1 H) 7.72 (s, 2 H) 7.99 (s, 1 H)

Preparation 6

(S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide

(S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide methanesulfonate (30 g) was dissolved in ethyl acetate (300 mL) in a 1 L DURAN bottle with stirring. To this solution, aqueous sodium carbonate (27.06 g in 300 mL water) was gradually added whilst stirring. The mixture was transferred to a separating funnel and shaken with venting. The lower aqueous layer was separated off. Anhydrous magnesium sulphate was added to a 500 mL DURAN bottle on to which the organic solution was added. The bottle was shaken and the contents filtered into a 500 mL round bottomed flask; 60 mL ethyl acetate was used to rinse the vessels, then filtered and combined with the extract.

The ethyl acetate was removed by distillation using rotary evaporation. For the final part of the distillation the temperature of the water bath was increased to 35°C and the pressure reduced gradually to produce an indicated value of 50 mBar. At this point a viscous oil was remaining, little ethyl acetate was being driven off and the oil was starting to bubble and the distillation was

stopped. The unstoppered flask was placed in an oven at ambient temperature under vacuum for 3 days. Following drying, a thick viscous oil with some motility was observed. The oil was seeded with approx 20 mg of material of (S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide (preparation 5) and this was mixed with a spatula and the inside of the flask was scratched. The flask was placed under a jet of nitrogen to encourage evaporation of residual ethyl acetate. The resulting solids were broken up and delumped and the material dried overnight. The solids were further broken up and dried under nitrogen. The solid was isolated and powdered in a pestle and mortar. 22.1 g product 88% theoretical yield.

¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.49 (d, *J*=7.09 Hz, 3 H) 2.33 (s, 3 H) 2.52 - 2.57 (m, 1 H) 2.70 (s, 3 H) 2.75 - 2.90 (m, 4 H) 3.19 - 3.27 (m, 1 H) 4.24 (dd, *J*=9.41, 3.55 Hz, 1 H) 5.30 (q, *J*=6.77 Hz, 1 H) 6.78 (td, *J*=8.56, 2.69 Hz, 1 H) 6.92 (dd, *J*=10.15, 2.57 Hz, 1 H) 7.29 (dd, *J*=8.56, 6.36 Hz, 1 H) 7.72 (s, 2 H) 7.99 (s, 1 H)

Preparation 7

(S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide Succinate

A solution of (S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide (preparation 6) (25 mg/mL in ethyl acetate, 0.051 mmol, 1 mL) was added to succinic acid (6 mg, 0.051 mmol, 1 eq) in a HPLC vial and shaken overnight with temperature cycling (0-40°C). The resulting solid was filtered under vacuum.

¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.49 (d, *J*=7.09 Hz, 3 H) 2.33 (s, 3 H) 2.37 (s, 4 H) 2.56 - 2.63 (m, 1 H) 2.66 - 2.72 (m, 4 H) 2.78 - 2.87 (m, 1 H) 2.93 (d, *J*=19.81 Hz, 3 H) 4.28 (dd, *J*=9.66, 3.06 Hz, 1 H) 5.27 - 5.33 (m, 1 H) 6.76 - 6.81 (m, 1 H) 6.92 - 6.95 (m, 1 H) 7.29 (dd, *J*=8.31, 6.11 Hz, 1 H) 7.71 (s, 2 H) 7.99 (s, 1 H)

Preparation 8

(S)-N-((R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide Hemi-Sulphate

5M sulphuric acid (diluted to 0.5M in IPA, 0.05 mL, 0.5 eq) was added to a preparation 6 solution (25 mg/mL in IPA, 0.051 mmol, 1 mL) in a HPLC vial and shaken overnight with temperature cycling (0-40°C). The resulting solid was filtered under vacuum.

¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.49 (d, *J*=6.85 Hz, 3 H) 2.35 (s, 3 H) 2.66 - 2.77 (m, 4 H) 2.80 - 2.95 (m, 1 H) 2.99 - 3.22 (m, 2 H) 3.27 (s, 2 H) 4.36 (dd, *J*=10.64, 3.06 Hz, 1 H) 5.28 - 5.36 (m, 1 H) 6.78 - 6.84 (m, 1 H) 6.96 (dd, *J*=10.03, 2.69 Hz, 1 H) 7.29 (dd, *J*=8.68, 6.24 Hz, 1 H) 7.71 (s, 2 H) 8.00 (s, 1 H) Ion Chromatography – Sulphate 7.8% w/w

EXAMPLES

Formulations according to the invention were evaluated in the following or similar studies.

