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(73) Patenthaver: **Le Vet B.V., Wilgenweg 7, 3421 TV Oudewater, Holland**

(72) Opfinder: **BOEREN, Marinus Maria Martinus, c/o Le Vet. B.V., Wilgenweg 7, 3421 TV OUDEWATER, Holland**
PARIDAANS, Rudolf Johannes, c/o Le Vet. B.V., Wilgenweg 7, 3421 TV OUDEWATER, Holland

(74) Fuldmægtig i Danmark: **Valet Patent Services LLP, Siedlungsstr. 4a, 85253 Erdweg, Tyskland**

(54) Benævnelse: **FORMULARING AF MAROPITANT**

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DESCRIPTION

[0001] The present invention relates to a pharmaceutical composition comprising maropitant, a method for preparing the composition, the use of the composition as a medicament, and the use of the composition in the treatment of emesis in mammals, in particular cats and dogs.

[0002] Maropitant, a substituted quinuclidine having the chemical name (2S,3S)-(Diphenylmethyl)-N-[2-methoxy-5-(2-methyl-2-propanyl)benzyl]quinuclidin-3-amine, the systematic (IUPAC) name being (2S,3S)-*N*-(5-*tert*-Butyl-2-methoxybenzyl)-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-amine, is a neurokinin (NK1) receptor antagonist that blocks the pharmacological action of substance P in the central nervous system (CNS). Maropitant is used in the prevention and treatment of vomiting in dogs and the treatment of vomiting in cats.

[0003] WO 2005/082416 describes the development of a pharmaceutical formulation of maropitant citrate, sulfobutyl ether β-cyclodextrin and meta-cresol. WO 2005/082416 shows that meta-cresol was the only preservative tested that was also stable on storage and had an acceptable injection site tolerance. Other preservatives such as benzoic acid, ethanol, propylene glycol and the combination of 0.5 % chlorobutanol and 0.5 % phenylethanol, were all shown to have poor injection site tolerance.

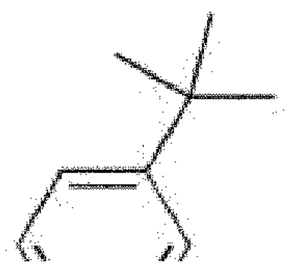
[0004] Although meta-cresol was identified as being the most suitable preservative by the inventors of WO 2005/082416, studies have since shown that injection of a pharmaceutical formulation of maropitant citrate, sulfobutyl ether β-cyclodextrin and meta-cresol leads to pain and adverse reactions in animal subjects, in particular cats. For example, pain on injection of maropitant citrate, sulfobutyl ether β-cyclodextrin and meta-cresol was observed in 75% of cats injected with 3 and 5 mg/kg, whereas in the control group injected placebo (saline) only 5% of cats registered a pain response.

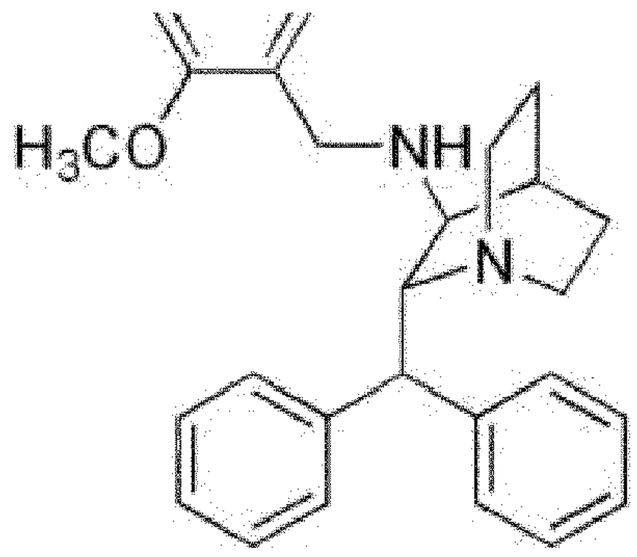
[0005] There is therefore a need for an injectable solution of maropitant which causes less pain on injection.

[0006] It is an object of the present invention to provide an injectable maropitant composition that has an improved injection site tolerance.

[0007] The object of the present invention is solved by a pharmaceutical composition comprising, or being:
an aqueous solution of:

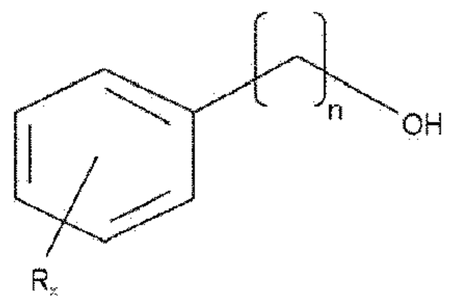
1. a) maropitant citrate, the maropitant having the structural formula I:





Formula I

2. b) a acceptable β-cyclodextrin,
3. c) 7 - 18 mg/ml of phenylmethanol which is a pharmaceutically acceptable preservative according to formula II:



Formula II

wherein R_x is selected from the group of consisting of hydrogen, C_1-C_5 hydrocarbyl, heteroatom or halogen substituted C_1-C_5 hydrocarbyl, halogens and heteroatoms, x being an integer between 1 and 5, n being an integer between 1 and 4.

