

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

-----**RECENT MAJOR CHANGES**-----

Indications and Usage, Intensive Care Unit Sedation (1.1)	09/2016
Dosage and Administration, Recommended Dosage (2.2) and Dosage Modifications in Geriatric Patients (2.3)	09/2016
Warnings and Precautions, Withdrawal Adverse Reactions (5.5)	09/2016

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

Dexmedetomidine Hydrochloride Injection is a central alpha-2 adrenergic agonist indicated for:

- Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Dexmedetomidine Hydrochloride Injection by continuous infusion not to exceed 24 hours. (1.1)
- Sedation of non-intubated patients prior to and/or during surgical and other procedures. (1.2)

-----**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 intensive care or 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 Intensive Care Unit Sedation (2.2)	
Procedure	Recommended Loading Infusion Dosage
ICU Sedation	1 mcg/kg over 10 minutes
Maintenance of Intensive Care Unit Sedation (2.2)	
Procedure	Recommended Maintenance Infusion Dosage
Maintenance	0.2 to 0.7 mcg/kg/hour.
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
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- Geriatric patients (age greater than 65 years): Consider a dose reduction for ICU sedation. Recommended loading infusion dosage for initiation of procedural sedation is 0.5 mcg/kg over 10 minutes. Consider dosage reduction for maintenance of procedural sedation. (2.3, 8.5)
- Hepatic impairment: Consider dosage reduction. (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 in ICU sedation (incidence greater than 2% and greater in patients receiving dexmedetomidine HCl than placebo) were hypotension, nausea, bradycardia, fever, atrial fibrillation and anemia. (6.1)
- The most common adverse reactions in procedural sedation (incidence greater than 2% and greater in patients receiving dexmedetomidine HCl than placebo) were hypotension, respiratory depression, bradycardia, nausea, and dry mouth. (6.1)
- Adverse reactions associated with infusions greater than 24 hours in duration include ARDS, respiratory failure, and agitation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact WG Critical Care at 1-866-562-4708 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: 09/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Intensive Care Unit Sedation

Dexmedetomidine Hydrochloride Injection is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Dexmedetomidine Hydrochloride Injection should be administered by continuous infusion not to exceed 24 hours.

Dexmedetomidine Hydrochloride Injection has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Dexmedetomidine Hydrochloride Injection prior to extubation.

1.2 Procedural Sedation

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 intensive care or 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 Intensive Care Unit Sedation	
Procedure	Recommended Loading Infusion Dosage
ICU Sedation	<ul style="list-style-type: none"> • 1 mcg/kg over 10 minutes • For adult patients being converted from alternate sedative therapy, a loading dose may not be required [see <i>Dosage and Administration (2.2)</i>].
Maintenance of Intensive Care Unit Sedation	
Procedure	Recommended Maintenance Infusion Dosage
Maintenance	<ul style="list-style-type: none"> • 0.2 to 0.7 mcg/kg/hour. • Adjust the maintenance infusion rate to achieve the targeted level of sedation.
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	<ul style="list-style-type: none"> • 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.

33 **2.3 Dosage Modifications in Geriatric Patients**

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

39 **2.4 Dosage Modifications in Patients with Hepatic Impairment**

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

42 **2.5 Dosage Modifications due to Drug Interactions**

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

45 **2.6 Preparation of Diluted Dexmedetomidine HCl Solution for Administration**

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

48

- 49 • 2 mL of Dexmedetomidine HCl Injection to 48 mL of 0.9% Sodium Chloride Injection
50 to a total volume of 50 mL or
- 51 • 4 mL of Dexmedetomidine HCl Injection to 96 mL of 0.9% Sodium Chloride Injection to
52 a total of volume of 100 mL

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

56 Prior to use, may store the diluted dexmedetomidine HCl solution for up to 4 hours at room
57 temperature or up to 24 hours at 2° to 8°C.

