HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DEXMEDETOMIDINE HYDROCHLORIDE INJECTION safely and effectively. See full prescribing information for DEXMEDETOMIDINE HYDROCHLORIDE INJECTION.

DEXMEDETOMIDINE HYDROCHLORIDE injection, for intravenous use

Initial U.S. Approval: 1999

----------INDICATIONS AND USAGE----------

Dexmedetomidine Hydrochloride Injection is a central alpha-2 adrenergic agonist indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures. (1)

----------DOSAGE AND ADMINISTRATION----------

- Dilute in 0.9% Sodium Chloride Injection to concentration of 4 mcg/mL prior to administration. (2.1, 2.6)
- To be administered only by health care providers skilled in management of patients in the operating room setting. (2.1)
- Administer intravenously using a controlled infusion device. (2.1)
- Administration duration should not exceed 24 hours. (2.1)
- Continuously monitor blood pressure, heart rate, and oxygen levels during administration and as clinically appropriate after discontinuation. (2.1)

Initiation of Procedural Sedation (2.2)	
Procedure	**Recommended Loading Infusion Dosage**
More invasive procedures or awake fiberoptic intubation	1 mcg/kg over 10 minutes
Less invasive procedures such as ophthalmic surgery	0.5 mcg/kg over 10 minutes
Maintenance of Procedural Sedation (2.2)	
Procedure	**Recommended Maintenance Infusion Dosage**
All procedures except awake fiberoptic intubation	Generally, initiate at 0.6 mcg/kg/hour and titrate to achieve desired clinical effect with dosages ranging from 0.2 to 1 mcg/kg/hour.
Awake fiberoptic intubation	Administer 0.7 mcg/kg/hour until the endotracheal tube is secured

- Geriatric patients (age greater than 65 years): Recommended loading infusion dosage for initiation of procedural sedation is 0.5 mcg/kg over 10 minutes. Consider dosage reduction for maintenance. (2.3, 8.5)
- Hepatic impairment: Consider dosage reduction for initiation and maintenance of procedural sedation. (2.4, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

Injection (100 mcg/mL):

- 400 mcg in 4 mL in a multiple-dose vial. (3)
- 1000 mcg in 10 mL in a multiple-dose vial. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Bradycardia and Sinus Arrest: Consider decreasing or stopping dexmedetomidine HCl infusion; decreasing or stopping other medications that depress sinus node function; administering anticholinergic agents (e.g., glycopyrrolate, atropine); and/or administering pressor agents. (5.1)
- Hypotension: Consider decreasing or stopping dexmedetomidine HCl infusion; increasing rate of intravenous fluid administration; elevating lower extremities, and/or administering pressor agents. (5.2)
- Transient Hypertension: Observed primarily during administration of loading dose. Consider reducing loading infusion rate. (5.3)
- Arousability: Patients can become aroused/alert with stimulation; this alone should not be considered as lack of efficacy. (5.4)
- Prolonged exposure to dexmedetomidine beyond 24 hours may be associated with tolerance and tachyphylaxis and a dose-related increase in adverse events. (5.6)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence greater than 10%) were hypotension, respiratory depression, and bradycardia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact HQ Specialty Pharma Corporation at 1-XXX-XXX-XXXX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Anesthetics, sedatives/hypnotics, opioids: Can potentiate sedating effects. Consider reducing dosage of dexmedetomidine HCl or co-administered drug. (2.5, 7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Dexmedetomidine Hydrochloride Injection is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Dexmedetomidine HCl Injection must be diluted prior to administration *[see Dosage and Administration (2.6)]*.
- Dexmedetomidine HCl Injection should be administered only by health care providers skilled in the management of patients in the operating room setting.
- Administer by continuous intravenous infusion using a controlled infusion device.
- Administration duration should not exceed 24 hours *[see Warnings and Precautions (5.5, 5.6)]*.
- Continuously monitor blood pressure, heart rate and oxygen levels during the use of Dexmedetomidine HCl Injection and as clinically appropriate after discontinuation.
- Use administration components made with synthetic or coated natural rubber gaskets. Dexmedetomidine HCl Injection has the potential for absorption into some types of natural rubber.