[0008] The inventors have found that injectable compositions according to the invention comprising phenylmethanol do not cause pain on injection in cats and dogs, in other words have an excellent injection site tolerance. Furthermore, phenylmethanol has antimicrobial effects when included in a composition comprising maropitant citrate and a pharmaceutically acceptable β-cyclodextrin.

[0009] The term "pharmaceutically acceptable" means that the substance or composition must be compatible chemically and toxicologically with the other ingredients of the composition and with the mammal being treated therewith.

[0010] By "injection site tolerance" is meant that when the composition according to the invention is injected into a subject, for example a cat, a low pain response is observed. Typically, pain response is determined by observing behavioural changes of the subject for example scratching, hissing, whining, startled look, flight response, desire to hide.

[0011] The pain score associated with the injection of a composition according to the present invention in cats leads to a modal score of 1 on a five-point pain scale (with a score of 1 indicating minimal or no pain response and a score of 5 indicating a severe pain response was observed). This is a considerable improvement over the commercially available composition of maropitant citrate (monohydrate), sulfobutyl ether β-cyclodextrin and meta-cresol which gives a modal score of 3 on the pain scale.

[0012] The inventors have, for the first time, been able to identify the cause of the pain response in the commercially used maropitant injectable formulations and have identified a composition which does not lead to pain on injection. The excellent acceptance of the injectable formulation according to the invention is surprising in light of the knowledge that in rats subcutaneous injection of benzyl alcohol leads to inflammatory responses (p.180, Water-insoluble Drug Formulation, 2nd Ed., Lui, Rong, CRC Press, Boca Raton, 2008). The inventors observe that, when phenylmethanol is used as preservative, a surprising lack of inflammatory and pain responses are observed on injection in cats and dogs, in particular when used in the claimed concentration of 7 - 18 mg/ml.

[0013] The inventors have found that inclusion of 7 - 18 mg/ml phenylmethanol as pharmaceutically acceptable preservative, results in the desired level of antimicrobial effects according to the requirements of Ph. Eur. A criteria and Ph. Eur. B criteria. Not only are the antimicrobial effects acceptable but the compositions of the present invention also have an acceptable and improved injection site tolerance.

[0014] In an attractive embodiment, the pharmaceutically acceptable preservative is free of chlorobutanol, preferably free of chlorinated compounds. Most preferably, the aqueous solution is free of chlorinated organic compounds, as such compounds would reduce the injection site tolerance. The inventors have found that by using at least 7 - 18 mg/ml phenylmethanol as pharmaceutically acceptable preservative, it is not necessary to include chlorobutanol to achieve the desired antimicrobial effects. Moreover, compositions according to the present invention show an improved injection site tolerance compared to compositions of the prior art which comprise chlorobutanol.

[0015] In an attractive embodiment, the pharmaceutically acceptable preservative is present at a concentration of 7-15 mg/ml, preferably 7-13 mg/ml, more preferably 8-12 mg/ml, even more preferably 9-11 mg/ml or even at about 10 mg/ml. The term 'about' means that 5% more or less is allowed, i.e. defining a range of 9.5-10.5 mg/ml. More preferably, the term 'about' means that 3% more or less is allowed, most preferably 1% or even 0%. Surprisingly, it has been found that concentrations of the pharmaceutically acceptable preservative of 10 mg/ml, and even up to 15 or even 17 or 18 mg/ml pharmaceutically acceptable preservative provides for the desirable osmolality, whilst showing good injection site tolerance.

[0016] It has been found that phenylmethanol which has a short hydrocarbyl group between the phenyl group and hydroxyl group is advantageous as a particularly low pain score in observed on injection into cats and dogs.

[0017] Pharmaceutically acceptable preservative being selected from the group consisting of phenylmethanol, 2-phenylethanol, 3-phenyl-1-propanol and 4-phenyl-1-butanol provide a composition that has a much better injection site tolerance than commercially available injectable maropitant compositions.

[0018] A particularly acceptable injection site tolerance is achieved by using a composition according to the invention comprising phenylmethanol. When the antimicrobial preservative is phenylmethanol, a pain score of 1 is observed, compared to a pain score of 3 using a commercially available composition comprising meta-cresol.

