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- (54) **DEXMEDETOMIDINE PREMIX FORMULATION**
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(57) **ABSTRACT**

The presently disclosed subject matter relates to pharmaceutical compositions comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the composition is formulated as a liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed container as a premixture. The pharmaceutical compositions can be used, for example, in perioperative care of a patient or for sedation.

**9 Claims, No Drawings**



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**DEXMEDETOMIDINE PREMIX  
FORMULATION****CROSS-REFERENCE TO RELATED  
APPLICATIONS**

This application is a continuation of and claims priority under 35 U.S.C. §120 to U.S. Ser. No. 13/678,260 filed Nov. 15, 2012, which is a continuation of U.S. Ser. No. 13/541,524 filed Jul. 3, 2012, now U.S. Pat. No. 8,338,470, which is a continuation of U.S. Ser. No. 13/343,672 filed Jan. 4, 2012, now U.S. Pat. No. 8,242,158, the contents of each of which are hereby incorporated by reference in their entireties, and to each of which priority is claimed.

**1. FIELD OF THE INVENTION**

The present invention relates to patient-ready, premixed formulations of dexmedetomidine, or a pharmaceutically acceptable salt thereof, that can be used, for example, in perioperative care of a patient or for sedation.

**2. BACKGROUND OF THE INVENTION**

Racemic 4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, which is known under the name medetomidine, is a selective and potent  $\alpha_2$ -adrenoceptor agonist. Medetomidine has been used as an antihypertensive agent and as a sedative-analgesic agent. It has further been observed that this compound also possesses anxiolytic effects and can therefore be used in the treatment of general anxiety, panic disorder and various types of withdrawal symptoms.

The d-enantiomer of medetomidine, the generic name of which is dexmedetomidine, is described in U.S. Pat. No. 4,910,214 as an  $\alpha_2$ -adrenoceptor agonist for general sedation/analgesia and the treatment of hypertension or anxiety. U.S. Pat. Nos. 5,344,840 and 5,091,402 discuss dexmedetomidine in perioperative and epidural use, respectively. For example, when used in perioperative care, dexmedetomidine can reduce the amount of anesthetic necessary to anesthetize a patient. Additionally, U.S. Pat. No. 5,304,569 discusses the use of dexmedetomidine in treating glaucoma, and U.S. Pat. No. 5,712,301 discusses the use of dexmedetomidine for preventing neurodegeneration caused by ethanol consumption. Furthermore, U.S. Pat. No. 6,716,867 discloses methods of sedating a patient while in an intensive care unit by administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the patient.

Dexmedetomidine can be administered to a patient in a variety of ways. For example, U.S. Pat. Nos. 4,544,664 and 4,910,214 disclose the administration of dexmedetomidine via parenteral, intravenous, and oral routes. U.S. Pat. No. 4,670,455 describes intramuscular and intravenous administration, while U.S. Pat. Nos. 5,124,157 and 5,217,718 describe a method and device for administering dexmedetomidine through the skin. Additionally, U.S. Pat. No. 5,712,301 states that dexmedetomidine can be administered transcutaneously.

To date, dexmedetomidine has been provided as a concentrate that must be diluted prior to administration to a patient. The requirement of a dilution step in the preparation of the dexmedetomidine formulation is associated with additional costs and inconvenience, as well as the risk of possible contamination or overdose due to human error. Thus, a dexmedetomidine formulation that avoids the expense, inconvenience,

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delay and risk of contamination or overdose would provide significant advantages over currently available concentrated formulations.

**3. SUMMARY OF THE INVENTION**

The present invention relates to premixed pharmaceutical compositions of dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration. Thus, the compositions of the present invention are formulated as a premixed composition comprising dexmedetomidine.

In certain non-limiting embodiments, the premixed dexmedetomidine composition is a liquid comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, at a concentration of between about 0.05  $\mu\text{g}/\text{mL}$  and about 15  $\mu\text{g}/\text{mL}$ .

In other non-limiting embodiments, the premixed dexmedetomidine composition is a liquid comprising dexmedetomidine at a concentration of about 4  $\mu\text{g}/\text{mL}$ .

In other non-limiting embodiments, the premixed dexmedetomidine composition comprises dexmedetomidine mixed or dissolved in a sodium chloride saline solution.

In certain embodiments, the premixed dexmedetomidine composition is disposed within a sealed container or vessel.

In certain embodiments, the dexmedetomidine composition is disposed in a container or vessel and is formulated as a premixture.

In certain embodiments, the premixed dexmedetomidine composition is disposed within a sealed container as a total volume of about 20 mL, 50 mL or 100 mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention comprises dexmedetomidine, or a pharmaceutically acceptable salt thereof, at a concentration of between about 0.05  $\mu\text{g}/\text{mL}$  and about 15  $\mu\text{g}/\text{mL}$ , and sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.

In other non-limiting embodiments, the premixed dexmedetomidine composition of the present invention comprises dexmedetomidine, or a pharmaceutically acceptable salt thereof, at a concentration of about 4  $\mu\text{g}/\text{mL}$  and sodium chloride at a concentration of about 0.90 weight percent.