2.2 Recommended Dosage

Dexmedetomidine HCl Injection must be diluted prior to administration *[see Dosage and Administration (2.6)]*. Table 1 displays the recommended loading and maintenance dosage of Dexmedetomidine HCl Injection in various procedures. Individualize dosages and titrate to desired sedation.

Table 1: Recommended Dosage for Dexmedetomidine HCl Injection

Initiation of Procedural Sedation	
Procedure	**Recommended Loading Infusion Dosage**
For more invasive procedures or for awake fiberoptic intubation	1 mcg/kg over 10 minutes
For less invasive procedures such as ophthalmic surgery	0.5 mcg/kg over 10 minutes
Maintenance of Procedural Sedation	
Procedure	**Recommended Maintenance Infusion Dosage**

For all procedures except awake fiberoptic intubation	• Generally, initiate the maintenance infusion at 0.6 mcg/kg/hour and titrate to achieve desired clinical effect with dosages ranging from 0.2 mcg/kg/hour to 1 mcg/kg/hour. • Adjust the maintenance infusion rate to achieve the targeted level of sedation.
For awake fiberoptic intubation	Administer 0.7 mcg/kg/hour until the endotracheal tube is secured.

2.3 Dosage Modifications in Geriatric Patients

For patients over 65 years of age, the recommended intravenous loading infusion dosage of Dexmedetomidine HCl Injection for initiation of procedural sedation is 0.5 mcg/kg infused over 10 minutes. Consider dosage reduction for maintenance of procedural sedation *[see Use in Specific Populations (8.5)]*.

2.4 Dosage Modifications in Patients with Hepatic Impairment

In patients with hepatic impairment, consider dosage reduction of Dexmedetomidine HCl Injection for initiation of procedural sedation and maintenance of procedural sedation *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications due to Drug Interactions

When co-administered with anesthetics, sedatives/hypnotics, or opioids, consider dosage reduction of Dexmedetomidine HCl Injection *[see Drug Interactions (7.1)]*.

2.6 Preparation of Diluted Dexmedetomidine HCl Solution for Administration

Dexmedetomidine HCl Injection must be diluted prior to administration to a final concentration of 4 mcg/mL by adding:

- 2 mL of Dexmedetomidine HCl Injection to 48 mL of 0.9% Sodium Chloride Injection to a total volume of 50 mL or
- 4 mL of Dexmedetomidine HCl Injection to 96 mL of 0.9% Sodium Chloride Injection to a total of volume of 100 mL

Gently shake and mix well. Prior to administration, visually inspect the diluted dexmedetomidine HCl solution for particulate matter and discoloration (the diluted solution should be a clear, colorless solution).

Prior to use, may store the diluted dexmedetomidine HCl solution for up to 4 hours at room temperature or up to 24 hours at 2^{o} to 8^{o}C.

Discard unused portion.

2.7 Drug Compatibility

Diluted dexmedetomidine HCl solution for administration is compatible with and may be co-administered with:

- 0.9% Sodium Chloride in Water Injection
- 5% Dextrose in Water Injection
- Mannitol Injection (20%)
- Lactated Ringer's Injection
- Magnesium Sulfate Injection (100 mg/mL)
- Potassium Chloride Injection (0.3%)

Diluted dexmedetomidine HCl solution is not compatible for co-administration through the same intravenous catheter with:

- Amphotericin B or diazepam
- Blood or plasma because physical compatibility has not been established.