[0019] In another embodiment, the composition comprises 8-12 mg/ml maropitant, as calculated by the weight of the free base. In case a maropitant salt is used, the higher molecular weight of the salt should be corrected for. This would e.g. mean that a 8 mg/ml maropitant solution can be obtained by dissolving 8 mg maropitant free base (having a molecular weight of 469 g/mol) per ml of water, or e.g. 11.6 g maropitant citrate monohydrate (having a molecular weight of 679 g/mol). In an attractive embodiment, maropitant citrate is provided by combining 8-12 mg/ml maropitant free base and 2-6 mg/ml citric acid.

[0020] Preferably, maropitant free base is used in combination with a pharmaceutical grade citric acid solution. Alternatively, maropitant can be present as a pharmaceutically acceptable salt, for example citrate.

[0021] In the present application "cyclodextrin" means a compound including cyclic (is 1→4) linked D-glucopyranose units, α-cyclodextrin refers to a cyclodextrin with 6 cyclic, linked D-glucopyranose units, β-cyclodextrin has 7 cyclic, linked D-glucopyranose units, and γ-cyclodextrin has 8 cyclic, linked D-glucopyranose units. The cyclic D-glucopyranose units define a hydrophobic cavity. Due to the conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone rather than perfect cylinders. The hydroxyl functions are orientated to the cone exterior with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. The central cavity is lined by the skeletal carbons and ethereal oxygens of the glucose residues, which gives it a lipophilic character.

[0022] Modifications to cyclodextrins can occur at one or more of the 2, 3 and 6 hydroxyl positions of one or more glucopyranose units. The sulfobutyl ether derivative of β-cyclodextrin (SBE-β-CD) has a range of six to seven sulfobutyl ether groups per cyclodextrin molecule Alternatively the hydroxyl groups can be modified by hydroxypropyl moieties resulting in hydroxylpropyl-β-cycodextrins (HP-β-CD)

[0023] In an embodiment, the pharmaceutically acceptable β-cyclodextrin is sulfobutyl ether β-cyclodextrin sodium or 2-hydroxypropyl β-cyclodextrin, preferably sulfobutyl ether β-cyclodextrin sodium.
It has been found that an acceptable injection site tolerance is observed when either sulfobutyl ether β-cyclodextrin sodium or 2-hydroxypropyl-β-cyclodextrin is used. For example, when the β-cyclodextrin is 2-hydroxypropyl-β-cyclodextrin, the observed modal pain score was 2 when a composition according to the present invention was subcutaneously injected into cats. This is an improvement on the commercially available composition, which has an observed modal pain score of 3.

[0024] It is particularly preferred to use sulfobutyl ether β-cyclodextrin sodium as the pharmaceutically acceptable cyclodextrin in the compositions according to the invention because when this composition was sub-cutaneously injected into cats the observed modal pain score was 1. The inventors have found that the combination of an aqueous solution of maropitant citrate, sulfobutyl ether β-cyclodextrin sodium and benzyl alcohol has a very acceptable injection site tolerance.

[0025] Furthermore the very low pKa of the sulfonic acid groups means that this modified cyclodextrin carries multiple negative charges at physiologically compatible pH values. Sulfobutyl ether β-cyclodextrin sodium is polyanionic in nature, and therefore interacts particularly well with maropitant. In addition, this sulfobutyl ether β-cyclodextrin sodium has exceptional solubility and parenteral safety.

[0026] Without wishing to be bound by theory, it is proposed that the low pain score associated with injection of compositions comprising sulfobutyl ether β-cyclodextrin is due to the osmolality of this composition being close to the physiological osmolality.

[0027] 'Osmolality' is the concentration of a solution expressed as the total number of solute particles per kilogram. According to USP Pharmacists' Pharmacopoeia, Supplement, 2nd Edition, 1st December 2009, section 785, page S5/38, the osmolality of a solution ξm is given by:

$$\xi_m = \Sigma v_i m_i \Phi_{m,i}$$

where v_i is the number of particles formed by the dissociation of one molecule of the i^{lh} solute;

$v_i = 1$ for nonionic (nondissociating) solutes;

mi is the molality of the i^{th} solute; and

$\varphi_{m,i}$ is the molal osmotic coefficient of the i^{th} solute.

[0028] The osmolality of a real solution corresponds to the molality of an ideal solution containing non-dissociating solutes and is expressed in osmoles or milliosmoles per kilogram of solvent (Osmol per kg or mOsmol per kg, respectively), a unit that is similar to the molality of the solution. Thus, osmolality is a measure of the osmotic pressure exerted by a real solution across a semipermeable membrane.