In vitro Studies

Example 1

The objective of this study was to compare the haemolytic potential of Compound (I) formulated in Sodium sulfobutylether-7-beta-cyclodextrin (SBE7-beta-CD) also known as Captisol™ versus compound (I) in 4.5% Mannitol and Acetate Buffer, in both beagle dog and human blood.

Glucose (aqueous solution at 5%) was used as a negative control and saponin (1% aqueous solution), which is a known inducer of haemolysis, was used as a positive control.

Vestipitant methanesulfonate was formulated in 4.5% Mannitol and acetate aqueous buffer 0.05M pH 4.5 or in 13% w/v Captisol™ in 0.05M acetate buffer, pH 4.5 at concentrations of 0.1, 0.5, 1, 2 and 3 mg/ml. All concentrations are expressed in term of the Vestipitant as a free base.

Whole blood samples from female beagle dogs and female human sources were pre-incubated at 37°C for 10 minutes, after which equivalent volumes of each Vestipitant formulation, vehicles and negative control solution were mixed 1:1 with whole blood. The endpoint used to assess the haemolytic potential was the measurements of plasma haemoglobin leakage. The % of haemoglobin leakage was expressed as a percentage of the positive control value for the saponin sample.

The results of these experiments are illustrated in Table 1 and in Table 2. These results indicate that drug-induced haemolysis of Vestipitant methanesulfonate was reduced when it is formulated in a cyclodextrin formulation according to the invention.

Table 1 Results of haemoglobin leakage in Human Blood treated with positive (Saponin 1% w/v) and negative (Glucose 5%) controls, Vestipitant and their corresponding Vehicle.

Vestipitant (mg/mL) in 4.5% Mannitol/Acetate	Haemoglobin Leakage (mg/dL)	Haemoglobin Leakage %	Vestipitant (mg/mL) in 13% w/v Captisol™	Haemoglobin Leakage (mg/dL)	Haemoglobin Leakage %
Vehicle	13.6	0.04	Vehicle	16.4	0.12
0.1	8.3	-0.12	0.1	15.1	0.08
0.5	35.9	0.70	0.5	15.8	0.10
1	809	23.66	1	16.2	0.12
2	2890	85.45	2	81.6	2.06
3	3510	103.86	3	85.3	2.17
Glucose 5%: 12.3 mg/dL					
Dilution factor ⁽¹⁾ : 4					
Saponin 1% ⁽²⁾ : 3380 mg/dL					

1. Value not referred to dilution of positive controls

2. Dilution factor for positive controls: 2

Table 2 Results of haemoglobin leakage in Beagle Dog Blood treated with positive (Saponin 1% w/v) and negative (Glucose 5%) controls, Vestipitant and their corresponding Vehicle

Vestipitant (mg/mL) in 4.5%	Haemoglobin Leakage (mg/dL)	Haemoglobin Leakage %	Vestipitant (mg/mL) in 13% w/v	Haemoglobin Leakage (mg/dL)	Haemoglobin Leakage %
Vehicle	15.8	-0.13	Vehicle	24.9	0.15
0.1	22.2	0.07	0.1	20.9	0.03
0.5	69.9	1.56	0.5	21.6	0.05
1	665	20.16	1	21.8	0.06
2	3040	94.38	2	147	3.97
3	3270	101.56	3	199	5.59
Glucose 5%: 20 mg/dL					
Dilution factor ⁽¹⁾ : 4					
Saponin 1% ⁽²⁾ : 3220 mg/dLt					

1. Value not referred to dilution of positive controls

5 2. Dilution factor for positive controls: 2

Example 2

10 The object of this study was to assess haemolytic potential of vestipitant in human whole blood (n=2 samples/sex) at different infusion rates when formulated at concentration of 2 mg/mL in 10% w/v Captisol™ in 50 mM Acetate Buffer, pH 4.5. Concentrations are expressed in term of the Vestipitant as a free base

The solution at 2 mg/mL and the vehicle were mixed with blood in a proportion that simulates infusion rates of 2.3, 4.5 and 6 mL/min. The haemolytic potential was assessed by measuring haemoglobin leakage on plasma obtained after exposure to test formulations.