3 DOSAGE FORMS AND STRENGTHS

Dexmedetomidine Hydrochloride Injection is clear and colorless, and is available in a 100 mcg/mL strength as follows:

- 400 mcg in 4 mL in a multiple-dose glass vial
- 1000 mcg in 10 mL in a multiple-dose glass vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Bradycardia and Sinus Arrest

Bradycardia and sinus arrest have been reported following administration of dexmedetomidine HCl to young, healthy adult volunteers with high vagal tone or following rapid intravenous or bolus administration of dexmedetomidine HCl. Bradycardia has also been reported in association with intravenous infusion of dexmedetomidine HCl. Some of these cases have resulted in fatalities. Dexmedetomidine HCl decreases sympathetic nervous system activity and has the potential to augment bradycardia induced by vagal stimuli. Elderly patients and patients with advanced heart block, severe ventricular dysfunction, hypovolemia, diabetes mellitus, and/or chronic hypertension are at increased risk of bradycardia following administration of dexmedetomidine HCl. Closely monitor heart rate and other hemodynamic parameters during administration of dexmedetomidine HCl. In patients who develop bradycardia, consider decreasing or stopping the dexmedetomidine HCl infusion; decreasing or stopping other medications that depress the sinus node function; administering anticholinergic agents (e.g.,

glycopyrrolate, atropine) to modify vagal tone; and/or administering pressor agents. In patients with significant cardiovascular dysfunction, more advanced resuscitative measures may be required.

5.2 Hypotension

Hypotension has been reported in association with intravenous infusion of dexmedetomidine HCl. Some of these cases have resulted in fatalities. Elderly patients *[see Use in Specific Populations (8.5)]* and patients with advanced heart block, severe ventricular dysfunction, hypovolemia, diabetes mellitus, and/or chronic hypertension are at increased risk of hypotension following administration of dexmedetomidine HCl. Closely monitor blood pressure and other hemodynamic parameters during administration of dexmedetomidine HCl. If hypotension occurs, consider decreasing or stopping the dexmedetomidine HCl infusion; increasing the rate of intravenous fluid administration; elevating the lower extremities; and/or administering pressor agents.

5.3 Transient Hypertension

Transient hypertension has been observed primarily during administration of the dexmedetomideine HCl loading dose and is likely due to the initial peripheral vasoconstrictive effects of dexmedetomidine. If treatment of the transient hypertension is necessary, consider reducing the loading infusion rate.

5.4 Arousability

Some patients receiving dexmedetomidine HCl have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

5.5 Withdrawal Adverse Reactions

In adult subjects, withdrawal symptoms were not seen after discontinuation of infusions of dexmedetomidine HCl less than 6 hours in duration.

5.6 Tolerance and Tachyphylaxis

Use of dexmedetomidine HCl beyond 24 hours has been associated with tolerance (reduction in response after longer duration; a higher dosage of dexmedetomidine HCl is required to produce the same effect that was obtained at a lower dosage); tachyphylaxis (a sudden decrease in response); and a dosage-related increase in adverse reactions. Administration duration should not exceed 24 hours *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Bradycardia and sinus arrest *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Transient hypertension *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reaction information is derived from the two trials for procedural sedation in which 318 adult patients received dexmedetomidine HCl (Studies 1 and 2) *[see Clinical Studies (14)]*. The mean total dose was 1.6 mcg/kg (range: 0.5 mcg/kg to 6.7 mcg/kg), mean dosage per hour was 1.3 mcg/kg/hour (range: 0.3 mcg/kg/hour to 6.1 mcg/kg/hour) and the mean duration of infusion was 1.5 hours (range: 0.1 hour to 6.2 hours). The population was between 18 to 93 years of age, 30% greater than or equal to 65 years of age, 52% male and 61% Caucasian.

Adverse reactions that occurred at an incidence of greater than 2% of patients receiving dexmedetomidine HCl and at an incidence greater than placebo are provided in Table 2. Pre-specified criteria for the vital signs to be reported as adverse reactions are footnoted below the table. The decrease in respiratory rate and hypoxia was similar between dexmedetomidine HCl and comparator groups in both studies.