[0029] It has been found that the osmolality of the composition according to the invention is between 290 and 310 mOsmol per kg. The inventors have found that by using 11 mg/ml phenylmethanol as the preservative, a composition having an osmolality of 301 mOsmol per kg is obtained, which is very close to the physiological osmolality (in cats and dogs) which is 300 mOsmol per kg. Similar osmolality values are obtained when using benzyl ethanol within he claimed range.

[0030] The effect of the close matching of the osmolality of the injected solution to that of the physiological osmolality means that the injected solution is effectively isotonic with the conditions of the animal receiving the injection, so that there is minimal physiological response in the said animal.

[0031] In contrast to the composition according to the present invention, the commercially available maropitant citrate monohydrate, sulfobutyl ether β-cyclodextrin and meta-cresol composition has an osmolality of about 214 mOsmol per kg. The inventors propose that this relatively low osmolality compared to the physiological osmolality is the cause of the high pain response in an animal. An osmolality quite significantly lower (i.e., more dilute) than the physiological osmolality will cause the red blood cells to take on extra fluid in an attempt to equilibrate osmolality on either side of the blood cell membrane. If they swell too much, they will burst, spilling their contents into the serum and, at least with the red blood cells, making them unavailable for oxygen transport, and thus causing pain for the recipient of the injection.

[0032] In another embodiment, the pharmaceutically acceptable β-cyclodextrin is present at a concentration of 40 - 80 mg/ml, preferably of 60 - 70 mg/ml. The inventors have found that inclusion of a β-cyclodextrin is essential for the solubility of the maropitant. The optimum concentration range has been found to be 60 - 70 mg/ml.

[0033] In an attractive embodiment, the aqueous solution is free of a co-solvent, such as ethanol, as such co-solvent will reduce the injection site tolerance.

[0034] In a second aspect of the present invention, the invention relates to a pharmaceutical composition for use as a medicament. The inventors have found that the composition according to the invention is clinically useful for the prevention and treatment of motion sickness and emesis in mammals and as an anti-nociceptive in mammals.

[0035] In a preferred embodiment, the pharmaceutical composition according to the invention is used in the treatment of emesis in mammals. In the context of the present invention, mammal includes animals such horse, sheep, goat, pig, cow, dog and cat.

[0036] In a particularly preferred embodiment, the pharmaceutical composition according to the invention for use in the treatment of emesis in cats and dogs. The present invention is particularly suited to the treatment of companion animals, such as cats and dogs.

[0037] In an embodiment, the pharmaceutical composition according to the invention is administered by parenteral injection. The compositions according to the invention are intended for administration as an injection or infusion. For example, the compositions may be administered intravenously (into a vein), subcutaneously (under the skin), and intramuscularly (into muscle). Preferably the compositions according to the present invention are administered subcutaneously. The present invention has the advantage that the composition according to the present invention has leads to a minimal, if any, pain response as observed on the said 5 point pain scale.

[0038] In a third aspect, the present invention relates to a method for preparing a pharmaceutical composition as defined above, comprising the steps of:

1. I) mixing, in an aqueous medium, the medium preferably being water:
    1. i) a source of maropitant,
    2. ii) a source of citrate,
    3. iii) a pharmaceutically acceptable β-cyclodextrin to the mixture, the pharmaceutically acceptable β-cyclodextrin preferably being sulfobutyl ether β-cyclodextrin sodium or 2-hydroxypropyl-β-cyclodextrin, most preferably sulfobutyl ether β-cyclodextrin,
    4. iv) a pharmaceutically acceptable preservative as defined in claim 1, to obtain an aqueous solution,
2. II) if the pH of the aqueous solution is outside the range of 3 - 6, adjusting the pH to between 3 and 6 by adding to the solution a pharmaceutically acceptable acid or base, the pharmaceutically acceptable base preferably being sodium hydroxide or ammonia, most preferably sodium hydroxide, the pharmaceutically acceptable acid preferably being selected from the group consisting of hydrochloric acid, formic acid, acetic acid and citric acid, preferably being citric acid.

[0039] The aqueous medium is preferably water, although any suitable a. The water can comprise additional solubles, that can e.g. be adjuvants in the solution. The skilled person is aware of suitable solubles that can be used in the solution. An aqueous medium can be used, which is preferably free of organic cosolvents.

[0040] Mixing the above compounds will result in dissolution thereof in the medium. The order of addition in the medium is not critical.

[0041] The inventors have found that the maropitant composition of the present invention can easily be prepared by providing an aqueous solution of a source of maropitant, for example as maropitant cations and citrate counter ions, and adding a suitable β-cyclodextrin to complex the maropitant cations and thus improve the solubility of the maropitant cations. Subsequently, the pharmaceutically acceptable preservative is added and the composition pH adjusted by titration with a pharmaceutically acceptable acid or base.