58 Discard unused portion.

59 **2.7 Drug Compatibility**

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

62

- 63 • 0.9% Sodium Chloride in Water Injection
- 64 • 5% Dextrose in Water Injection
- 65 • Mannitol Injection (20%)
- 66 • Lactated Ringer's Injection
- 67 • Magnesium Sulfate Injection (100 mg/mL)
- 68 • Potassium Chloride Injection (0.3%)

69

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

72

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

75 **3 DOSAGE FORMS AND STRENGTHS**

76

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

- 79 • 400 mcg in 4 mL in a multiple-dose glass vial
- 80 • 1000 mcg in 10 mL in a multiple-dose glass vial

81 **4 CONTRAINDICATIONS**

82 None.

83 **5 WARNINGS AND PRECAUTIONS**

84 **5.1 Bradycardia and Sinus Arrest**

85 Bradycardia and sinus arrest have been reported following administration of dexmedetomidine
86 HCl to young, healthy adult volunteers with high vagal tone or following rapid intravenous or
87 bolus administration of dexmedetomidine HCl. Bradycardia has also been reported in association
88 with intravenous infusion of dexmedetomidine HCl. Some of these cases have resulted in
89 fatalities. Dexmedetomidine HCl decreases sympathetic nervous system activity and has the
90 potential to augment bradycardia induced by vagal stimuli. Elderly patients and patients with
91 advanced heart block, severe ventricular dysfunction, hypovolemia, diabetes mellitus, and/or
92 chronic hypertension are at increased risk of bradycardia following administration of
93 dexmedetomidine HCl. Closely monitor heart rate and other hemodynamic parameters during
94 administration of dexmedetomidine HCl. In patients who develop bradycardia, consider
95 decreasing or stopping the dexmedetomidine HCl infusion; decreasing or stopping other
96 medications that depress the sinus node function; administering anticholinergic agents (e.g.,
97 glycopyrrolate, atropine) to modify vagal tone; and/or administering pressor agents. In patients
98 with significant cardiovascular dysfunction, more advanced resuscitative measures may be
99 required.

100 **5.2 Hypotension**

101 Hypotension has been reported in association with intravenous infusion of dexmedetomidine HCl.
102 Some of these cases have resulted in fatalities. Elderly patients [*see Use in Specific Populations*
103 (8.5)] and patients with advanced heart block, severe ventricular dysfunction, hypovolemia,
104 diabetes mellitus, and/or chronic hypertension are at increased risk of hypotension following
105 administration of dexmedetomidine HCl. Closely monitor blood pressure and other hemodynamic
106 parameters during administration of dexmedetomidine HCl. If hypotension occurs, consider
107 decreasing or stopping the dexmedetomidine HCl infusion; increasing the rate of intravenous
108 fluid administration; elevating the lower extremities; and/or administering pressor agents.

109 **5.3 Transient Hypertension**

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

114 **5.4 Arousability**

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

118 **5.5 Withdrawal Adverse Reactions**

119 Intensive Care Unit Sedation

120 With administration up to 7 days, regardless of dose, 12 (5%) dexmedetomidine HCl adult
121 subjects experienced at least 1 event related to withdrawal within the first 24 hours after
122 discontinuing study drug and 7 (3%) dexmedetomidine HCl adult subjects experienced at least 1
123 event 24 to 48 hours after end of study drug. The most common events were nausea, vomiting,
124 and agitation.

125 In adult subjects, tachycardia and hypertension requiring intervention in the 48 hours following
126 study drug discontinuation occurred at frequencies of <5%. If tachycardia and/or hypertension
127 occurs after discontinuation of dexmedetomidine HCl supportive therapy is indicated.