15 The results of these experiments, which are illustrated in Tables 3-5, demonstrated that Vestipitant at concentration of 2 mg/mL formulated in 10% w/v Captisol™ in 50 mM Acetate Buffer, pH 4.5 and administered at the infusion rates of 6 mL/min, 4.5 mL/min and 2.3 mL/min., caused no appreciable haemoglobin leakage.

Table 3 Results of Haemoglobin Leakage in Human Blood Treated with negative control (Glucose 5%) vestipitant 2 mg/mL in Captisol™ formulation and its corresponding Vehicle.. Infusion Rate of 2.3 mL/min was simulated

Donor (human blood)	Haemoglobin Leakage (mg/dL)			Haemoglobin Leakage %	
	Glucose 5% Negative control	Vehicle 10% w/v	Vestipitant 2 mg/mL	Vehicle	Vestipitant 2 mg/mL
M1	21.0	21.8	20.4	0.01	-0.01
M2	42.1	50.2	67.6	0.07	0.22
F1	32.5	52.9	61.1	0.17	0.24
F2	15.0	30.7	32.5	0.13	0.15
Dilution factor ¹ : 2.56					
Positive control ² : 11740 mg/dL					

M = male; F = female;

- 5 1. Value not referred to dilution of positive controls
2. Dilution factor for positive controls: 2

Table 4 Results of Haemoglobin Leakage in Human Blood Treated with negative control (Glucose 5%) vestipitant 2 mg/mL in Captisol™ formulation and its corresponding Vehicle.. Infusion Rate of 4.5 mL/min was simulated

Donor (human blood)	Haemoglobin Leakage (mg/dL)			Haemoglobin Leakage %	
	Glucose 5% Negative control	Vehicle	Vestipitant 2 mg/mL	Vehicle	Vestipitant 2 mg/mL
M1	21.7	25.7	12.2	0.03	-0.08
M2	43.1	58.9	22.7	0.13	-0.17
F1	27.3	50.3	47.5	0.20	0.17
F2	14.9	36.7	21.3	0.19	0.05
Dilution factor ¹ : 3.12					
Positive control ² : 11740 mg/dL					

M = male; F = female;

1. Value not referred to dilution of positive controls
2. Dilution factor for positive controls: 2

Table 5 Results of Haemoglobin Leakage in Human Blood Treated with negative control (Glucose 5%) vestipitant 2 mg/mL in Captisol™ formulation and its corresponding Vehicle. Infusion Rate of 6 mL/min was simulated

Donor (human blood)	Haemoglobin Leakage (mg/dL)			Haemoglobin Leakage %	
	Glucose 5% Negative	Vehicle	Vestipitant 2 mg/mL	Vehicle	Vestipitant 2 mg/mL
M1	17.0	16.9	23.6	0.00	0.06
M2	54.4	46.6	34.2	-0.07	-0.17
F1	19.2	42.6	49.7	0.20	0.26
F2	13.1	19.7	15.7	0.06	0.02
Dilution factor¹: 3.52					
Positive control²: 11740 mg/dL					

M = male; F = female;

1. Value not referred to dilution of positive controls
2. Dilution factor for positive controls: 2

Example 3

The object of this study was to assess vestipitant haemolytic potential in human whole blood (n=2 samples/sex) at different time of infusion, when formulated at concentration of 2 mg/mL in 10% w/v Captisol™ in 100 mM Acetate Buffer, pH 4.25.

The solution at 2 mg/mL and the vehicle were mixed with blood in a proportion that simulates infusion rates of 2.3, 4.5 and 6 mL/min. The haemolytic potential was assessed by measuring haemoglobin leakage on plasma obtained after exposure to test formulations.

The results of these experiments, which are illustrated in Tables 6-8, demonstrated that Vestipitant at concentration of 2 mg/mL formulated in 10% w/v Captisol™ in 100 mM Acetate Buffer, pH 4.25 and administered at the infusion rates of 6 mL/min, 4.5 mL/min and 2.3 mL/min., caused no appreciable haemoglobin leakage.