[0042] In an embodiment, the maropitant is provided by maropitant free base or a maropitant salt, said salt preferably being selected from the group consisting of hydrobromide, hydrochloride, hydroiodide, sulphate, acetate, malate, oxalate, lactate, citrate, fumerate, tartrate, mesylate and succinate. The inventors have found that both inorganic, for example hydrobromide, hydrochloride, hydroiodide and sulphate, as well as organic salts, for example acetate, malate, oxalate, lactate, citrate, fumerate, tartrate, mesylate and succinate, are suitable, and preferred, for use in the present invention.

[0043] In the present invention, "citrate anions" means the deprotonated form of 2-hydroxypropane-1,2,3-trioic acid, commonly known as citric acid. Citrate anions can be provided by 2-hydroxypropane-1,2,3-trioic acid or a pharmaceutically acceptable inorganic salt thereof. Suitable inorganic salts are, for example sodium citrate, and potassium citrate. Preferably, the pharmaceutically acceptable citrate source is citric acid as this does not introduce inorganic cations into the composition of the present invention and citric acid provides not only a suitable counter ion but also provides a means of adjusting the pH to the desired value.

[0044] In a preferred embodiment, maropitant is provided by maropitant free base and citrate anions are provided by citric acid. Maropitant free base is only soluble in organic solvents such as DMSO. The inventors have found, however, that an aqueous solution of maropitant can be prepared by addition of citric acid and a β-cyclodextrin. The advantage of this method compared to using maropitant citrate is that maropitant free base is easier to synthesise.

[0045] In an embodiment, the maropitant and citrate are provided together by maropitant citrate. For example, maropitant citrate monohydrate may be used which has a molecular weight of 678.81 and a theoretical potency based on the active ingredient of 690 mg/g.

[0046] In another embodiment, the pharmaceutically acceptable β-cyclodextrin is sulfobutyl ether 3-cyclodextrin sodium or 2-hydroxypropyl-β-cyclodextrin, preferably sulfobutyl ether β-cyclodextrin. It has been found that sulfobutyl ether β-cyclodextrin is particularly preferred due to the improved solubility of maropitant in the presence of sulfobutyl ether β-cyclodextrin.

[0047] In yet another disclosure, the pharmaceutically acceptable preservative is selected from the group consisting of phenylmethanol, 2-phenylethanol, 3-phenyl-1-propanol and 4-phenyl-1-butanol preferably phenylmethanol. The inventors have found that when phenylmethanol is included in the composition according to the present invention, a particularly good injection site tolerance is observed.

[0048] In an embodiment, the pharmaceutically acceptable base is sodium hydroxide or ammonia, preferably sodium hydroxide. It has been found that there are no adverse side effects when sodium hydroxide is included in the composition according to the present invention.

[0049] In an embodiment, the pharmaceutically acceptable acid is selected from the group consisting of hydrochloric acid, formic acid, acetic acid and citric acid, preferably being citric acid. It has been found that in order to bring the composition to the desirable pH of between 3 and 6, both inorganic acid, for example hydrochloric acid, or organic acids, for example formic acid, acetic acid and citric acid, can be used. Preferably, citric acid is used as this also provides a source of citrate anions, which is the preferred anion in order to achieve the desired injection site tolerance.

The invention will now be illustrated by the following non-limiting examples.

Examples

Materials

[0050] Maropitant (free base) was synthesised according to WO 1990005729 A1. Sulfobutyl ether β-cyclodextrin sodium was obtained from Fraupharma (Italy). 2-Hydroxypropyl β-cyclodextrin was obtained from Roquette (France). Phenylmethanol (benzyl alcohol) is obtained from Merck catalogue number 1.00981, 2-phenylethanol, was obtained from Merck, catalogue number 8.07006 and used without any further purification. Methyl parahydroxybenzoate and propyl parahydroxybenzoate were obtained from Merck, catalogue numbers 1.06757 and 1.07427 respectively.

Preparation of formulations

Formulations A1 - A4:

[0051] 10 mg/ml maropitant free base, 4.1 mg/ml citric acid and cyclodextrin and preservatives as shown in table 1. Formulations were titrated with sodium hydroxide and citric acid to obtain the optimum pH 4.2.