128 Procedural Sedation

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

131 **5.6 Tolerance and Tachyphylaxis**

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

137 **6 ADVERSE REACTIONS**

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

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

142 **6.1 Clinical Trials Experience**

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

146 Intensive Care Unit Sedation

147 Adverse reaction information is derived from the continuous infusion trials of dexmedetomidine
148 HCl for sedation in the Intensive Care Unit setting in which 1007 adult patients received
149 dexmedetomidine HCl. The mean total dose was 7.4 mcg/kg (range: 0.8 to 84.1), mean dose per
150 hour was 0.5 mcg/kg/hr (range: 0.1 to 6.0) and the mean duration of infusion of 15.9 hours
151 (range: 0.2 to 157.2). The population was between 17 to 88 years of age, 43% ≥65 years of age,
152 77% male and 93% Caucasian. Treatment-emergent adverse reactions occurring at an incidence
153 of >2% are provided in Table 2.

Table 2: Adverse Reactions with an Incidence >2%— Adult Intensive Care Unit Sedation Population <24 hours*

Adverse Event	All Dexmedetomidine HCl (N = 1007)	Randomized Dexmedetomidine HCl (N = 798)	Placebo (N = 400)	Propofol (N = 188)
	(%)	(%)	(%)	(%)
Hypotension	25%	24%	12%	13%
Hypertension	12%	13%	19%	4%
Nausea	9%	9%	9%	11%
Bradycardia	5%	5%	3%	0
Atrial Fibrillation	4%	5%	3%	7%
Pyrexia	4%	4%	4%	4%
Dry Mouth	4%	3%	1%	1%
Vomiting	3%	3%	5%	3%
Hypovolemia	3%	3%	2%	5%
Atelectasis	3%	3%	3%	6%
Pleural Effusion	2%	2%	1%	6%
Agitation	2%	2%	3%	1%
Tachycardia	2%	2%	4%	1%
Hyperthermia	2%	2%	3%	0
Chills	2%	2%	3%	2%
Hyperglycemia	2%	2%	2%	3%
Hypoxia	2%	2%	2%	3%
Post-procedural Hemorrhage	2%	2%	3%	4%
Pulmonary Edema	1%	1%	1%	3%
Ventricular Tachycardia	<1%	1%	1%	5%

*26 subjects in the all dexmedetomidine HCl group and 10 subjects in the randomized dexmedetomidine HCl group had exposure for greater than 24 hours.

154 Adverse reaction information was also derived from the placebo-controlled, continuous infusion
155 trials of dexmedetomidine HCl for sedation in the surgical intensive care unit setting in which
156 387 adult patients received dexmedetomidine HCl for less than 24 hours.

Table 3: Treatment-Emergent Adverse Events Occurring in >1% Of All Dexmedetomidine-Treated Adult Patients and at an Incidence Greater than Placebo in the Randomized Placebo-Controlled Continuous Infusion <24 Hours ICU Sedation Studies

Adverse Event	Randomized Dexmedetomidine (N = 387)	Placebo (N = 379)
Hypotension	28%	13%

Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Atrial Fibrillation	4%	3%
Anemia	3%	2%
Dry Mouth	3%	1%
Pleural Effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

157 In a controlled clinical trial, dexmedetomidine HCl was compared to midazolam for ICU sedation
 158 exceeding 24 hours duration in adult patients. Key treatment emergent adverse events occurring
 159 in dexmedetomidine or midazolam treated patients in the randomized active comparator
 160 continuous infusion long-term intensive care unit sedation study are provided in Table 4. The
 161 number (%) of subjects who had a dose-related increase in treatment-emergent adverse events by
 162 maintenance adjusted dose rate range in the dexmedetomidine HCl group is provided in Table 5.

Table 4: Key Treatment-Emergent Adverse Events Occurring in Dexmedetomidine- or Midazolam-Treated Adult Patients in the Randomized Active Comparator Continuous Infusion Long-Term Intensive Care Unit Sedation Study		
Adverse Event	Dexmedetomidine (N = 244)	Midazolam (N = 122)
Hypotension requiring intervention ¹	28%	27%
Bradycardia ²	42%	19%
Bradycardia requiring intervention	5%	1%
Pyrexia	7%	2%
Agitation	7%	6%
Hyperglycemia	7%	2%
Respiratory Failure	5%	3%
Renal Failure Acute	2%	1%
Acute Respiratory Distress Syndrome	2%	1%

¹ Hypotension was defined in absolute terms as Systolic blood pressure of <80 mmHg or Diastolic blood pressure of <50 mmHg or in relative terms as ≤30% lower than pre-study drug infusion value.
² Bradycardia was defined in absolute terms as <40 bpm or in relative terms as ≤30% lower than pre-study drug infusion value.