Table 6 Results of Haemoglobin Leakage in Human Blood Treated with Positive (Saponin 10 mg/mL), Negative control (Glucose 5%) vestipitant 2 mg/mL in Captisol™ formulation and its corresponding Vehicle. Infusion Rate of 2.3 mL/min was simulated

Donor (human blood)	Haemoglobin Leakage (g/L)				Haemoglobin	
	Saponin 10 mg/mL Positive Control ²	Glucose 5% Negative control	Vehicle	Vestipitant 2 mg/mL	Vehicle	Vestipitant 2 mg/mL
M1	180	0.256	0.256	1.28	0%	0.57%
M2	100	0.512	0.256	0.256	0%	0%
F1	120	0.00	0.00	0.256	0%	0.21%
F2	120	0.256	0.256	0.256	0%	0%
		Dilution factor ¹ : 2.56				

M = male; F = female;

1. Value not referred to dilution of positive controls
2. Dilution factor for positive controls: 200

Table 7 Results of Haemoglobin Leakage in Human Blood Treated with Positive (Saponin 10 mg/mL), Negative control (Glucose 5%) vestipitant 2 mg/mL in Captisol™ formulation and its corresponding Vehicle. Infusion Rate of 4.5 mL/min was simulated

Donor (human blood)	Haemoglobin Leakage (g/L)				Haemoglobin Leakage %	
	Saponin 10 mg/mL Positive Control ²	Glucose 5% Negative control	Vehicle	Vestipitant 2 mg/mL	Vehicle	Vestipitant 2 mg/mL
M1	180	0.312	0.312	0.624	0%	0.17%
M2	100	0.312	0.312	0.312	0%	0%
F1	120	0.00	0.00	0.312	0%	0.26%
F2	120	0.312	0.312	0.312	0%	0%
Dilution factor ¹ : 3.12						

M = male; F = female;

3. Value not referred to dilution of positive controls
4. Dilution factor for positive controls: 200

Table 8 Results of Haemoglobin Leakage in Human Blood Treated with Positive (Saponin 10 mg/mL), Negative control (Glucose 5%) vestipitant 2 mg/mL in Captisol™ formulation and its corresponding Vehicle. Infusion Rate of 6 mL/min was simulated

Donor (human blood)	Haemoglobin Leakage (g/L)				Haemoglobin Leakage %	
	Saponin 10 mg/mL Positive Control ²	Glucose 5% Negative control	Vehicle	Vestipitant 2 mg/mL	Vehicle	Vestipi tant 2 mg/ mL
M1	180	0.352	0.352	0.704	0%	0.20%
M2	100	0.352	0.352	0.704	0%	0.35%
F1	120	0.00	0.00	0.352	0%	0.29%
F2	120	0.352	0.352	0.352	0%	0%
Dilution factor ¹ : 3.52						

M = male; F = female;

5. Value not referred to dilution of positive controls
6. Dilution factor for positive controls: 200

In Vivo Studies

Example 4

The purpose of this study was to assess any potential local irritancy and haemolytic effects of vestipitant methanesulphonate dissolved in Captisol™ and a formulation containing Vestipitant dissolved in acetate buffer pH4.5 and mannitol when administered by intravenous injection in the dog (bolus).

Groups of beagle dogs (3/male/group) were given 2 mg/mL of vestipitant in acetate buffer pH4.5 (0.05M) and 4.5% v/v mannitol or 13% w/v sulfobutylether-7-beta-cyclodextrin sodium(SBE7-beta-CD) also known as Captisol™ in 0.05M acetate buffer, pH 4.5 at the same dose volume (10 mL/dog) by intravenous bolus injection.

Vestipitant was administered as intravenous bolus injection (the whole volume was administered over 30 seconds $\pm$ 5) using the right cephalic vein. Vehicle was previously administered by intravenous injection using the left cephalic vein. At least 30 minutes were allowed between the two injections. An additional 10 mL of saline was injected following dose administration only in group 5 treated with vestipitant dissolved in acetate buffer pH 4.5 (0.05M) in 4.5% v/v mannitol.