In certain embodiments, the compositions of the present invention are formulated as a pharmaceutical composition for administration to a subject for sedation, analgesia or treatment of anxiety or hypertension.

The present invention also relates to the perioperative treatment of a patient to reduce the response of the autonomic nervous system to stimuli during an operation by administering a dexmedetomidine composition of the invention.

In other non-limiting embodiments, the dexmedetomidine compositions of the present invention can be administered as an anxiolytic analgesic to a patient. In certain embodiments, the composition can be administered as a premedication prior to an operation with or without administration of an amount of an anesthetic effective to achieve a desired level of local or general anesthesia.

In other non-limiting embodiments, the dexmedetomidine compositions of the present invention can be administered as a sedative. In certain embodiments, the composition is administered preoperatively to potentiate the effect of an anesthetic, wherein administration of the composition reduces the amount of anesthetic required to achieve a desired level of anesthesia.

In certain embodiments of the present invention, the premixed dexmedetomidine composition is administered

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parenterally as a liquid, orally, transdermally, intravenously, intramuscularly, subcutaneously, or via an implantable pump.

#### 4. DETAILED DESCRIPTION

The present invention is based in part on the discovery that dexmedetomidine prepared in a premixed formulation that does not require reconstitution or dilution prior to administration to a patient, remains stable and active after prolonged storage. Such premixed formulations therefore avoid the cost, inconvenience, and risk of contamination or overdose that can be associated with reconstituting or diluting a concentrated dexmedetomidine formulation prior to administration to a patient.

For clarity and not by way of limitation, this detailed description is divided into the following sub-portions:

(4.1) Definitions;

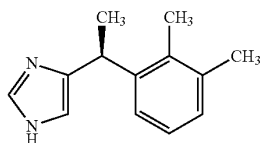
(4.2) Pharmaceutical formulations; and

(4.3) Methods of using premixed dexmedetomidine compositions.

##### 4.1 Definitions

The terms used in this specification generally have their ordinary meanings in the art, within the context of this invention and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compositions and methods of the invention and how to make and use them.

According to the present invention, the term “dexmedetomidine” as used herein refers to a substantially pure, optically active dextrorotatory stereoisomer of medetomidine, as the free base or pharmaceutically acceptable salt. In one, non-limiting embodiment, dexmedetomidine has the formula (S)-4-[1-(2,3-dimethylphenyl)ethyl]-3H-imidazole. A pharmaceutically acceptable salt of dexmedetomidine can include 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, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. Preferably, the dexmedetomidine salt is dexmedetomidine HCl. In other non-limiting embodiments, dexmedetomidine comprises the structure depicted below in Formula I:



Formula I

The terms “premix” or “premixture” as used herein refers to a pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient. For example, in contrast to non-premixed formulations of dexmedetomidine, the premixed compositions provided herein are suitable for administration to a patient without dilution by, for example, a clinician, hospital personnel, caretaker, patient or any other individual.

In certain embodiments, the compositions of the present invention can be formulated as “ready to use” compositions

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which refer to premixed compositions that are suitable for administration to a patient without dilution. For example, in certain embodiments, the compositions of the present invention are “ready to use” upon removing the compositions from a sealed container or vessel.

In certain embodiments, the compositions of the present invention can be formulated as a “single use dosage,” which refers to a premixed composition that is disposed within a sealed container or vessel as a one dose per container or vessel formulation.

According to the invention, a “subject” or “patient” is a human, a non-human mammal or a non-human animal. Although the animal subject is preferably a human, the compounds and compositions of the invention have application in veterinary medicine as well, e.g., for the treatment of domesticated species such as canine, feline, and various other pets; farm animal species such as bovine, equine, ovine, caprine, porcine, etc.; wild animals, e.g., in the wild or in a zoological garden; and avian species, such as chickens, turkeys, quail, songbirds, etc.

The term “purified” as used herein refers to material that has been isolated under conditions that reduce or eliminate the presence of unrelated materials, i.e., contaminants, including native materials from which the material is obtained. As used herein, the term “substantially free” is used operationally, in the context of analytical testing of the material. Preferably, purified material substantially free of contaminants is at least 95% pure; more preferably, at least 97% pure, and more preferably still at least 99% pure. Purity can be evaluated, for example, by chromatography or any other methods known in the art. In a specific embodiment, purified means that the level of contaminants is below a level acceptable to regulatory authorities for safe administration to a human or non-human animal.

The term “pharmaceutically acceptable,” when used in connection with the pharmaceutical compositions of the invention, refers to molecular entities and compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a human. Preferably, as used herein, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term “carrier” refers to a diluent, adjuvant, excipient, dispersing agent or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils. For example, water, aqueous solutions, saline solutions, aqueous dextrose or glycerol solutions can be employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in, for example, “Remington’s Pharmaceutical Sciences” by Philip P. Gerbino, 21st Edition (or previous editions).