163 The following adverse events occurred between 2 and 5% for dexmedetomidine HCl and
 164 Midazolam, respectively: renal failure acute (2.5%, 0.8%), acute respiratory distress syndrome
 165 (2.5%, 0.8%), and respiratory failure (4.5%, 3.3%).

Table 5. Number (%) of Adult Subjects Who Had a Dose-Related Increase in Treatment Emergent Adverse Events by Maintenance Adjusted Dose Rate Range in the

Dexmedetomidine HCl Group			
Dexmedetomidine HCl mcg/kg/hr			
Adverse Event	≤0.7* (N = 95)	>0.7 to ≤1.1* (N = 78)	>1.1* (N = 71)
Constipation	6%	5%	14%
Agitation	5%	8%	14%
Anxiety	5%	5%	9%
Edema Peripheral	3%	5%	7%
Atrial Fibrillation	2%	4%	9%
Respiratory Failure	2%	6%	10%
Acute Respiratory Distress Syndrome	1%	3%	9%

*Average maintenance dose over the entire study drug administration

166 Procedural Sedation

167 Adverse reaction information is derived from the two trials for procedural sedation in which 318
 168 adult patients received dexmedetomidine HCl (Studies 1 and 2) [see *Clinical Studies (14.2)*]. The
 169 mean total dose was 1.6 mcg/kg (range: 0.5 mcg/kg to 6.7 mcg/kg), mean dosage per hour was
 170 1.3 mcg/kg/hour (range: 0.3 mcg/kg/hour to 6.1 mcg/kg/hour) and the mean duration of infusion
 171 was 1.5 hours (range: 0.1 hour to 6.2 hours). The population was between 18 to 93 years of age,
 172 30% greater than or equal to 65 years of age, 52% male and 61% Caucasian.

173 Adverse reactions that occurred at an incidence of greater than 2% of patients receiving
 174 dexmedetomidine HCl and at an incidence greater than placebo are provided in Table 6. Pre-
 175 specified criteria for the vital signs to be reported as adverse reactions are footnoted below the
 176 table. The decrease in respiratory rate and hypoxia was similar between dexmedetomidine HCl
 177 and comparator groups in both studies.

178 **Table 6: Adverse Reactions* in Clinical Trials of Dexmedetomidine HCl for Adult**
 179 **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.

180 **6.2 Postmarketing Experience**

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

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

187 **Table 7: Adverse Reactions Experienced During Post-approval Use of Dexmedetomidine**
188 **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

189 **7 DRUG INTERACTIONS**

190 **7.1 Drugs that Can Potentiate the Sedating Effects of Dexmedetomidine HCl**

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

194 **7.2 Drugs without Clinically Significant Drug Interactions with Dexmedetomidine HCl**