Table 1: Antimicrobial testing of Maropitant formulations A1-A4

Example	Cyclodextrin	Preservative	Ph. Eur. A criteria	Ph. Eur. B criteria
A1	63 mg/ml SEB	10 mg/ml phenylmethanol	Complies	Complies
A2	63 mg/ml SEB	1 mg/ml methyl parahyd roxybenzoate 0.1 mg/ml propyl parahyd roxybenzoate	Does not comply	Does not comply
A3	63 mg/ml SEB	11 mg/ml phenylmethanol	Complies	Complies
A4	45 mg/ml HP	10 mg/ml phenylmethanol	Complies	Complies

SEB = sulfobutyl ether β-cydodextrin sodium
HP = 2-Hydroxypropyl β-cyclodextrin

[0052] Antimicrobial efficacy was tested according to European Pharmacopoeia 8.0 chapter 5.1.3, 01/2011:50103. Briefly, the test consists of challenging the formulation with a prescribed inoculum of suitable micro-organisms, storing in inoculated formulation at a prescribed

temperature, withdrawing a sample of the formulation at specified time intervals and counting the organisms in the samples so removed. The acceptance criteria for the injectable formulations tested correspond to those of Table 5.1.3.1 of Eu. Pharm. 8.0.

Osmolality

[0053] Osmolality was measured according European Pharmacopoeia 8.0 01/2012 (Eu. Pharm 8.0), chapter 2.2.35. Briefly, reference solutions according to Table 2.2.35-1 of Eu. Pharm 8.0 were prepared. The zero of the apparatus was determined using water. The apparatus was calibrated using the reference solutions. Before testing each sample, the measurement cell was rinsed with the sample to be tested, see table 2.

Table 2: Osmolality of formulations A1 - 4

Example	Osmality / mOsm/kg
A1	274
A2	42
A3	301
A4	122

Example 5

Injection site tolerance

[0054] The formulations given in table 1 were assessed for injection site tolerance as follows. 10 Cats were injected with a formulation according to the following tables 3 - 5. The injection site tolerance was scored on a scale of 1 - 5, where 1 indicates a minimal pain response was observed and 5 indicates severe pain response was observed.

Table 3: Injection site tolerance of commercially available Cerenia® which contains maropitant citrate, sulfobutyl ether β-cyclodextrin sodium & metacresol

Cerenia	Weight (kg)	Volume of injected fluid(ml)	Scoring (1-2-3-4-5)
Cat 1	3,3	0,2	1
Cat 2	5	0,5	3
Cat 3	3,5	0,2	3
Cat 4	3	0,2	3
Cat 5	2,8	0,2	1
Cat 6	6	0,4	3

Cerenia	Weight (kg)	Volume of injected fluid(ml)	Scoring (1-2-3-4-5)
Cat 7	2,6	0,2	4
Cat 8	4	0,2	2
Cat 9	4	0,2	2
Cat 10	3,5	0,2	2
MEAN SCORE			2.4
MODE SCORE			3

Table 4: Injection site tolerance of test formulation A4 (10 mg/ml maropitant free base, 4.1 mg/ml citric acid, 45 mg/ml 2-Hydroxypropyl β-cyclodextrin, 10 mg/ml phenylmethanol)

Test formulation 1	Weight (kg)	Volume of injected fluid(ml)	Scoring (1-2-3-4-5)
Cat 1	2,5	0,15	1
Cat 2	2,5	0,15	2
Cat 3	2,7	0,15	2
Cat 4	4	0,2	2
Cat 5	3	0,15	1
Cat 6	2,9	0,15	2
Cat 7	3	0,15	2
Cat 8	4,9	0,25	1
Cat 9	3	0,15	3
Cat 10	2,6	0,13	1
MEANS SCORE			1.6
MODE SCORE			2

Table 5: Injection site tolerance of test formulation A1 (10 mg/ml maropitant free base, 4.1 mg/ml citric acid, 63 mg/ml sulfobutyl ether β-cyclodextrin sodium, 10 mg/ml phenylmethanol)

Test formulation 2	Weight (kg)	Amount injected fluid (ml)	Scoring (1-2-3-4-5)
Cat 1	3,5	0,2	1
Cat 2	5,5	0,24	1
Cat 3	4,0	0,2	1
Cat 4	3,5	0,17	1
Cat 5	3	0,15	2
Cat 6	2,9	0,15	1
Cat 7	3,0	0,15	1
Cat 8	3,15	0,15	1
Cat 9	2,8	0,14	1

Test formulation 2	Weight (kg)	Amount injected fluid (ml)	Scoring (1-2-3-4-5)
Cat 10	3	0,15	3
Cat 11	2,5	0,12	1
MEAN SCORE			1.2
MODE SCORE			1

[0055] The results show that formulations containing phenylmethanol have a much better injection site tolerance than the commercially available Cerenia. Injection of a formulation comprising 2-hydroxypropyl β-cyclodextrin and phenymethanol (test formulation A4) led to a one point decrease in pain score, with the mode being a score of 2 compared to 3.

