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(54) Title: A TRANSMUCOSAL VETERINARY COMPOSITION COMPRISING DETOMIDINE

(57) Abstract: The present invention relates to a veterinary composition in a semisolid form adapted for transmucosal administration for providing sedation and analgesia in large animals such as horses and cattle. The semisolid transmucosal composition of the invention comprises detomidine or a pharmaceutically acceptable salt thereof as an active ingredient. The composition provides a rapid onset of action while having low irritation potential in the oral mucosa.



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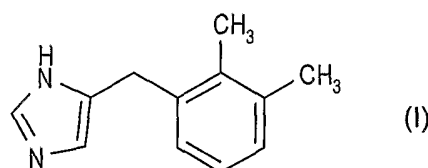
## A TRANSMUCOSAL VETERINARY COMPOSITION COMPRISING DETOMIDINE

Field of the invention

5       The present invention relates to methods and pharmaceutical compositions that are administered to animals, particularly for providing sedation, analgesia, restraint and anxiolytic effect in large animals such as horses and cattle.

Background of the invention

10       Detomidine which is 4-[(2,3-dimethylbenzyl)]imidazole of formula I



is a well known pharmaceutical agent currently used as its hydrochloride salt in veterinary use. Detomidine injectable solution (Domosedan<sup>®</sup>, Dormosedan<sup>®</sup>) is used for sedation and analgesia of horses and cattle during various examinations and  
15       treatments. Detomidine and its preparation are described in U.S. Patents 4,443,466 and 4,584,383.

Administration of detomidine hydrochloride by injection provides rapid and reliable sedation in large animals, but the dosage form has to be given by a skilled animal care provider such as a veterinarian. Moreover, some large animals are  
20       “needle shy” which can make the administration by injection difficult. Therefore, other means for administering detomidine have been attempted.

Transmucosal administration by “squirting” detomidine injectable solution sublingually has been described (Malone, J. H. and Clarke K. W., J. Vet. Anaest., 20, Dec 1993, 73-77). Useful sedation was achieved at the dose of 40 µg/kg by this

method, but the rate at which the sedation developed (45 minutes for maximal effects) was substantially slower than after intramuscular injection.

In another study, detomidine injectable solution was delivered from a plastic syringe into the buccal or oral cavity of the horse as such or mixed with different  
5 food mediums such as apple sauce and gum mixture or molasses (Ramsay, E. C. et al, Veterinary Anaesthesia and Analgesia, 2002, 29, 219-222). The dose of 60  $\mu\text{g/kg}$  was needed to produce adequate level of sedation, which produced profound head droop in horses in approximately 45 minutes.

Finally, transmucosal adhesive patches for veterinary use have been described  
10 in the International Patent Publication WO 00/19987 detomidine being mentioned as one of the suitable active agents. However, the present applicant has found that such transmucosal patch dosage forms of detomidine cause substantial, unacceptable local irritation if applied to oral mucosa of large animals such as horse. This irritation is most likely caused by the active agent detomidine itself and therefore it was found to  
15 be a major obstacle for the therapeutic administration of detomidine via transmucosal patch formulations.

Hence, there is still a need for improved products for the administration of detomidine in large animals such as horses and cattle, such products providing rapid onset of action, easy administration and low irritation potential.  
20

### Summary of the invention

The present invention relates to a pharmaceutical composition in a semisolid form adapted for transmucosal administration for providing sedation, analgesia, restraint and anxiolytic effect in animals, comprising detomidine or a  
25 pharmaceutically acceptable salt thereof as an active ingredient. In particular, the composition is in the form of transmucosal gel or emulsion.

It has been unexpectedly found that a semisolid composition of the invention, when applied on the oral mucosa of large animals such as horse, can provide a rapid onset of action comparable to intramuscular injection while having low irritation

potential in the oral mucosa even after repeated dosing. The composition provides also longer duration of action than intravenous or intramuscular injections. Thus, the present invention provides a significant improvement over existing methods of administering detomidine to large animals such as horse and cattle.

5           Thus, according to one embodiment of the invention, the present invention provides a pharmaceutical veterinary composition in a semisolid form adapted for transmucosal administration comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient.