Table 2: Adverse Reactions* in Clinical Trials of Dexmedetomidine HCl for Adult Procedural Sedation

Adverse Reaction	**Dexmedetomidine HCl (N = 318) (%)**	**Placebo (N = 113) (%)**
Hypotension[1]	54%	30%
Respiratory Depression[2]	37%	32%
Bradycardia[3]	14%	4%
Nausea	3%	2%
Dry Mouth	3%	1%

* Adverse reactions that occurred at an incidence of greater than 2% of patients receiving dexmedetomidine HCl and at an incidence greater than placebo

[1] Hypotension was defined in absolute and relative terms as systolic blood pressure of less than 80 mmHg or less than or equal to 30% lower than pre-study drug infusion value, or diastolic blood pressure of less than 50 mmHg.

[2] Respiratory depression was defined in absolute and relative terms as respiratory rate (RR) less than 8 beats per minute or greater than 25% decrease from baseline.

[3] Bradycardia was defined in absolute and relative terms as less than 40 beats per minute or less than or equal to 30% lower than pre-study drug infusion value.

6.2 Postmarketing Experience

The following adverse reactions, which do not appear elsewhere in this section, have been identified during post-approval use of dexmedetomidine HCl. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypotension and bradycardia were the most common adverse reactions associated with the use of dexmedetomidine HCl during post approval use.

Table 3: Adverse Reactions Experienced During Post-approval Use of Dexmedetomidine HCl

Blood and Lymphatic System Disorders	Anemia
Cardiac Disorders	Arrhythmia, atrial fibrillation, atrioventricular block, cardiac arrest, cardiac disorder, extrasystoles, myocardial infarction, supraventricular tachycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia
Eye Disorders	Photopsia, visual impairment
Gastrointestinal Disorders	Abdominal pain, diarrhea, vomiting
General Disorders and Administration Site Conditions	Chills, hyperpyrexia, pain, pyrexia, thirst
Hepatobiliary Disorders	Hepatic function abnormal, hyperbilirubinemia
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, electrocardiogram T wave inversion, gammaglutamyltransferase increased, Electrocardiogram QT prolonged
Metabolism and Nutrition Disorders	Acidosis, hyperkalemia, hypoglycemia, hypovolemia, hypernatremia
Nervous System Disorders	Convulsion, dizziness, headache, neuralgia, neuritis, speech disorder
Psychiatric Disorders	Agitation, confusional state, delirium, hallucination, illusion
Renal and Urinary Disorders	Oliguria, polyuria
Respiratory, Thoracic and Mediastinal Disorders	Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion, respiratory acidosis
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis, pruritus, rash, urticaria
Surgical and Medical Procedures	Light anesthesia
Vascular Disorders	Blood pressure fluctuation, hemorrhage, hypertension

7 DRUG INTERACTIONS

7.1 Drugs that Can Potentiate the Sedating Effects of Dexmedetomidine HCl

Anesthetics (e.g., isoflurane, sevoflurane, propofol), sedatives/hypnotics (e.g., midazolam), and opioids (e.g., alfentanil) can potentiate the sedating effects of dexmedetomidine HCl. Consider reducing the dosage of dexmedetomidine HCl or the co-administered drug.

7.2 Drugs without Clinically Significant Drug Interactions with Dexmedetomidine HCl

Dexmedetomidine HCl had no clinically meaningful effect on the magnitude of neuromuscular blockade associated with rocuronium *[see Clinical Pharmacology (12.2)]*.

In clinical trials where other vasodilators or negative chronotropic agents were co-administered with dexmedetomidine HCl an additive hypotensive or bradycardic effect was not observed. Nonetheless, close monitoring of hemodynamic parameters (e.g., blood pressure, heart rate) is recommended if other vasodilators or negative chronotropic agents are co-administered with dexmedetomidine HCl.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies conducted with dexmedetomidine hydrochloride in pregnant women to inform any drug-associated risks. A published *in vitro* human placenta study reported placental transfer of dexmedetomidine hydrochloride. Rats subcutaneously administered dexmedetomidine HCl during organogenesis showed pregnancy loss and reduced live pups at doses equivalent to the maximum recommended human dose (MRHD). Reduced fetal weights were observed in rats administered subcutaneously dexmedetomidine HCl at a dose that is less than one-half of the MRHD during gestation and lactation. In this study, elevated fetal and embryocidal toxicity and delayed motor development were observed in second generation offspring. No fetal malformations were observed in animal reproduction studies with subcutaneous administration of dexmedetomidine HCl during organogenesis in rats and rabbits at doses approximately equal to and one-half the MRHD, respectively *[see Data]*. The background risk in the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data