[0056] Injection of a formulation comprising sulfobutyl ether β-cyclodextrin and phenylmethanol (test formulation A1) instead of sulfobutyl ether β-cyclodextrin and meta-cresol (Cerenia - control) led to a surprising 2 point decrease in pain score, with a mode of 1 compared to 3. Clearly, phenylmethanol provides an injectable composition with improved injection site tolerance compared to the commercially used meta-cresol.

Example 6

[0057] Testing of different maropitant citrate formulations. 10 mg/ml maropitant free base corresponds to the same maropitant content as 14.5 mg/ml maropitant citrate monohydrate. Similarly, 4.1 mg/ml citric acid corresponds, in terms of citrate anions, to 4.6 mg/ml sodium citrate.

Formulation series A:

[0058] 10 mg/ml maropitant free base, 4.1 mg/ml citric acid, 63 mg/ml sulfobutyl ether β-cyclodextrin and preservatives as shown in table 6.

Formulation series B:

[0059] 14.5 mg/ml maropitant citrate monohydrate, 63 mg/ml sulfobutyl ether β-cyclodextrin and preservatives as shown in table 6.

Formulation series C

[0060] 10 mg/ml maropitant free base, 4.6 mg/ml sodium citrate, 63 mg/ml sulfobutyl ether β-cyclodextrin, and preservatives as shown in table 6, adjusted to pH 4.4 using hydrochloric acid and sodium hydroxide.

Table 6: Testing of maropitant formulations A, B and C and antimicrobial preservatives

Example	Maropitant formulation	Antimicrobial preservative	Injection site tolerance
5.1	A	10 mg / ml Phenylmethanol	1
5.2		10 mg / ml Phenyl ethanol	2
5.3		4.1 mg/ml Meta-cresol	3
5.4	B	10 mg / ml Phenylmethanol	1
5.5		10 mg / ml Phenyl ethanol	2
5.6		4.1 mg/ml Meta-cresol	3
5.7	C	10 mg / ml Phenylmethanol	1
5.8		10 mg / ml Phenyl ethanol	2
5.9		4.1 mg/ml Meta-cresol	3

As can be seen, an acceptable injection site tolerance (1) is obtained when maropitant citrate is provided by either maropitant free base and citric acid (A), maropitant citrate (B) or maropitant free base and sodium citrate (C). The component effecting injection site tolerance is the antimicrobial preservative. When meta-cresol is used a poor injection site tolerance is obtained (3), whereas phenylethanol and phenylmethanol have good (2) and very good (1) tolerances respectively. When 1 mg/ml methyl parahydroxybenzoate together with 0.1 mg/ml propyl parahydroxybenzoate was used as preservative (not shown) the desired level of antimicrobial efficacy was not obtained.

[0061] The results show that compounds corresponding to general Formula II, exhibit the desired injection site tolerance and antimicrobial efficacy, whereas those compounds not falling within the scope of general Formula II, do not show the desired injection site tolerance and antimicrobial efficacy.

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- WO2005082416A [0003] [0003] [0004]
- WO1990005729A1 [0050]

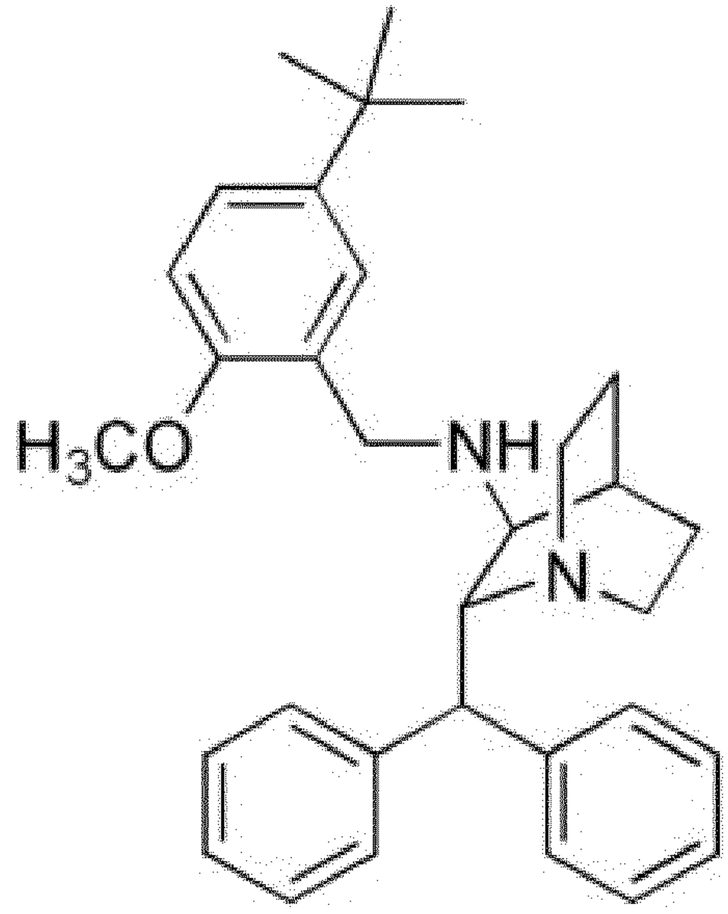
Non-patent literature cited in the description