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

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

202 **8 USE IN SPECIFIC POPULATIONS**

203 **8.1 Pregnancy**

204 Risk Summary

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

219 Data

220 *Animal Data*

221 Teratogenic effects were not observed in rats following subcutaneous administration of
222 dexmedetomidine HCl during the period of fetal organogenesis (from gestation day 5 to 16) with
223 doses up to 200 mcg/kg (representing a dose approximately equal to the MRHD based on body
224 surface area) or in rabbits following intravenous administration of dexmedetomidine HCl during
225 the period of fetal organogenesis (from gestation day 6 to 18) with doses up to 96 mcg/kg
226 (representing approximately half the human exposure at the MRHD based on plasma area under
227 the time-curve comparison). However, fetal toxicity, as evidenced by increased post-implantation
228 losses and reduced live pups, was observed in rats at a subcutaneous dose of 200 mcg/kg. The no-
229 effect dose in rats was 20 mcg/kg (representing a dose less than the MRHD based on a body
230 surface area comparison). In another reproductive toxicity study when dexmedetomidine HCl was
231 administered subcutaneously to pregnant rats at 8 mcg/kg and 32 mcg/kg (representing a dose less
232 than the MRHD based on a body surface area comparison) from gestation day 16 through
233 weaning, lower offspring weights were observed. Additionally, when offspring of the 32 mcg/kg
234 group were allowed to mate, elevated fetal and embryocidal toxicity and delayed motor
235 development was observed in second generation offspring.

236 **8.2 Lactation**

237 Risk Summary

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

245 Clinical Considerations

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

249 **8.4 Pediatric Use**

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

252 **8.5 Geriatric Use**

253 Intensive Care Unit Sedation

254 A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200
255 patients were 75 years of age and over. In patients greater than 65 years of age, a higher incidence
256 of bradycardia and hypotension was observed following administration of dexmedetomidine HCl

257 [see *Warnings and Precautions (5.1, 5.2)*]. Therefore a dose reduction may be considered in
258 patients over 65 years of age [see *Dosage and Administration (2.3) and Clinical Pharmacology*
259 *(12.3)*].

260 Procedural Sedation

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

268 **8.6 Hepatic Impairment**

269 Since dexmedetomidine HCl clearance decreases with increasing severity of hepatic impairment,
270 consider dosage reduction in patients with hepatic impairment [see *Dosage and Administration*
271 *(2.4) and Clinical Pharmacology (12.3)*].

272 **9 DRUG ABUSE AND DEPENDENCE**

273 **9.3 Dependence**

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

279 **10 OVERDOSAGE**

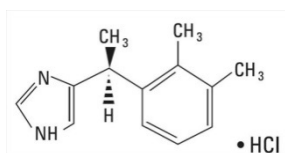
280 Overdosage of dexmedetomidine HCl can cause the adverse reactions generally associated with
281 dexmedetomidine HCl administration [see *Warnings and Precautions (5) and Adverse Reactions*
282 *(6)*]. However, these reactions may be more severe. Heart block (e.g., first degree
283 atrioventricular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

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

289 **11 DESCRIPTION**

290 Dexmedetomidine Hydrochloride Injection is a sterile, nonpyrogenic solution suitable for
291 intravenous infusion following dilution. Dexmedetomidine HCl is a central alpha-2 adrenergic
292 agonist. Structurally it is the S-enantiomer of medetomidine and is chemically described as (+)-4-
293 (S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine HCl has

294 a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2 \cdot HCl$ and the structural
295 formula is:



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

302 12 CLINICAL PHARMACOLOGY

303 12.1 Mechanism of Action

304 Dexmedetomidine HCl is a central alpha-2 adrenergic agonist with sedative properties. Alpha₂
305 selectivity was observed in animals following slow intravenous infusion of low and medium
306 doses (10 mcg/kg to 300 mcg/kg). Both alpha₁ and alpha₂ activity was observed following slow
307 intravenous infusion of high doses (greater than or equal to 1000 mcg/kg) or with rapid
308 intravenous administration.

309 12.2 Pharmacodynamics

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

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

317 12.3 Pharmacokinetics

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

323 Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr
324 when administered by intravenous infusion for up to 24 hours. Table 8 shows the main
325 pharmacokinetic parameters when dexmedetomidine HCl was infused (after appropriate loading
326 doses) at maintenance infusion rates of 0.17 mcg/kg/hr (target plasma concentration of 0.3
327 ng/mL) for 12 and 24 hours, 0.33 mcg/kg/hr (target plasma concentration of 0.6 ng/mL) for 24
328 hours, and 0.70 mcg/kg/hr (target plasma concentration of 1.25 ng/mL) for 24 hours.