There were no differences in macroscopic and microscopic changes following to the injection of 2mg/mL vestipitant dissolved in 13% w/v sulfobutylether-7-beta-cyclodextrin, sodium (SBE7-beta-CD) also known as Captisol™ when compared to administration of Captisol™ alone.

Following injection of 2mg/mL vestipitant dissolved in acetate buffer pH 4.5 (0.05M) in 4.5% v/v mannitol and diluted with 50% dextrose, macroscopic and microscopic findings were seen at the injection sites (right cephalic veins) in all animals treated when compared to vehicle alone. These consisted of occluding thrombi with degeneration/regeneration (minimal to mild) of the vein wall. Perivascular mixed inflammatory cell infiltrate (minimal to mild), and oedema (minimal) of the subcutis were also present. These findings accounted for macroscopic observation of dark thickening of the vein and gelatinous appearance of the surrounding tissue.

Clinical Study

Example 5

The safety, tolerability and pharmacokinetics of the formulation of Example 6 was assessed in a phase I study in healthy human subjects.

This study was a single-blind, randomized, placebo-controlled, and dose escalation study. A single intravenous infusion was administered to each subject. Eight subjects were enrolled at each dose level, to ensure that approximately six subjects were randomized to receive vestipitant (2 mg/mL) Captisol™ formulation of Example 4 and two subjects were randomized to receive placebo(0.9% w/v sodium chloride solution). Subjects took part in only one cohort. A total of 41 subjects were dosed with Example 4.

The initial dose was a single intravenous dose of 12 mg vestipitant infused over 2 min. Subsequent dose levels were 18 mg and 24 mg, also infused over 2 min, followed by 24 mg infused over 1 minute and 24mg, 36mg and 48mg doses each administered over 30 seconds.

Specific laboratory studies to evaluate haemolysis were investigated, including haptoglobin, potassium, lactate dehydrogenase, phosphate, total and direct bilirubin, erythrocyte count, hemoglobin, hematocrit, reticulocyte count, peripheral blood smear, and urine hemosiderin. There

were no laboratory indications of haemolysis at any dose tested; there was no difference between any vestipitant dose and placebo with any of these laboratory parameters.

This study indicated that the formulation of vestipitant showed no laboratory evidence of haemolysis, even at high doses, further indicating that the addition of Captisol™ was able to prevent localized haemolysis and tolerability issues observed with previous formulations in animal studies.

The following are examples of pharmaceutical formulations of the present invention. They are intended to illustrate particular embodiments of the invention and are not intended to limit the specification and the claims in any manner.

Examples of pharmaceutical formulations according to the present invention.

Example 6

The vials were washed, rinsed with water for injection and sterilized by dry heat. The stoppers were washed and sterilized in an autoclave.

A portion of water for injection was added into the manufacturing vessel. While stirring, Vestipitant methanesulfonate was added to the water. Once the it was completely dissolved, the glacial acetic acid, sodium acetate trihydrate and Captisol™ were added with stirring, adding each component only when the previous has completely dissolved.

The solution was diluted to the final volume with the remaining portion of water for injection. The final solution is stirred.

The solution is aseptically filtered through two sterile filters (0.22 µm), filled into 17 mL vial and sealed with rubber stoppers. An overseal is placed on each vial and crimped.

Component	Quantity (mg/vial)
Vestipitant methanesulphonate*	21.53
β-Cyclodextrin sulfobutyl ether, sodium Captisol™	900.00
Sodium acetate trihydrate	45.00
Glacial acetic acid	37.80
Water for Injection	qs to 9 mL
Nitrogen	-

*Quantity equals to 2mg/ml as Vesipitant free base

Example 7

The vehicle without Vestipitant methanesulfonate was first prepared by adding a portion of water for injection, the glacial acetic acid, sodium acetate trihydrate and Captisol™ into the manufacturing vessel. A portion of the vehicle solution was added into the manufacturing vessel. Vestipitant methanesulfonate was added to the vehicle solution The solution was diluted

to the final volume with the remaining portion of water for injection. The final solution was stirred.