The term “pharmaceutical composition” as used in accordance with the present invention relates to compositions that can be formulated in any conventional manner using one or more pharmaceutically acceptable carriers or excipients. A “pharmaceutically acceptable” carrier or excipient, as used herein, means approved by a regulatory agency of the Federal or a state government, or as listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, and more particularly in humans.

The term “dosage” is intended to encompass a formulation expressed in terms of  $\mu\text{g}/\text{kg}/\text{day}$ ,  $\mu\text{g}/\text{kg}/\text{hr}$ ,  $\text{mg}/\text{kg}/\text{day}$  or  $\text{mg}/\text{kg}/\text{hr}$ . The dosage is the amount of an ingredient administered in accordance with a particular dosage regimen. A “dose” is an amount of an agent administered to a mammal in

a unit volume or mass, e.g., an absolute unit dose expressed in mg or  $\mu\text{g}$  of the agent. The dose depends on the concentration of the agent in the formulation, e.g., in moles per liter (M), mass per volume (m/v), or mass per mass (m/m). The two terms are closely related, as a particular dosage results from the regimen of administration of a dose or doses of the formulation. The particular meaning in any case will be apparent from context.

The terms "therapeutically effective dose," "effective amount," and "therapeutically effective amount" refer to an amount sufficient to produce the desired effect.

In some non-limiting embodiments, a "therapeutically effective dose" means an amount sufficient to reduce by at least about 15%, preferably by at least 50%, more preferably by at least 90%, and most preferably prevent, a clinically significant deficit in the activity, function and response of the host. Alternatively, a therapeutically effective amount is sufficient to cause an improvement in a clinically significant condition in the host. These parameters will depend on the severity of the condition being treated, other actions, such as diet modification, that are implemented, the weight, age, and sex of the subject, and other criteria, which can be readily determined according to standard good medical practice by those of skill in the art.

In other non-limiting embodiments a therapeutic response may be any response that a user (e.g., a clinician) will recognize as an effective response to the therapy. Thus, a therapeutic response will generally be an induction of a desired effect, such as, for example, sedation or analgesia.

The term "about" or "approximately" as used herein means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

#### 4.2 Pharmaceutical Compositions

The compounds and compositions of the invention may be formulated as pharmaceutical compositions by admixture with a pharmaceutically acceptable carrier or excipient. In certain non-limiting embodiments, the compounds or compositions are provided in a therapeutically effective amount to an animal, such as a mammal, preferably a human, in need of treatment therewith for inducing a sedative, anxiolytic, analgesic, or anesthetic effect.

In certain non-limiting embodiments, dexmedetomidine is formulated as a composition, wherein the dexmedetomidine is the only therapeutically active ingredient present in the composition. In another non-limiting embodiments, dexmedetomidine is formulated as a composition, wherein the dexmedetomidine is formulated in combination with at least one or more other therapeutically active ingredient. The formulation is preferably suitable for parenteral administration, including, but not limited to, intravenous, subcutaneous, intramuscular and intraperitoneal administration; however, formulations suitable for other routes of administration such as oral, intranasal, mucosal or transdermal are also contemplated.

The pharmaceutical formulations suitable for injectable use, such as, for example, intravenous, subcutaneous, intramuscular and intraperitoneal administration, include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the form can be sterile and can be fluid to the extent that easy syringability exists. It can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, saline, ethanol, polyol (for example, glycerol, propylene glycol, and polyethylene glycol, and the like), suitable mixtures thereof, and oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, benzyl alcohol, sorbic acid, and the like.

In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin. Sterile injectable solutions may be prepared by incorporating the dexmedetomidine in the required amounts in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter or terminal sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

Preferably the formulation may contain an excipient. Pharmaceutically acceptable excipients which may be included in the formulation are buffers such as citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer; amino acids; urea; alcohols; ascorbic acid; phospholipids; proteins, such as serum albumin, collagen, and gelatin; salts such as EDTA or EGTA, and sodium chloride; liposomes; polyvinylpyrrolidone; sugars, such as dextran, mannitol, sorbitol, and glycerol; propylene glycol and polyethylene glycol (e.g., PEG-4000, PEG-6000); glycerol; glycine; lipids; preservatives; suspending agents; stabilizers; and dyes. As used herein, the term "stabilizer" refers to a compound optionally used in the pharmaceutical compositions of the present invention in order to avoid the need for sulphite salts and increase storage life. Non-limiting examples of stabilizers include antioxidants. Buffer systems for use with the formulations include citrate; acetate; bicarbonate; and phosphate buffers.

The formulation also may contain a non-ionic detergent. Preferred non-ionic detergents include Polysorbate 20, Polysorbate 80, Triton X-100, Triton X-114, Nonidet P-40, Octyl  $\alpha$ -glucoside, Octyl  $\beta$ -glucoside, Brij 35, Pluronic, and Tween 20.

The parenteral formulations of the present invention can be sterilized. Non-limiting examples of sterilization techniques include filtration through a bacterial-retaining filter, terminal sterilization, incorporation of sterilizing agents, irradiation, and heating.

The route of administration may be oral or parenteral, including intravenous, subcutaneous, intra-arterial, intraperi-



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