329

Table 8: Mean ± SD Pharmacokinetic Parameters				
Parameter	Loading Infusion (min)/Total Infusion Duration (hrs)			
	10 min/12 hrs	10 min/24 hrs	10 min/24 hrs	35 min/24 hrs
	Dexmedetomidine HCL Target Plasma Concentration (ng/mL) and Dose (mcg/kg/hr)			
	0.3/0.17	0.3/0.17	0.6/0.33	1.25/0.70
t_{1/2}[*], hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
CL, liter/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}, liter	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg C_{ss} #, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20
* Presented as harmonic mean and pseudo standard deviation.				
# Mean C _{ss} = Average steady-state concentration of dexmedetomidine HCL. The mean C _{ss} was calculated based on post-dose sampling from 2.5 to 9 hours samples for 12 hour infusion and post-dose sampling from 2.5 to 18 hours for 24 hour infusions.				
The loading doses for each of the above indicated groups were 0.5, 0.5, 1 and 2.2 mcg/kg, respectively.				

330

331 Dexmedetomidine pharmacokinetic parameters after dexmedetomidine HCL maintenance doses of
332 0.2 to 1.4 mcg/kg/hr for >24 hours were similar to the PK parameters after dexmedetomidine
333 HCL maintenance dosing for < 24 hours in other studies. The values for clearance (CL), volume
334 of distribution (V), and t_{1/2} were 39.4 L/hr, 152 L, and 2.67 hours, respectively.

335 Distribution

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

340

341 Elimination

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

345

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

353 hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and
354 dexmedetomidine-N-methyl O-glucuronide.

355

356 *Excretion:* A mass balance study demonstrated that after nine days an average of 95% of the
357 radioactivity, following intravenous administration of radiolabeled dexmedetomidine, was
358 recovered in the urine and 4% in the feces. No unchanged dexmedetomidine was detected in
359 the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within
360 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated
361 that products of N-glucuronidation accounted for approximately 34% of the cumulative
362 urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy-
363 dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxylic acid-
364 dexmedetomidine together represented approximately 14% of the dose in urine. N-
365 methylation of dexmedetomidine to form 3-hydroxy N-methyl dexmedetomidine, 3-carboxy
366 N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for
367 approximately 18% of the dose in urine. The N-Methyl metabolite itself was a minor
368 circulating component and was undetected in urine. Approximately 28% of the urinary
369 metabolites have not been identified.

370

371 Specific Populations

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

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

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

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

388

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

392 Drug Interaction Studies

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

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

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

405 **13 NONCLINICAL TOXICOLOGY**

406 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

407 Carcinogenesis

408 Animal carcinogenicity studies have not been performed with dexmedetomidine.

409 Mutagenesis

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

417 Impairment of Fertility

418 Fertility in male or female rats was not affected after daily subcutaneous injections of
419 dexmedetomidine HCl at doses up to 54 mcg/kg (less than the maximum recommended human
420 intravenous dose on a mcg/m² basis) administered from 10 weeks prior to mating in males, and 3
421 weeks prior to mating and during mating in females.

422 **13.2 Animal Toxicology and/or Pharmacology**

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

430 **14 CLINICAL STUDIES**

431 The safety and efficacy of dexmedetomidine HCl have been evaluated in four randomized,
432 double-blind, placebo-controlled multicenter clinical trials in 1185 adult patients.

433 **14.1 Intensive Care Unit Sedation**

434 Two randomized, double-blind, parallel-group, placebo-controlled multicenter clinical trials
435 included 754 adult patients being treated in a surgical intensive care unit. All patients were
436 initially intubated and received mechanical ventilation. These trials evaluated the sedative
437 properties of dexmedetomidine HCl by comparing the amount of rescue medication (midazolam
438 in one trial and propofol in the second) required to achieve a specified level of sedation (using the
439 standardized Ramsay Sedation Scale) between dexmedetomidine HCl and placebo from onset of
440 treatment to extubation or to a total treatment duration of 24 hours. The Ramsay Level of
441 Sedation Scale is displayed in Table 9.