Component	Quantity (mg/ml)
Vestipitant methanesulphonate)	2.39
β -Cyclodextrin sulfobutyl ether, sodium Captisol™	100.00
Sodium acetate trihydrate	2.45
Glacial acetic acid	2.1
Water for Injection	qs to 1 mL

Example 8

- 5 The vehicle without Vestipitant methansulfonate was first prepared by adding a portion of water for injection, the glacial acetic acid, sodium acetate trihydrate and Captisol™ into the manufacturing vessel. A portion of the vehicle solution was added into the manufacturing vessel. Vestipitant methanesulfonate was added to the vehicle solution. The solution was diluted to the final volume with the remaining portion of vehicle solution.

Component	Quantity (mg/mL)
Vestipitant methanesulphonate	2.39
β -Cyclodextrin sulfobutyl ether, sodium Captisol™	80.00
Sodium acetate trihydrate	2.45
Glacial acetic acid	2.1
Water for Injection	qs to 1 mL

10

Example 9

- The vehicle without Vestipitant methanesulfonate was first prepared by adding a portion of water for injection into the manufacturing vessel. While stirring, Captisol™, sodium acetate trihydrate and the glacial acetic acid, were added with stirring, adding each component only when the previous has completely dissolved. The vehicle solution was diluted to the final volume with the remaining portion of water for injection. The vehicle was stored for further use.

15

A portion of the vehicle solution was added into the manufacturing vessel. Vestipitant methanesulfonate was added to the vehicle solution. The solution was sonicated until all

Vestipitant methanesulfonate had dissolved. The solution was diluted to the final volume with the remaining portion of vehicle solution. The final solution was stirred and aseptically filtered through a sterile filter (0.22 μm).

Component	Quantity (mg/mL)
Vestipitant methanesulphonate	2.39
β -Cyclodextrin sulfobutyl ether, sodium Captisol™	130.00
Sodium acetate trihydrate	2.45
Glacial acetic acid	2.1
Water for Injection	qs to 1 mL

CLAIMS

1. An intravenous (IV) aqueous pharmaceutical formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide
5 or a pharmaceutically acceptable salt thereof and at least one cyclodextrin.
2. A formulation according to claim 1, wherein the pharmaceutically acceptable salt is methanesulphonate.
- 10 3. A formulation according to claims 1, wherein 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide as a free base is present in a concentration from 1 to 3 mg/ml.
- 15 4. A formulation according to any of claims 1 to 3, wherein the cyclodextrin is selected from the group consisting of α , β , or γ cyclodextrins .
5. A formulation according to claim 4, wherein the cyclodextrin is a β cyclodextrin.
- 20 6. A formulation according to claim 5, wherein the cyclodextrin is β cyclodextrin sulfobutyl ether, sodium (Captisol™).
7. A formulation according to any of the claims 1 to 6, wherein the cyclodextrin is present in an amount from 5% to 15% (w/v).
- 25 8. A formulation according to any of the claims 1 to 7, which further comprises a buffering agent.
9. A formulation according to claim 8, wherein the buffering agent is acetic acid/ alkali metal acetate.
- 30 10. A formulation according to any of the claims 1 to 9, having a pH in the range from 4 to 5.
11. Use of an intravenous (IV) aqueous pharmaceutical formulation according to any of the claims 1 to 10, in the manufacture of a medicament for the treatment of emesis, such as post operative nausea and vomiting, or sleep disorders.
- 35 12. A formulation according to any of the claims 1 to 10, for use in the treatment of emesis, such as post operative nausea and vomiting, or sleep disorders.
- 40 13. A process for preparing a formulation according to any of the claims from 1 to 10, which process comprises dissolving 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof and at least one cyclodextrin in an aqueous solution for intravenous administration.