10           According to another embodiment of the invention, the present invention provides a pharmaceutical veterinary composition in the form of a transmucosal gel or emulsion, comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient.

15           According to one particularly preferred embodiment of the invention, the present invention provides a pharmaceutical veterinary composition in the form of a transmucosal gel, comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient.

20           According to another embodiment of the invention, the present invention provides a veterinary kit comprising a) a composition in a semisolid form adapted for transmucosal administration comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient, b) a package for containing said composition, and c) instructions for administering said composition on the mucosa, particularly oral mucosa, of an animal.

25           According to another embodiment of the invention, the present invention provides a veterinary kit comprising a) a composition in the form of a transmucosal gel or emulsion, comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient, b) a package for containing said composition, and c) instructions for administering said composition on the mucosa, particularly oral mucosa, of an animal.

According to one particularly preferred embodiment of the invention, the present invention provides a veterinary kit comprising a) a composition in the form of a transmucosal gel, comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient, b) a package for containing said composition, and c)  
5 instructions for administering said composition on the mucosa, particularly oral mucosa, of an animal.

According to another embodiment of the invention, the present invention provides a method of veterinary sedation comprising applying effective amount of a composition in a semisolid form adapted for transmucosal administration comprising  
10 detomidine or a pharmaceutically acceptable salt thereof as an active ingredient, on the mucosa, particularly oral mucosa, of an animal.

According to still another embodiment of the invention, the present invention provides the use of a composition in a semisolid form adapted for transmucosal administration comprising detomidine or a pharmaceutically acceptable salt thereof  
15 as an active ingredient, in the manufacture of a medicament for administration on the mucosa, particularly oral mucosa, of an animal.

#### Detailed description of the invention

The present invention relates to a pharmaceutical veterinary composition in  
20 the semisolid form adapted for transmucosal administration, comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient. The term “semisolid” mean here the mechano-physical state that is flowable under moderate stress. Preferably, the composition is easily syringable, meaning that it can readily be dispensed from a conventional tube of the kind well known for topical formulations  
25 or from needleless syringe. The semisolid composition should be viscous enough for being able to remain in the mouth of the animal, however the viscosity should not be so high that the composition could be swallowed. Preferably, the semisolid material should have a viscosity between about from about 500 to about 200,000 mPas, preferably from about 1,000 to about 100,000 mPas, more preferably from about  
30 5,000 to about 50,000 mPas, for example from about 8,000 to about 30,000 mPas.

The semisolid composition of the present invention has a spreadable consistency upon administration. Thus, the present composition differs from earlier attempts in that it is not in the form of a patch, matrix, film or wafer, which dosage forms have a drawback of potential irritation.

5           The composition of the invention can be applied on any suitable mucosa of an animal including oral, nasal, vaginal and rectal mucosa. In particular, the composition of the invention is applied on the oral mucosa of an animal, e.g. buccal, lingual, sublingual or gingival mucosa. Preferably, it is applied sublingually from where detomidine is adsorbed through the mucous membranes of the oral cavity into  
10 the circulation and induces the desired pharmacological effect. The transmucosal, e.g. sublingual, route eliminates the pain caused by the needle penetrating the skin and is a particularly feasible route when the animal, e.g. a horse, for some reason can not be injected (needle shy patients). The composition of the invention is suitably applied sublingually in a small volume using a suitable applicator such as a syringe  
15 or the like. The composition remains in its application place and is not readily swallowed. It is especially useful for providing restraint, sedation, analgesia and/or anxiolytic effect in large animals, particularly in horses, ponies and cattle, during various examinations, treatments and transportations. The administration of the semisolid dosage is easy and can be performed by the animal owner or handler who  
20 is not skilled in parenteral drug administration. The onset of the effect, e.g. sedation, is rapid, and generally starts in horse within 30 minutes, preferably within 25 minutes, more preferably within 20 minutes, from the time application. The duration of the sedative effect is preferably from about 180 to about 300 minutes.