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

442 In the first study, 175 adult patients were randomized to receive placebo and 178 to receive
443 dexmedetomidine HCl by intravenous infusion at a dose of 0.4 mcg/kg/hr (with allowed
444 adjustment between 0.2 and 0.7 mcg/kg/hr) following an initial loading infusion of one mcg/kg
445 intravenous over 10 minutes. The study drug infusion rate was adjusted to maintain a Ramsay
446 sedation score of ≥ 3 . Patients were allowed to receive “rescue” midazolam as needed to augment
447 the study drug infusion. In addition, morphine sulfate was administered for pain as needed. The
448 primary outcome measure for this study was the total amount of rescue medication (midazolam)
449 needed to maintain sedation as specified while intubated. Patients randomized to placebo received
450 significantly more midazolam than patients randomized to dexmedetomidine HCl (see Table 10).

451 A second prospective primary analysis assessed the sedative effects of dexmedetomidine HCl by
452 comparing the percentage of patients who achieved a Ramsay sedation score of ≥ 3 during
453 intubation without the use of additional rescue medication. A significantly greater percentage of
454 patients in the dexmedetomidine HCl group maintained a Ramsay sedation score of ≥ 3 without
455 receiving any midazolam rescue compared to the placebo group (see Table 10).

	Placebo (N = 175)	Dexmedetomidine HCl (N = 178)	p-value
Mean Total Dose (mg) of Midazolam	19 mg	5 mg	0.0011*
Standard deviation	53 mg	19 mg	
Categorized Midazolam Use			
0 mg	43 (25%)	108 (61%)	<0.001**
0–4 mg	34 (19%)	36 (20%)	
>4 mg	98 (56%)	34 (19%)	
ITT (intent-to-treat) population includes all randomized patients. * ANOVA model with treatment center. ** Chi-square.			

456 A prospective secondary analysis assessed the dose of morphine sulfate administered to patients
457 in the dexmedetomidine HCl and placebo groups. On average, dexmedetomidine HCl-treated
458 patients received less morphine sulfate for pain than placebo-treated patients (0.47 versus 0.83
459 mg/h). In addition, 44% (79 of 178 patients) of dexmedetomidine HCl patients received no
460 morphine sulfate for pain versus 19% (33 of 175 patients) in the placebo group.

461 In a second study, 198 adult patients were randomized to receive placebo and 203 to receive
462 dexmedetomidine HCl by intravenous infusion at a dose of 0.4 mcg/kg/hr (with allowed
463 adjustment between 0.2 and 0.7 mcg/kg/hr) following an initial loading infusion of one mcg/kg
464 intravenous over 10 minutes. The study drug infusion was adjusted to maintain a Ramsay
465 sedation score of ≥ 3 . Patients were allowed to receive “rescue” propofol as needed to augment the
466 study drug infusion. In addition, morphine sulfate was administered as needed for pain. The
467 primary outcome measure for this study was the total amount of rescue medication (propofol)
468 needed to maintain sedation as specified while intubated.

469 Patients randomized to placebo received significantly more propofol than patients randomized to
470 dexmedetomidine HCl (see Table 11).

471 A significantly greater percentage of patients in the dexmedetomidine HCl group compared to the
472 placebo group maintained a Ramsay sedation score of ≥ 3 without receiving any propofol rescue
473 (see Table 11).

Table 11: Propofol Use as Rescue Medication During Intubation (ITT) Study Two			
	Placebo (N = 198)	Dexmedetomidine HCl (N = 203)	p-value
Mean Total Dose (mg) of Propofol	513 mg	72 mg	<0.0001*
Standard deviation	782 mg	249 mg	
Categorized Propofol Use			
0 mg	47 (24%)	122 (60%)	<0.001**
0–50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	
* ANOVA model with treatment center.			
** Chi-square.			