Teratogenic effects were not observed in rats following subcutaneous administration of dexmedetomidine HCl during the period of fetal organogenesis (from gestation day 5 to 16) with doses up to 200 mcg/kg (representing a dose approximately equal to the MRHD based on body surface area) or in rabbits following intravenous administration of dexmedetomidine HCl during the period of fetal organogenesis (from gestation day 6 to 18) with doses up to 96 mcg/kg (representing approximately half the human exposure at the MRHD based on plasma area under

the time-curve comparison). However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live pups, was observed in rats at a subcutaneous dose of 200 mcg/kg. The no-effect dose in rats was 20 mcg/kg (representing a dose less than the MRHD based on a body surface area comparison). In another reproductive toxicity study when dexmedetomidine HCl was administered subcutaneously to pregnant rats at 8 mcg/kg and 32 mcg/kg (representing a dose less than the MRHD based on a body surface area comparison) from gestation day 16 through weaning, lower offspring weights were observed. Additionally, when offspring of the 32 mcg/kg group were allowed to mate, elevated fetal and embryocidal toxicity and delayed motor development was observed in second generation offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of dexmedetomidine hydrochloride in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Radio-labeled dexmedetomidine administered subcutaneously to lactating female rats was excreted in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for dexmedetomidine hydrochloride and any potential adverse effects on the breastfed infant from dexmedetomidine hydrochloride or from the underlying maternal condition.

Clinical Considerations

A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 half-lives) after receiving dexmedetomidine hydrochloride in order to minimize potential drug exposure to a breastfed infant.

8.4 Pediatric Use

Safety and efficacy of dexmedetomidine HCl have not been established for Procedural Sedation in pediatric patients.

8.5 Geriatric Use

A total of 131 patients in the procedural sedation clinical studies were 65 years of age and over. A total of 47 patients were 75 years of age and over. Hypotension occurred in a higher incidence in dexmedetomidine HCl-treated patients 65 years or older (72%) and 75 years or older (74%) as compared to patients less than 65 years (47%). In patients greater than 65 years of age, reduce the loading infusion dosage for initiation of procedural sedation and consider reducing the maintenance infusion dosage for maintenance of procedural sedation *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Since dexmedetomidine HCl clearance decreases with increasing severity of hepatic impairment, consider dosage reduction in patients with hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

The dependence potential of dexmedetomidine HCl has not been studied in humans. However, since studies in rodents and primates have demonstrated that dexmedetomidine HCl exhibits pharmacologic actions similar to those of clonidine, it is possible that dexmedetomidine HCl may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation [*see Warnings and Precautions (5.5)*].

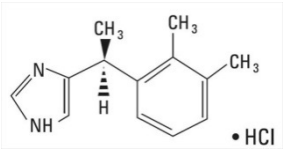
10 OVERDOSAGE

Overdosage of dexmedetomidine HCl can cause the adverse reactions generally associated with dexmedetomidine HCl administration *[see Warnings and Precautions (5) and Adverse Reactions (6)]*. However, these reactions may be more severe. Heart block (e.g., first degree atrioventricular block, second degree heart block) has been reported following overdosage with dexmedetomidine HCl. Cardiac arrest has been reported following loading bolus administration of undiluted Dexmedetomidine HCl Injection.

Dexmedetomidine HCl Injection must be diluted prior to administration *[see Dosage and Administration (2.1)]*. Management of overdosage should include general supportive measures to sustain the patient through any period of toxicity that may occur.

