PRODUCT MONOGRAPH

[Pr] dexmedeTOMidine Hydrochloride For Injection

100 mcg/mL dexmedetomidine (as dexmedetomidine hydrochloride)

Mfr. Std.

(Concentrate, 2 mL vial)

Alpha$_2$-adrenergic agonist

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous infusion	Solution for Injection,100 mcg/mL in a 2 mL vial (Concentrate)	Sodium Chloride

INDICATIONS AND CLINICAL USE

Dexmedetomidine Hydrochloride for Injection is indicated for:

- **Intensive Care Unit Sedation**

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

Dexmedetomidine Hydrochloride for 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 for Injection prior to extubation.

- **Conscious Sedation**

Dexmedetomidine Hydrochloride for Injection is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures by continuous intravenous infusion for the following procedures:

- Monitored Anesthesia Care (MAC) with an adequate nerve block and/or local infiltration; and
- Awake Fiberoptic Intubation (AFI) with adequate topical preparation of the upper airway with local lidocaine formulations.

Due to insufficient safety and efficacy data, Dexmedetomidine Hydrochloride for Injection is not recommended for use in procedures other than the two listed above.

Geriatrics (> 65 years of age): Dosage adjustment in this population is recommended (see DOSAGE AND ADMINISTRATION).

Pediatrics: Dexmedetomidine Hydrochloride for Injection is not recommended in children (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Dexmedetomidine Hydrochloride for Injection should be administered only by persons skilled in the management of patients in the intensive care or operating room setting. Due to the known pharmacological effects of dexmedetomidine hydrochloride, patients should be continuously monitored while receiving Dexmedetomidine Hydrochloride for Injection.

Respiration should be monitored in non-intubated patients because of the risk of respiratory depression and in some cases apnea.

Cardiovascular

Hypotension, Bradycardia and Sinus Arrest: Clinically significant episodes of bradycardia and sinus arrest have been reported with dexmedetomidine hydrochloride administration in young, healthy adult volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration.

Reports of hypotension and bradycardia have been associated with dexmedetomidine hydrochloride infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of dexmedetomidine hydrochloride, increasing the rate of intravenous fluid administration, elevation of the lower extremities, and use of pressor agents. Because dexmedetomidine hydrochloride has the potential to augment bradycardia induced by vagal stimuli; clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (e.g., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treatment of most episodes of dexmedetomidine hydrochloride -induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

Caution should be exercised when administering Dexmedetomidine Hydrochloride for Injection to patients with advanced heart block and/or severe ventricular dysfunction. Because dexmedetomidine hydrochloride decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension and in elderly patients.

In situations where other vasodilators or negative chronotropic agents are administered, co-administration of dexmedetomidine hydrochloride could have an additive pharmacodynamic effect and should be administered with caution.

Transient Hypertension: Transient hypertension has been observed during the loading dose and maintenance period in association with the peripheral vasoconstrictive effects of dexmedetomidine hydrochloride in some patients. Transient hypertension is often referred to as paradoxical hypertension in the literature. Reduction of the infusion rate may be desirable. Treatment with a vasodilator may be needed. The use of other concomitant medications with an effect on the cardiovascular system should be reviewed to rule out potential drug interactions.

Dependence/Tolerance

Dexmedetomidine hydrochloride is not a controlled substance under the Controlled Drugs and Substances Act, but it is used only by health care professionals. The dependence potential of dexmedetomidine hydrochloride has not been studied in humans. Dexmedetomidine hydrochloride exhibits pharmacologic actions similar to those of clonidine, it may be possible that dexmedetomidine produces a clonidine-like withdrawal syndrome upon discontinuation.

Endocrine and Metabolism

The available evidence is inadequate to confirm if dexmedetomidine is associated with significant adrenocortical suppression. The adequacy of the adrenocortical function should be individually assessed and managed.