14. A process according to claim 13, which comprises dissolving glacial acetic acid, sodium acetate to an aqueous solution for intravenous administration of the compound (I) in the form of a methanesulphonate salt, followed by the addition of Captisol™.
- 5 15. A method of treatment of emesis, such as post operative nausea and vomiting, or sleep disorders, which method comprises intravenously administering to a human patient in need thereof an effective amount of an aqueous formulation according to any of the claims 1 to 10.
- 10 16. A method of reducing haemolysis activity of 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof, comprising adding at least one cyclodextrin to a formulation comprising 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a pharmaceutically acceptable salt thereof.
- 15 17. Use of an aqueous pharmaceutical formulation for intravenous (IV) administration according to any of the claims from 1 to 10, in the manufacture of a medicament for the treatment of emesis wherein the formulation delivers from 6 to 36 mg of 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide as free base by intravenous administration over a period of time from 30 seconds to 2 minutes.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/061550

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K31/496 A61K47/48	A61K47/40 A61K9/00 A61P1/08 A61P25/20
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 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) EPO-Internal, BIOSIS, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DI FABIO ROMANO ET AL: "Discovery Process and Pharmacological Characterization of 2-(S)-(4-Fluoro-2-methylphenyl)piperazine-1-carboxylic Acid [1-(R)-(3,5-Bis-trifluoromethylphenyl)ethyl]methylamide (Vestipitant) as a Potent, Selective, and Orally Active NK1 Receptor Antagonist", JOURNAL OF MEDICINAL CHEMISTRY, vol. 52, no. 10, May 2009 (2009-05), pages 3238-3247, XP002682278, ISSN: 0022-2623 figure Scheme 3 page 3242, column 2, line 26 - line 39 page 3246, column 1, line 54 - line 63 ----- -/-	1-17
☒ 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 "E" earlier application or patent but published on or after the international filing date "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) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "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 "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 24 August 2012		Date of mailing of the international search report 12/09/2012
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 Giró, Annalisa

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/061550

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BROCCO M ET AL: "Cellular and behavioural profile of the novel, selective neurokinin1 receptor antagonist, vestipitant: A comparison to other agents", EUROPEAN NEUROPSYCHOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, AMSTERDAM, NL, vol. 18, no. 10, 1 October 2008 (2008-10-01), pages 729-750, XP023980739, ISSN: 0924-977X, DOI: 10.1016/J.EURONEURO.2008.06.002 [retrieved on 2008-07-26] paragraph [2.6.] paragraph [2.18.] tables 2-5	1-17
Y	----- WO 2004/091624 A1 (GLAXO GROUP LTD [GB]; MELOTTO SERGIO [IT]; CORSI MAURO [IT]; CARLETTI) 28 October 2004 (2004-10-28) page 1, line 3 - line 21 page 13, line 4 - line 14 -----	1-17
Y	KONO K ET AL: "Injectable soln. having reduced haemolytic activity - contg. benzyl alcohol as pain-killer, and cyclodextrin as activity, reducer", WPI / THOMSON, 30 January 1982 (1982-01-30), XP002449438, abstract -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/061550

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004091624	A1	28-10-2004	
		AU 2004229179 A1	28-10-2004
		AU 2004229181 A1	28-10-2004
		BR PI0409377 A	25-04-2006
		BR PI0409379 A	25-04-2006
		CA 2522311 A1	28-10-2004
		CA 2522313 A1	28-10-2004
		CN 1809355 A	26-07-2006
		CN 1809359 A	26-07-2006
		CO 5700753 A2	30-11-2006
		EP 1613325 A1	11-01-2006
		EP 1615641 A1	18-01-2006
		EP 1615642 A1	18-01-2006
		EP 1653956 A1	10-05-2006
		IS 8128 A	15-11-2005
		IS 8129 A	15-11-2005
		JP 2006523649 A	19-10-2006
		JP 2006523650 A	19-10-2006
		JP 2006523651 A	19-10-2006
		JP 2006523652 A	19-10-2006
		KR 20060003875 A	11-01-2006
		KR 20060003876 A	11-01-2006
		MA 27730 A1	02-01-2006
		MA 27731 A1	02-01-2006
		MX PA05011063 A	12-12-2005
		MX PA05011064 A	18-04-2006
		US 2006217395 A1	28-09-2006
		US 2006241124 A1	26-10-2006
		US 2006241143 A1	26-10-2006
		US 2006287325 A1	21-12-2006
		WO 2004091615 A1	28-10-2004
		WO 2004091616 A1	28-10-2004
		WO 2004091617 A1	28-10-2004
		WO 2004091624 A1	28-10-2004
		ZA 200508067 A	28-02-2007
		ZA 200508068 A	28-02-2007