11 DESCRIPTION

Dexmedetomidine Hydrochloride Injection is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine HCl is a central alpha-2 adrenergic agonist. Structurally it is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine HCl has a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2$ • HCl and the structural formula is:



Dexmedetomidine HCl is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Dexmedetomidine HCl is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7. Each mL contains 118 mcg of dexmedetomidine HCl equivalent to 100 mcg (0.1 mg) of dexmedetomidine, 1.6 mg of methylparaben, 0.2 mg of propylparaben and 9 mg of sodium chloride in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexmedetomidine HCl is a central alpha-2 adrenergic agonist with sedative properties. $Alpha_2$ selectivity was observed in animals following slow intravenous infusion of low and medium

doses (10 mcg/kg to 300 mcg/kg). Both $alpha_1$ and $alpha_2$ activity was observed following slow intravenous infusion of high doses (greater than or equal to 1000 mcg/kg) or with rapid intravenous administration.

12.2 Pharmacodynamics

In a study in 10 healthy volunteers, respiratory rate and oxygen saturation remained within normal limits and there was no evidence of respiratory depression when dexmedetomidine HCl was administered by intravenous infusion at dosages between 0.2 mcg/kg/hour and 0.7 mcg/kg/hour.

In a study of 10 healthy adult volunteers, administration of dexmedetomidine HCl for 45 minutes at a plasma concentration of 1 ng/mL resulted in no clinically meaningful increases in the magnitude of neuromuscular blockade associated with rocuronium administration.

12.3 Pharmacokinetics

Following intravenous administration, dexmedetomidine exhibited the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{1/2}$) of approximately 6 minutes; a terminal elimination half-life ($t_{1/2}$) of approximately 2 hours; and steady-state volume of distribution (V_{ss}) of approximately 118 liters. Clearance was estimated to be approximately 39 L/hour. The mean body weight associated with this clearance estimate was 72 kg.

Distribution

The steady-state volume of distribution (V_{ss}) of dexmedetomidine was approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female subjects. The average protein binding was 94% and was constant across the different plasma concentrations tested.

Elimination

The distribution half-life ($t_{1/2}$) of dexmedetomidine is approximately 6 minutes, the terminal elimination half-life ($t_{1/2}$) is approximately 2 hours, and clearance is estimated to be approximately 39 L/hour.

Metabolism: Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. The major metabolic pathways of dexmedetomidine are: direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6) of dexmedetomidine to generate 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxy-dexmedetomidine; and N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronide.

Excretion: A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following intravenous administration of radiolabeled dexmedetomidine, was

recovered in the urine and 4% in the feces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated that products of N-glucuronidation accounted for approximately 34% of the cumulative urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxylic acid-dexmedetomidine together represented approximately 14% of the dose in urine. N-methylation of dexmedetomidine to form 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for approximately 18% of the dose in urine. The N-Methyl metabolite itself was a minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have not been identified.

Specific Populations

Age: Geriatric Population: The pharmacokinetic profile of dexmedetomidine HCl was not altered by age. There were no differences in the pharmacokinetics of dexmedetomidine HCl in young (18 to 40 years), middle age (41 to 65 years), and elderly (greater than 65 years) subjects.

Sex: There was no observed difference in dexmedetomidine HCl pharmacokinetics in male and female subjects. Protein binding was similar in males and females.

Hepatic Impairment: In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine HCl were lower than in healthy subjects. The mean clearance values for patients with mild, moderate, and severe hepatic impairment were 74%, 64% and 53% of those observed in the normal healthy subjects, respectively. Mean clearances for free drug were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

The fraction of dexmedetomidine HCl that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to subjects with normal hepatic function.

Renal Impairment: Dexmedetomidine HCl pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL, and V_{ss}) were not significantly different in subjects with severe renal impairment (creatinine clearance: less than 30 mL/minute) compared to subjects with normal renal function.

Drug Interaction Studies

In Vitro Studies: In vitro studies in human liver microsomes demonstrated no evidence of cytochrome P450 mediated drug interactions that are likely to be of clinical relevance.

No pharmacokinetic interactions between dexmedetomidine HCl and isoflurane, propofol, alfentanil and midazolam have been demonstrated *[see Drug Interactions (7.1)]*.