Hyperthermia

Dexmedetomidine hydrochloride may induce hyperthermia that may be resistant to traditional cooling methods. Dexmedetomidine Hydrochloride for Injection should be discontinued in the event of a sustained unexplained fever and hyperthermia should be managed with conventional medical measures. It is not known whether dexmedetomidine is safe to use in malignant hyperthermia-sensitive individuals therefore it is not recommended.

Hepatic/Biliary/Pancreatic

Since dexmedetomidine hydrochloride clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Renal

The glucuronidation and oxidation products of dexmedetomidine are eliminated through the kidney. General caution is advised in patients with severe renal impairment, especially in those with comorbidities.

Cases of polyuria, with or without hypernatremia, have been reported in patients receiving dexmedetomidine hydrochloride infusion. In clinical trials, the rate of hypernatremia was approximately 1% in adults as well as children. Dose reduction or discontinuation should be considered in patients treated with dexmedetomidine hydrochloride who develop polyuria.

Peri-Operative Considerations

Arousability: Some patients receiving dexmedetomidine hydrochloride 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.

Withdrawal

Intensive Care Unit

Dexmedetomidine Hydrochloride for Injection is indicated only for sedation of initially intubated and mechanically ventilated adult patients recovering in a post-operative care unit or an intensive care setting. During the use of Dexmedetomidine Hydrochloride for Injection in an intensive care setting, the patients must be monitored continuously, particularly for their cardiovascular safety indicators.

With administration of dexmedetomidine hydrochloride to adults for longer than 24 hours, regardless of the dose, the most common dexmedetomidine hydrochloride withdrawal related adverse events in the 48 hours after discontinuation were anxiety (6%), agitation (5%), nausea (4%), withdrawal syndrome (4%), and vomiting (3%). Symptomatic management of these adverse events may be needed.

Tachycardia and hypertension associated with elevated catecholamine may occur, with or following the events listed above. Tachycardia requiring intervention in the 48 hours following discontinuation of dexmedetomidine hydrochloride occurred in 8% of patients, and hypertension requiring intervention in the 48 hours following discontinuation of dexmedetomidine hydrochloride occurred in 4% of patients. If tachycardia and/or hypertension occurs after discontinuation of dexmedetomidine hydrochloride supportive therapy is indicated.

Conscious Sedation

Withdrawal symptoms were not seen after discontinuation of short term infusion of dexmedetomidine hydrochloride (<6 hours) in adult subjects.

Patient Counselling Information

Dexmedetomidine Hydrochloride for Injection is indicated for short-term intravenous sedation. Dosage must be individualized and titrated to the desired clinical effect. Blood pressure, heart rate and oxygen levels will be monitored both continuously during the infusion of Dexmedetomidine Hydrochloride for Injection and as clinically appropriate after discontinuation.

- When Dexmedetomidine Hydrochloride for Injection is infused for more than 6 hours, patients should be informed to report nervousness, agitation, and headaches that may occur for up to 48 hours after discontinuation of Dexmedetomidine Hydrochloride for Injection.
- Additionally, patients should be informed to report symptoms that may occur within 48 hours after the administration of Dexmedetomidine Hydrochloride for Injection such as: weakness, confusion, excessive sweating, weight loss, abdominal pain, salt cravings, diarrhea, constipation, dizziness or light-headedness.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Dexmedetomidine has been shown to cross the placental barrier in both animal and human published studies.

The limited available information on dexmedetomidine hydrochloride use during pregnancy is not sufficient to inform a drug-associated risk of birth defects or miscarriage. Dexmedetomidine Hydrochloride for Injection should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

It has been reported that prenatal exposure to dexmedetomidine may be associated with some degree of functional impairment at birth in some neonates.

Labor and Delivery: Perioperative administration of dexmedetomidine in pregnant women receiving general anesthesia for elective caesarean section was associated with a longer time to clinical recovery and extubation compared with other anesthetic agents.

Therefore, Dexmedetomidine Hydrochloride for Injection is not recommended during labor and delivery including cesarean section deliveries.

Nursing Women: Dexmedetomidine is excreted in human milk with detectable levels of dexmedetomidine falling below the limit of detection after 24 hours. The effects on milk production and the risk to breastfed children are unknown. Therefore, the benefits of breastfeeding and potential risk to the breastfed infant should be considered along with the mother's clinical need for dexmedetomidine.