- **LUI, RONG**Water-insoluble Drug FormulationCRC Press20080000180- [0012]
- Pharmacopoeia200912015-38- [0027]

Krav:

1. Farmaceutisk sammensætning omfattende: en vandig opløsning af:

a) maropitantcitrat, hvor maropitant har strukturformlen I:



Formula I

b) et farmaceutisk acceptabelt β-cyclodextrin,
c) 7-18 mg/ml phenylmethanol.

2. Den farmaceutiske sammensætning ifølge krav 1, hvor det farmaceutisk acceptable konserveringsmiddel er til stede i en koncentration på 8-12 mg/ml, fortrinsvis 9-11 mg/ml, mest foretrukket omkring 10 mg/ml.

3. Den farmaceutiske sammensætning ifølge et hvilket som helst af de foregående krav, hvor konserveringsmidlet er fri for chlorbutanol, fortrinsvis fri for klorerede forbindelser, mest foretrukket er den vandige opløsning fri for klorerede organiske forbindelser.

4. Den farmaceutiske sammensætning ifølge et hvilket som helst af de foregående krav, omfattende 8-12 mg/ml maropitant, beregnet ved vægten af den frie maropitant base.

5. Den farmaceutiske sammensætning ifølge et hvilket som helst af de foregående krav, omfattende 40-80, fortrinsvis 60-70 mg/ml af det farmaceutisk acceptable β-cyclodextrin.

6. Den farmaceutiske sammensætning ifølge et hvilket som helst af de foregående krav, hvor det farmaceutisk acceptable β-cyclodextrin er natrium sulfobutylether-cyclodextrin eller 2-hydroxypropyl-β-cyclodextrin, fortrinsvis sulfobutylether β-cyclodextrin.

7. Den farmaceutiske sammensætning ifølge et hvilket som helst af de foregående krav, hvor opløsningens osmolaritet er mellem 290 og 310 mOsm/kg.

8. Den farmaceutiske sammensætning ifølge et hvilket som helst af de foregående krav, der har en pH på 3-6.

9. Den farmaceutiske sammensætning ifølge et hvilket som helst af de foregående krav til anvendelse som et medikament.

10. Den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 1-8, til anvendelse til behandling og forebyggelse af emesis hos pattedyr, især katte og hunde.

11. Den farmaceutiske sammensætning til anvendelse ifølge krav 9 eller 10, hvor sammensætningen administreres ved parenteral injektion.

12. Fremgangsmåde til fremstilling af et farmaceutisk præparat ifølge et hvilket som helst af kravene 1-8, som omfatter trinnene:

I) blanding i et vandigt medium, idet mediet fortrinsvis er vand:

i) en mængde af maropitant,
ii) en mængde af citrat,
iii) et farmaceutisk acceptabelt β-cyclodextrin til blandingen, hvor det farmaceutisk acceptable β-cyclo-dextrin fortrinsvis er natrium sulfobutylether-cyclodextrin eller 2-hydroxypropyl-β-cyclodextrin, mest foretrukket sulfobutylether β-cyclodextrin,
iv) et farmaceutisk acceptabelt konserveringsmiddel som defineret i krav 1 til opnåelse af en vandig opløsning,

II) hvis pH i den vandige opløsning er uden for området 3-6, justeres pH til mellem 3 og 6 ved tilsætning til opløsningen af en farmaceutisk acceptabel syre eller base, hvor den farmaceutisk acceptable base fortrinsvis er natriumhydroxid eller ammoniak, mest foretrukket natriumhydroxid, hvor den farmaceutisk acceptable syre fortrinsvis vælges fra gruppen bestående af saltsyre, myresyre, eddikesyre og citronsyre, fortrinsvis citronsyre.

13. Fremgangsmåden ifølge krav 12, hvor mængden af maropitant er valgt fra gruppen bestående af maropitant fri base eller et maropitant salt, hvor saltet

fortrinsvis er valgt fra gruppen bestående af hydrobromid, hydrochlorid, hydroiodid, sulfat, acetat, malat, oxalat, lactat, fumerat, tartrat, mesylat og succinat, idet mængden fortrinsvis er maropitantfri base, idet citrat mængden fortrinsvis er valgt fra gruppen bestående af natriumcitrat, kaliumcitrat og citronsyre, fortrinsvis citronsyre, eller hvor mængden til både maropitant og citrat er maropitantcitrat.