Drugs Highly Bound to Plasma Proteins: Dexmedetomidine is highly bound to plasma proteins. The potential for protein binding displacement of dexmedetomidine by other drugs highly bound to proteins (i.e., fentanyl, ketorolac, theophylline, digoxin and lidocaine) was explored *in vitro*, and negligible changes in the plasma protein binding of dexmedetomidine were observed. The potential for protein binding displacement of other drugs highly bound to proteins (i.e., phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin) by dexmedetomidine was explored *in vitro* and none of these compounds appeared to be significantly displaced by dexmedetomidine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Animal carcinogenicity studies have not been performed with dexmedetomidine.

Mutagenesis

Dexmedetomidine was not mutagenic *in vitro*, in either the bacterial reverse mutation assay (*E. coli* and *Salmonella typhimurium*) or the mammalian cell forward mutation assay (mouse lymphoma). Dexmedetomidine was clastogenic in the *in vitro* human lymphocyte chromosome aberration test with, but not without, rat S9 metabolic activation. In contrast, dexmedetomidine was not clastogenic in the *in vitro* human lymphocyte chromosome aberration test with or without human S9 metabolic activation. Although dexmedetomidine was clastogenic in an *in vivo* mouse micronucleus test in NMRI mice, there was no evidence of clastogenicity in CD-1 mice.

Impairment of Fertility

Fertility in male or female rats was not affected after daily subcutaneous injections of dexmedetomidine HCl at doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis) administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in females.

13.2 Animal Toxicology and/or Pharmacology

There were no differences in the adrenocorticotropic hormone (ACTH)-stimulated cortisol response in dogs following a single dose of dexmedetomidine compared to saline control. However, after continuous subcutaneous infusions of dexmedetomidine at 3 mcg/kg/hour and 10 mcg/kg/hour for one week in dogs (exposures estimated to be within the clinical range), the ACTH-stimulated cortisol response was diminished by approximately 27% and 40%, respectively, compared to saline-treated control animals indicating a dose-dependent adrenal suppression.

14 CLINICAL STUDIES

14.1 Procedural Sedation

The safety and efficacy of dexmedetomidine HCl for sedation of non-intubated patients prior to and/or during surgical and other procedures were evaluated in two randomized, double-blind, placebo-controlled multicenter clinical trials:

- Study 1 evaluated the sedative properties of dexmedetomidine HCl in patients having a variety of elective surgeries/procedures performed under monitored anesthesia care.
- Study 2 evaluated dexmedetomidine HCl in patients undergoing awake fiberoptic intubation prior to a surgical or diagnostic procedure.

In Study 1, the sedative properties of dexmedetomidine HCl were evaluated by comparing the percent of patients not requiring rescue midazolam to achieve a specified level of sedation using the standardized Observer's Assessment of Alertness/Sedation Scale (see Table 4).

Table 4: Observer's Assessment of Alertness/Sedation in Adult Procedural Sedation Study 1

Assessment Categories				
Responsiveness	**Speech**	**Facial Expression**	**Eyes**	**Composite Score**
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	–	–	2
Does not respond to mild prodding or shaking	–	–	–	1 (deep sleep)

Patients were randomized to receive either:

- dexmedetomidine HCl 1 mcg/kg loading dosage given over 10 minutes followed by a maintenance infusion started at 0.6 mcg/kg/hour
- dexmedetomidine HCl 0.5 mcg/kg loading dosage followed by a maintenance infusion started at 0.6 mcg/kg/hour
- placebo (normal saline) loading dosage given over 10 minutes and followed by a placebo maintenance infusion

The maintenance infusion in the two dexmedetomidine groups could be titrated between 0.2 mcg/kg/hour to 1 mcg/kg/hour to achieve the targeted sedation score (Observer's Assessment of Alertness/Sedation Scale less than or equal to 4). Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an Observer's Assessment of Alertness/Sedation Scale less than or equal to 4. After achieving the desired level of sedation, a local or regional anesthetic block was performed. Demographic characteristics were similar between the dexmedetomidine HCl and placebo groups. Efficacy results showed that dexmedetomidine HCl groups were more effective than the placebo group when used to sedate non-intubated patients requiring monitored anesthesia care during surgical and other procedures (see Table 6).