474 A prospective secondary analysis assessed the dose of morphine sulfate administered to patients
475 in the dexmedetomidine HCl and placebo groups. On average, dexmedetomidine HCl-treated
476 patients received less morphine sulfate for pain than placebo-treated patients (0.43 versus 0.89
477 mg/h). In addition, 41% (83 of 203 patients) of dexmedetomidine HCl patients received no
478 morphine sulfate for pain versus 15% (30 of 198 patients) in the placebo group.

479 In a controlled clinical trial, dexmedetomidine HCl was compared to midazolam for ICU sedation
480 exceeding 24 hours duration. Dexmedetomidine HCl was not shown to be superior to midazolam
481 for the primary efficacy endpoint, the percent of time patients were adequately sedated (81%
482 versus 81%). In addition, administration of dexmedetomidine HCl for longer than 24 hours was
483 associated with tolerance, tachyphylaxis, and a dose-related increase in adverse events [*see*
484 *Adverse Reactions (6.1)*].

485 **14.2 Procedural Sedation**

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

- 489 • Study 1 evaluated the sedative properties of dexmedetomidine HCl in patients having a
490 variety of elective surgeries/procedures performed under monitored anesthesia care.

491 • Study 2 evaluated dexmedetomidine HCl in patients undergoing awake fiberoptic
492 intubation prior to a surgical or diagnostic procedure.

493 In Study 1, the sedative properties of dexmedetomidine HCl were evaluated by comparing the
494 percent of patients not requiring rescue midazolam to achieve a specified level of sedation using
495 the standardized Observer’s Assessment of Alertness/Sedation Scale (see Table 12).

496 **Table 12: 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)

497
498 Patients were randomized to receive either:

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

505 The maintenance infusion in the two dexmedetomidine groups could be titrated between 0.2
506 mcg/kg/hour to 1 mcg/kg/hour to achieve the targeted sedation score (Observer’s Assessment of
507 Alertness/Sedation Scale less than or equal to 4). Patients were allowed to receive rescue
508 midazolam as needed to achieve and/or maintain an Observer’s Assessment of Alertness/Sedation
509 Scale less than or equal to 4. After achieving the desired level of sedation, a local or regional
510 anesthetic block was performed. Demographic characteristics were similar between the
511 dexmedetomidine HCl and placebo groups. Efficacy results showed that dexmedetomidine HCl
512 groups were more effective than the placebo group when used to sedate non-intubated patients
513 requiring monitored anesthesia care during surgical and other procedures (see Table 13).

514 In Study 2, the sedative properties of dexmedetomidine HCl were evaluated by comparing the
515 percent of patients requiring rescue midazolam to achieve or maintain a specified level of
516 sedation using the Ramsay Sedation Scale score more than or equal to 2 (see Table 9). Patients
517 were randomized to receive:

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

521 After achieving the desired level of sedation, topicalization of the airway occurred. Patients were
522 allowed to receive rescue midazolam as needed to achieve and/or maintain a Ramsay Sedation
523 Scale more than or equal to 2. Demographic characteristics were similar between the
524 dexmedetomidine HCl and comparator groups. For efficacy results see Table 13.

525 **Table 13: Key Efficacy Results of Adult Procedural Sedation Studies (Study 1 and Study 2)**

Treatment Arm	Number of Patients Enrolled ^a	% Not Requiring 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	–

526 SD = Standard deviation

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

528 b Normal approximation to the binomial with continuity correction

529 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

NDC No.	Strength	Package
44567-600-04	400 mcg/4 mL	4 vials/carton
44567-601-04	1000 mcg/10 mL	4 vials/carton

532

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

534 **17 PATIENT COUNSELING INFORMATION**

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

537

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

542 Important Potential Adverse Reactions Following Drug Discontinuation

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

547 Made in Finland

548 Manufactured for:

549 **WG Critical Care, LLC**

550 Paramus, NJ 07652

551 Revised: September 2016