          The amount of detomidine or a pharmaceutically acceptable salt thereof in the  
25 composition is selected such as to provide the desired pharmacological effect. The actual amount of the drug administered may depend on numerous factors, such as the species, age and weight of the subject to be treated, the desired duration of use and the effect to be achieved. It should be noted that the present invention is intended to encompass all of the potential uses of the present composition which derive from the  
30 activity of detomidine as an adrenergic alpha-2-receptor agonist, e.g. its use as a sedative, anxiolytic, analgesic, and the like. Typically, detomidine or a pharmaceutically acceptable salt thereof, preferably hydrochloride salt, is administered to a

subject in dosés ranging from about 1 to about 200  $\mu\text{g/kg}$ , more typically from about 10 to about 100  $\mu\text{g/kg}$ , preferably from about 20 to about 80  $\mu\text{g/kg}$ .

The concentration of detomidine or a pharmaceutically acceptable salt thereof is generally within the range of about 0.1 to about 5 % (w/w), preferably from about 0.2 to about 2 % (w/w), suitably from about 0.5 to about 1 % (w/w), per weight of the composition.

Pharmaceutically acceptable salts of detomidine can be prepared by known methods. Suitable salts include acid addition salts formed, for example, with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid and the like. Detomidine hydrochloride is the preferred salt.

The semisolid composition of the invention may be for example a gel, cream, ointment or paste. Preferably the composition of the invention is in the form of a gel or emulsion. Gel form is particularly preferred.

Semisolid dosage forms of the invention can be prepared by methods well known in the art. They can be prepared by combining the drug substance with conventional pharmaceutical diluents and carriers commonly used in semisolid formulations.

Emulsions of the present invention consist of an aqueous phase and an oil phase. The compositions may take the form of a water-in-oil (W/O) emulsion or, preferably, an oil-in-water (O/W) emulsion. Suitably, the emulsions comprise from about 50 to about 95 % (w/w), preferably from about 70 to about 90 % (w/w), per weight of the composition, of water. The oil phase of the emulsion may comprise, for example, petrolatum, liquid paraffin, vegetable oils including peanut oil or castor oil, waxes, caprylic/capric triglyceride, fatty alcohols such as stearyl alcohol or cetyl alcohol, and the like. Suitably, the oil phase takes from about 1 to about 30 % (w/w), preferably from about 3 to about 20 % (w/w), per weight of the composition.

The emulsions may further comprise various additives such as emulsifiers, buffers, wetting agents, stabilizers, preservatives, thickening agents and the like.

It may be desired to employ an emulsifier in order to form a stable emulsion. Suitable emulsifiers are, for example, anionic, cationic or non-ionic emulsifiers.

- 5 Typical emulsifiers include polyoxyethylated fatty esters, polyoxyethylated fatty alcohol ethers, glyceryl esters, sorbitan esters, polyethylene glycol stearates and polyoxyethylene derivatives of sorbitan esters. Specific examples include polyethylene glycol 100 stearate (PEG-100 stearate), glyceryl monostearate, glyceryl monoleate, stearic acid, polyoxyethylene cetyl ether, polyoxyethylene cetostearyl  
10 ether, polyoxyethylene stearyl ether, sorbitan monostearate, and polysorbate 60. Suitably, emulsifiers are employed from about 0.5 to about 10 % (w/w), preferably from about 1 to about 3 % (w/w), per weight of the composition.

- Emulsion may also comprise thickening agents such as soft paraffin, cellulose derivatives, carbomers, cetearyl alcohol, propylene glycol, butylene glycol,  
15 polyethylene glycols, hydrogenated lanolin, beeswax, and the like.

The drug substance is preferably included in the aqueous phase in the emulsions of the invention.

- Gel, as referred to herein, is a single phase semisolid system consisting of organic macromolecules (gelling agent) uniformly distributed throughout a liquid in  
20 such a manner that no apparent boundaries exists between the dispersed macromolecules and the liquid. A veterinary transmucosal composition in the form of a gel has been found to be a particularly suitable embodiment of the invention.

- Gel structure is obtainable by using a suitable gelling agent. The amount of gelling agent is selected such that the resulting gel has the desired rheological  
25 properties. The gel according to the invention is preferably an aqueous gel (hydrogel), wherein the liquid solvent comprises water. However, the aqueous gel formulation may also comprise suitable water-miscible co-solvents. The active ingredient is uniformly dissolved or dispersed in the gel composition.