In Study 2, the sedative properties of dexmedetomidine HCl were evaluated by comparing the percent of patients requiring rescue midazolam to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale score more than or equal to 2 (see Table 5). Patients were randomized to receive:

- A loading infusion of dexmedetomidine HCl 1 mcg/kg over 10 minutes followed by a fixed maintenance infusion of 0.7 mcg/kg/hour, or
- A placebo (normal saline) given over 10 minutes followed by a placebo infusion.

After achieving the desired level of sedation, topicalization of the airway occurred. Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain a Ramsay Sedation Scale more than or equal to 2. Demographic characteristics were similar between the dexmedetomidine HCl and comparator groups. For efficacy results see Table 6.

Table 5: Ramsay Level of Sedation in Adult Procedural Sedation Study 2

Clinical Score	Level of Sedation Achieved
6	Asleep, no response
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
3	Patient responds to commands
2	Patient cooperative, oriented, and tranquil
1	Patient anxious, agitated, or restless

Table 6: Key Efficacy Results of Adult Procedural Sedation Studies (Study 1 and Study 2)

Treatment Arm	Number of Patients Enrolled[a]	% Not Requiring Midazolam Rescue	Confidence[b] Interval on the Difference vs. Placebo	Mean (SD) Total Dose of Rescue Midazolam Required	Confidence[b] Intervals of the Mean Rescue Dose
Study 1					
Dexmedetomidine HCl 0.5 mcg/kg (loading) followed by maintenance infusion started at 0.6 mcg/kg/hour	134	40%	37% (27, 48)	1.4 (1.7) mg	-2.7 (-3.4, -2) mg
Dexmedetomidine HCl 1 mcg/kg (loading) followed by maintenance infusion started at 0.6 mcg/kg/hour	129	54%	51% (40, 62)	0.9 (1.5) mg	-3.1 (-3.8, -2.5) mg
Placebo	63	3%	–	4.1 (3) mg	–
Study 2					
Dexmedetomidine HCl 1 mcg/kg (loading) followed by a fixed maintenance infusion of 0.7 mcg/kg/hour	55	53%	39% (20, 57)	1.1 (1.5) mg	-1.8 (-2.7, -0.9) mg
Placebo	50	14%	–	2.9 (3) mg	–

SD = Standard deviation

a Based on ITT population defined as all randomized and treated patients.

b Normal approximation to the binomial with continuity correction

16 HOW SUPPLIED/STORAGE AND HANDLING

Dexmedetomidine Hydrochloride Injection is clear and colorless, and is available in a 100 mcg/mL strength in clear glass, multiple-dose vials as follows:

NDC No.	Strength	Package
XXXX-XXXX-XX	400 mcg/4 mL	4 vials/carton
XXXX-XXXX-XX	1000 mcg/10 mL	4 vials/carton

Store vials at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients, their families, or caregivers to report to their health care provider symptoms that occur within 48 hours after the administration of Dexmedetomidine HCl Injection such as:

- Nervousness, agitation, and headaches which may be associated with an infusion lasting for more than 6 hours
- Weakness, confusion, excessive sweating, weight loss, abdominal pain, salt cravings, diarrhea, constipation, dizziness or light-headedness

Important Potential Adverse Reactions Following Drug Discontinuation

Advise the patient, their families, or caregivers to contact their health care provider if they develop any of the following symptoms within 48 hours of receiving Dexmedetomidine HCl Injection: weakness, confusion, excessive sweating, weight loss, abdominal pain, salt cravings, diarrhea, constipation, dizziness or light-headedness.

Made in Finland

Manufactured for:
HQ Specialty Pharma Corporation
Paramus, NJ 07652

Revised: July 2015