Preferably, the transmucosal gel formulation according to the invention comprises detomidine or a pharmaceutically acceptable salt thereof, a gelling agent, a transmucosal penetration enhancer, water-miscible organic co-solvent and water.

The gelling agent may be any suitable hydrophilic gel forming polymer.

- 5 Preferably, the gelling agent is selected from cellulose derivatives, polyacrylic acids and polyoxyethylene/polyoxypropylene copolymers. Cellulose derivatives and polyacrylic acids are particularly preferred gelling agents.

Suitable cellulose derivatives for use as gelling agents include cellulose ethers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxyethyl methylcellu-  
10 lose, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, hydroxycellulose and the like. Preferred cellulose ethers include hydroxypropyl cellulose and hydroxyethyl cellulose.

Suitable polyacrylic acids for use as gelling agents include carbomers (also called carboxyvinyl polymers). Carbomers are polyalkenyl polyether cross-linked  
15 polymers acrylic acids, typically polyallyl sucrose or polyallyl pentaerythritol cross-linked polymers of acrylic acid. They are available e.g. under the tradename Carbopol in various grades. Aqueous carbomer dispersions are acidic due to free carboxyl groups of the carbomer polymer. Neutralization of the aqueous dispersions of carbomer polymers causes spontaneous thickening through formation of water-  
20 soluble salts of polymer resins.

The gel should be viscous enough for being able to remain in the mouth of the animal, however the viscosity should not be so high that the gel could be swallowed by the animal.

The gelling agents are generally used in an amount suitable to provide a gel  
25 with a viscosity from about 500 to about 200,000 mPas, preferably from about 1,000 to about 100,000 mPas, more preferably from about 5,000 to about 50,000 mPas, for example from about 8,000 to about 30,000 mPas, measured on a Brookfield Digital Viscometer DV-II, LV-4 (cylindrical spindle), spindle factor 64, 12 rpm, 25°C.

Such suitable viscosity may be obtained by adjusting the amount of gelling agent and/or by adjusting the pH of the composition. This is especially relevant where the gelling agent is a polyacrylic acid such as carbomer as its viscosity is dependent on the pH of the composition.

5           The amount of the gelling agent depends on the nature of the gelling agent and the desired viscosity. It is preferred that the gel has a spreadable consistency which allows easy sublingual administration of a small volume of the gel from a syringe or the like. Preferably, the gel composition of the invention is free of bioadhesive components, such as elastomers or the like. Moreover, the gel  
10       composition of the invention is preferably not a film-forming type gel composition.

          Generally the amount of the gelling agent in the composition of the invention is from about 0.3 to about 40 % (w/w), per weight of the composition. In case where the gelling agent is a cellulose derivative, the amount of the gelling agent is typically from about 0.5 to about 40 % (w/w), more preferably from about 1 to about 30 %  
15       (w/w), per weight of the composition. In case where the gelling agent is a polyacrylic acid such as carbomer, the amount of the gelling agent is typically from about 0.3 to about 5.0 % (w/w), more preferably from about 0.5 to about 3.0 % (w/w), per weight of the composition.

          In case where the gelling agent is hydroxypropyl cellulose, it is suitably used  
20       in an amount ranging from about 5 to about 40 % (w/w), preferably from about 10 to about 25 % (w/w), per weight of the composition.

          The pH of the composition is suitably within the range of from about 4 to about 8, preferably from about 5 to about 7, more preferably from about 5.5 to about 6.5, particularly between about 5.8 and 6.2. The pH may be adjusted with a suitable  
25       basic compound, such as sodium hydroxide, fatty amine or a tertiary amine, or with an acidic compound, such as hydrochloric acid. A gelling agent is typically a slightly acidic material.

          Transmucosal penetration enhancers are agents capable of increasing the rate at which the drug permeates through the mucosal membranes and enters the  
30       bloodstream. Suitable transmucosal penetration enhancers include for example

surfactants, e.g. anionic surfactants such as salts of fatty acids of 5 to 30 carbon atoms, e.g. sodium lauryl sulphate and other sulphate salts of fatty acids, cationic surfactants such as alkylamines of 8 to 22 carbon atoms, e.g. oleylamine, and nonionic surfactants such as polysorbates and poloxamers; aliphatic monohydric  
5 alcohols of 8 to 22 carbon atoms such as decanol, lauryl alcohol, myristyl alcohol, palmityl alcohol, linolenyl alcohol and oleyl alcohol; fatty acids of 5 to 30 carbon atoms such as oleic acid, stearic acid, linoleic acid, palmitic acid, myristic acid, lauric acid and capric acid and their esters such as ethyl caprylate, isopropyl myristate, methyl laurate, hexamethylene palmitate, glyceryl monolaurate,  
10 polypropylene glycol monolaurate and polyethylene glycol monolaurate; diethyleneglycol monoethyl ether (Transcutol); menthol and other essential oils; salicylic acid and its derivatives; alkyl methyl sulfoxides such as decyl methyl sulfoxide and dimethyl sulfoxide (DMSO); 1-substituted azacycloalkan-2-ones such as 1-dodecylazacyclo-heptan-2-one sold under the trademark AZONE; amides such  
15 as octylamide, oleicamide, hexamethylene lauramide, lauric diethanolamide, polyethylene glycol 3-lauramide, N,N-diethyl-m-toluanide and crotamiton; and any other compounds compatible with detomidine and having transmucosal permeation enhancing activity. One or several of the above transmucosal penetration enhancers can be used. The amount of the transmucosal penetration enhancer in the  
20 composition is generally from about 0.1 to about 20 % (w/w), preferably from about 0.2 to about 15 % (w/w), more preferably from about 0.5 to about 10 % (w/w) per weight of the composition, depending on the transmucosal permeation enhancer used.

Preferred transmucosal penetration enhancers are fatty acids of 5 to 30 carbon  
25 atoms, particularly isopropyl myristate; sulphate salts of 5 to 30 carbon fatty acids, particularly sodium lauryl sulphate; and DMSO. Sodium lauryl sulphate is particularly preferred.

In case the transmucosal penetration enhancer is sodium lauryl sulphate, it is used in an amount ranging from about 0.1 to about 5 % (w/w), preferably from about  
30 0.2 to about 3 % (w/w), suitably from about 0.5 to about 2 % (w/w), per weight of the composition.

Water-miscible organic co-solvents suitable for use in the gel compositions of present invention include polyalcohols or glycols such as propylene glycol, butylene glycol, ethylene glycol, preferably propylene glycol or C<sub>2</sub>-C<sub>4</sub> alkanols such as ethanol, isopropanol, n-propanol or butanol; or combinations thereof. Preferred are non-volatile organic co-solvents, particularly propylene glycol. The amount of the water-miscible organic co-solvent in the composition is generally from about 5 to about 50 % (w/w), preferably from about 10 to about 45 % (w/w), more preferably from about 15 to about 40 % (w/w), for example from about 20 to about 35 % (w/w), per weight of the composition.

The amount of water in the gel composition is generally from about 15 to about 90 % (w/w), preferably from about 20 to about 80 % (w/w), more preferably from about 30 to about 75 % (w/w), for example from about 40 to about 70 % (w/w), per weight of the composition.

According to one preferred embodiment of the invention, the transmucosal gel formulation of the invention comprises, per weight of the composition, 0.1 – 5 % (w/w) of detomidine or a pharmaceutically acceptable salt thereof; 0.3 – 40 % (w/w) of a gelling agent; 0.2 – 15 % (w/w) of a transmucosal penetration enhancer; 5 – 50 % (w/w) of a water-miscible organic co-solvent; and 30 - 80 % (w/w) of water.

The gel composition of the invention can optionally also include other excipients commonly used in the art, for example, preservatives and/or antioxidants such as benzyl alcohol, methyl and propyl parabens, butylhydroxytoluene or butylhydroxyanisole; sweeteners; colouring agents; flavouring agents; buffers; pH adjusting agents; and solubilizers such as glycerol and the like.

The composition of the invention is preferably given to a subject animal sublingually from a prefilled syringe in a volume ranging from about 1 to 10 ml, more preferably from about 2 to 5 ml, for example 3 ml.

The composition of the invention comprises preferably a colouring agent. For example, a coloured gel can be easily distinguished from saliva following the administration. If the gel product is discharged from the mouth of the animal the

owner will be able to note the approximate loss of gel. The owner will also easily note any accidental dosing in case the product comes into contact with his skin.

Preferably, the composition of the invention consists essentially of non-food ingredients. The term "non-food ingredients" means here ingredients that are not conventionally used as food substance or nutrient for humans or animals.

The composition can be provided in the form of a veterinary kit that comprises composition of the invention, a package for containing said composition, and instructions for administering said composition on the oral mucosa of an animal. Preferably, said package is an applicator, e.g. a syringe capable of dosing fixed volumes of the composition of the invention. Syringe is preferably prepared from polymer material, such as HDPE. Suitably, the volume of the syringe ranges from about 1 to 20 ml, more preferably from about 2 to 10 ml. For example, composition of the invention can be packaged into 4 ml, 5 ml or 10 ml HDPE syringes.

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

### Examples

#### Example 1.

Ingredient	% (w/w)
Detomidine HCl	1.0
Hydroxypropyl Cellulose	20
Propylene Glycol	30
DMSO	5
Sodium Hydroxide (1 M)	1.1
Water	42.9
pH	5.8-6.2

The gel formulation of Example 1 was prepared by dissolving the drug substance to water. To this mixture propylene glycol, dimethylsulphoxide and sodium hydroxide were added under stirring. Finally hydroxypropyl cellulose was added and the formulation was homogenized by stirring.

## Example 2.

Ingredient	% (w/w)
Detomidine HCl	0.75
Hydroxyethyl Cellulose	2.2
Propylene Glycol	30
Sodium Lauryl Sulphate	1
Sodium Hydroxide (1 M)	q.s.
Water	To 100
pH	5.8-6.2

The gel formulation of Example 2 was prepared by dissolving the drug substance to water. To this mixture propylene glycol and sodium lauryl sulphate were added  
5 under stirring. Finally hydroxyethyl cellulose was added and the formulation was homogenized by stirring after adjusting the pH by addition of sodium hydroxide.

## Example 3.

Ingredient	% (w/w)
Detomidine HCl	0.75
Carbopol	1.0
Propylene Glycol	30
Isopropyl myristate	1
Sodium Hydroxide (1 M)	q.s.
Water	To 100
pH	5.8-6.2

The gel formulation of Example 3 was prepared by dissolving the drug substance to  
10 water. To this mixture propylene glycol was added under stirring. Carbopol and isopropyl myristate were first mixed in a pestle and mortar and then added slowly into the solution under stirring. Finally the formulation was homogenized by stirring after adjusting the pH by addition of sodium hydroxide.

## Example 4.

Ingredient	%
Detomidine HCl	0.72
Hydroxypropyl Cellulose	15
Propylene Glycol	30
Sodium Lauryl Sulphate	1
Sodium Methyl Paraben	0.1
Sodium Propyl Paraben	0.1
FD&C Blue No 1	0.003
Sodium Hydroxide (5 %) / HCl (8.5 %)	q.s.
Water	53.075
pH	6.0

The gel formulation of Example 4 was prepared by adding propylene glycol, parabens, sodium lauryl sulphate and water in a vessel. The mixture was stirred until it was miscible and homogenous. Drug substance and colouring agent were added under stirring. The mixture was warmed to 50°C. Hydroxypropyl cellulose was slowly added under stirring. The gel was cooled to room temperature under gentle stirring and pH of the composition was adjusted to 6.0 by dropwise addition of HCl solution. Clear blue gel was obtained after standing. Gel was packaged into 5 ml HDPE syringes.

## Example 5.

Ingredient	% (w/w)
Detomidine HCl	0.75
Butylene glycol	5.0
Decyl oleate	5.0
Cetearyl alcohol	3.6
PEG-6 stearate	2.0
Glycol stearate	1.0
PEG-32 stearate	1.0
Sodium cetearyl sulphate	0.4
Water	To 100.0

The emulsion formulation of Example 5 is prepared by adding butylene glycol, decyl oleate, cetearyl alcohol, PEG-6 stearate, glycol stearate, PEG-32 stearate and sodium cetearyl sulphate in a vessel. The mixture is warmed to 80°C and homogenized. Water (part) is added and the mixture is warmed to 100°C under stirring. The

mixture is cooled to 80°C and the drug substance dissolved in the rest of water is added to the mixture. The mixture is homogenized under vacuum and cooled.

Example 6.

Ingredient	% (w/w)
Detomidine HCl	0.75
Caprylic/Capric triglyceride	3.0
Polydecene	3.0
Petrolatum	3.0
Glycerin	2.6
PEG-100 stearate	1.5
Glyceryl stearate	1.5
Cetearyl alcohol	1.0
Phenoxyethanol	0.8
Sodium carbomer	0.3
Water	To 100.0

5

The emulsion formulation of Example 6 is prepared by adding polydecene, petrolatum, cetearyl alcohol, glyceryl stearate, PEG-100 stearate and caprylic/capric triglyceride in a vessel. The mixture is warmed to 80°C and homogenized. Glycerin, phenoxyethanol and the drug substance dissolved in a part of water are mixed and warmed to 75°C and then added to the mixture under stirring. The mixture is cooled to 40°C. Sodium carbomer and the rest of water (20°C) is mixed and homogenized in another vessel and then added to the mixture. pH is adjusted to 6 and the mixture is homogenized under vacuum and cooled.

10



## CLAIMS

1. A pharmaceutical veterinary composition in a semisolid form adapted for transmucosal administration comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient.
2. A pharmaceutical veterinary composition in the form of a transmucosal gel or emulsion, comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient.
3. A composition according to claim 2, which is in the form of a transmucosal gel.
4. A pharmaceutical veterinary composition in the form of a transmucosal gel, comprising detomidine or a pharmaceutically acceptable salt thereof, a gelling agent, a transmucosal penetration enhancer, water-miscible organic co-solvent and water.
5. A pharmaceutical veterinary composition according to claim 4 comprising, per weight of the composition, 0.1 – 5 % (w/w) of detomidine or a pharmaceutically acceptable salt thereof; 0.3 – 40 % (w/w) of a gelling agent; 0.2 – 15 % (w/w) of a transmucosal penetration enhancer; 5 – 50 % (w/w) of a water-miscible organic co-solvent; and 30 - 80 % (w/w) of water.
6. A pharmaceutical composition according to claim 4 or 5, wherein the water-miscible organic co-solvent is a glycol or C<sub>2</sub>-C<sub>4</sub> alcohol.
7. A pharmaceutical composition according to claim 6, wherein the water-miscible organic co-solvent is propylene glycol.
8. A pharmaceutical composition according to claim 7, wherein the amount of propylene glycol is from about 10 to about 45 % (w/w), preferably from about 15 to about 40 % (w/w), per weight of the composition.
9. A pharmaceutical composition according to claim 4 or 5, wherein the gelling agent is selected from cellulose derivatives, polyacrylic acids and polyoxyethylene/polyoxypropylene copolymers.
10. A pharmaceutical composition according to claim 9 wherein the gelling agent is hydroxypropyl cellulose or hydroxyethyl cellulose.
11. A pharmaceutical composition according to claim 10, wherein the amount of the gelling agent is from about 0.5 to about 40 % (w/w), more preferably from about 1 to about 30 % (w/w), per weight of the composition.
12. A pharmaceutical composition according to claim 9, wherein the gelling agent is a carbomer.

13. A pharmaceutical composition according to claim 12, wherein the amount of the carbomer is from about 0.3 to about 5.0 % (w/w), more preferably from about 0.5 to about 3.0 % (w/w), per weight of the composition.

14. A pharmaceutical composition according to claim 4 or 5, wherein the  
5 transmucosal penetration enhancer is a fatty acid of 5 to 30 carbon atoms, a sulphate salts of a 5 to 30 carbon fatty acid or DMSO.

15. A pharmaceutical composition according to claim 14, wherein the amount of the transmucosal penetration enhancer is from about 0.5 to about 10 % (w/w) per weight of the composition.

10 16. A pharmaceutical composition according to claim 4 or 5, having pH value from about 5 to about 7, more preferably from about 5.5 to about 6.5.

17. A veterinary kit comprising a) a composition in a semisolid form adapted for transmucosal administration comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient, b) a package for containing said composition, and  
15 c) instructions for administering said composition on the mucosa of an animal.

18. A veterinary kit according to claim 17, wherein said mucosa is oral mucosa.

19. A veterinary kit according to claim 17, wherein the composition is in the form of a transmucosal gel or emulsion,

20 20. A veterinary kit according to claim 19 wherein the composition is in the form of a transmucosal gel.

21. A kit according to any of claims 17-20, wherein the package is in the form of a syringe.

22. A method of veterinary sedation comprising applying effective amount of a composition in a semisolid form adapted for transmucosal administration,  
25 comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient, on the mucosa of an animal.

23. A method according to claim 22, wherein said mucosa is oral mucosa.

24. A method according to claim 22 or 23, wherein the composition to be applied is in the form of a transmucosal gel or emulsion.

30 25. A method according to claim 24, wherein the composition to be applied is in the form of a transmucosal gel.

26. Use of a composition in a semisolid form adapted for transmucosal administration comprising detomidine or a pharmaceutically acceptable salt thereof as an active ingredient, in the manufacture of a medicament for administration on the  
35 mucosa of an animal.

27. Use according to claim 26, wherein said mucosa is oral mucosa.

28. Use according to claim 26 or 27, wherein the composition is in the form of a transmucosal gel or emulsion.

29. Use according to claim 28, wherein the composition is in the form of a transmucosal gel.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/FI2005/000470

## A. CLASSIFICATION OF SUBJECT MATTER

A61K31/415 A61K9/00 A61K47/10 A61K47/38 A61K47/02  
A61P25/20

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, PASCAL, SCISEARCH, CHEM ABS Data, INSPEC

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/052347 A (LOHMANN THERAPIE SYST LTS 'DE!; VON FALKENHAUSEN CHRISTIAN 'DE!; KRUMM) 24 June 2004 (2004-06-24) examples	1-29
X	----- RAMSAY, EDWARD C. ET AL: "Serum concentrations and effects of detomidine delivered orally to horses in three different mediums" VETERINARY ANAESTHESIA AND ANALGESIA , 29(4), 219-222 CODEN: VANAFV; ISSN: 1467-2987, 2002, XP009060790 cited in the application the whole document ----- -/--	1-29

☒ 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 document 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.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

6 February 2006

Date of mailing of the international search report

16/02/2006

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/FI2005/000470

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/19987 A (3M INNOVATIVE PROPERTIES COMPANY; MATSON, CHARLES, J; CHEN, YEN-LANE;) 13 April 2000 (2000-04-13) cited in the application table 3	1-29
X	----- US 6 562 363 B1 (MANTELLE JUAN ET AL) 13 May 2003 (2003-05-13) column 41, lines 30-37 column 8, line 60	1-29
X	----- US 2004/081699 A1 (RADEMACHER TINA ET AL) 29 April 2004 (2004-04-29) the whole document -----	1-29

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/FI2005/000470

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 22-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/FI2005/000470

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004052347	A	24-06-2004	AU 2003289929 A1 DE 10256774 A1	30-06-2004 24-06-2004
WO 0019987	A	13-04-2000	AT 273698 T AU 768040 B2 AU 1100100 A BR 9915020 A CA 2345808 A1 CN 1321086 A CZ 20011188 A3 DE 69919554 D1 DE 69919554 T2 EP 1117390 A1 ES 2228125 T3 HU 0103543 A2 JP 2002526403 T MX PA01003310 A NO 20011656 A NZ 510771 A PL 347061 A1 PT 1117390 T	15-09-2004 27-11-2003 26-04-2000 14-08-2001 13-04-2000 07-11-2001 15-08-2001 23-09-2004 01-09-2005 25-07-2001 01-04-2005 28-01-2002 20-08-2002 15-05-2003 02-04-2001 29-08-2003 11-03-2002 31-01-2005
US 6562363	B1	13-05-2003	NONE	
US 2004081699	A1	29-04-2004	BR 0207614 A CA 2438651 A1 CN 1599599 A DE 10107659 A1 WO 02066016 A2 EP 1368004 A2 JP 2004529101 T MX PA03007434 A ZA 200306563 A	13-01-2004 29-08-2002 23-03-2005 05-09-2002 29-08-2002 10-12-2003 24-09-2004 18-11-2003 10-02-2004