Pediatrics: Dexmedetomidine Hydrochloride for Injection is not recommended in children (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Pharmacology).

Geriatrics: The pharmacokinetic profile of dexmedetomidine hydrochloride was not altered by age. There were no differences in the pharmacokinetics of dexmedetomidine hydrochloride in young (18–40 years), middle age (41–65 years), and elderly (>65 years) subjects. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function.

Intensive Care Unit Sedation

A total of 1094 patients in the clinical studies were 65 years of age and over. A total of 372 patients were 75 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of dexmedetomidine hydrochloride. Therefore a dose reduction should be considered in patients over 65 years of age (see DOSAGE AND ADMINISTRATION).

Conscious Sedation

A total of 131 patients in the 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 hydrochloride-treated patients 65 years or older (72%) and 75 years or older (74%) as compared to patients <65 years (47%). Pre-specified criteria for the vital signs to be reported as adverse reactions are footnoted below Table 3 (see ADVERSE REACTIONS). A reduced loading dose

of 0.5 mcg/kg given over 10 minutes is recommended and a reduction in the maintenance infusion should be considered for patients greater than 65 years of age (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Use of dexmedetomidine hydrochloride has been associated with the following serious adverse reactions:

- Hypotension, bradycardia and sinus arrest (see WARNINGS AND PRECAUTIONS),
- Transient hypertension (see WARNINGS AND PRECAUTIONS).

Most common treatment-emergent adverse reactions, occurring in greater than 2% of adult patients in both Intensive Care Unit and conscious sedation studies include hypotension, bradycardia and dry mouth.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Intensive Care Unit Sedation

Adverse event information derived from the placebo-controlled, continuous infusion trials of dexmedetomidine hydrochloride for sedation in the surgical intensive care unit setting in which 387 adult patients received dexmedetomidine hydrochloride. In these studies, the mean total dose was 7.06 mcg/kg (SD = 2.86), mean dose per hour was 0.51 mcg/kg/hr (SD = 0.39) and the mean duration of infusion of 15.6 hours (range: 0.17 to 29.08). Midazolam or propofol was used as the rescue medication for adult patients on dexmedetomidine hydrochloride or placebo. The population was between 19 to 83 years of age, 43% > 65 years of age, 73% male and 97% Caucasian. Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia (see Table 1).

Table 1: Treatment-Emergent Adverse Events Occurring in >1% Of All Adult Dexmedetomidine-Treated Patients in the Randomized Placebo-controlled Continuous Infusion Short-Term Intensive Care Unit Sedation Studies

Adverse Event	Randomized Dexmedetomidine* (N=387)	Placebo with Midazolam Rescue (N=181)	Placebo with Propofol Rescue (N=198)
Hypotension	28%	15%	10%
Hypertension	16%	13%	23%
Nausea	11%	9%	10%
Bradycardia	7%	3%	2%

Table 1: Treatment-Emergent Adverse Events Occurring in >1% Of All Adult Dexmedetomidine-Treated Patients in the Randomized Placebo-controlled Continuous Infusion Short-Term Intensive Care Unit Sedation Studies

Adverse Event	Randomized Dexmedetomidine* (N=387)	Placebo with Midazolam Rescue (N=181)	Placebo with Propofol Rescue (N=198)
Fever	5%	6%	4%
Vomiting	4%	6%	6%
Atrial Fibrillation	4%	4%	3%
Hypoxia	4%	5%	3%
Tachycardia	3%	7%	3%
Hemorrhage	3%	6%	4%
Anemia	3%	4%	1%
Dry Mouth	3%	2%	<1%
Rigors	2%	3%	4%
Agitation	2%	3%	3%
Hyperpyrexia	2%	3%	2%
Pain	2%	3%	1%
Hyperglycemia	2%	3%	1%
Acidosis	2%	<1%	3%
Pleural Effusion	2%	<1%	2%
Oliguria	2%	1%	<1%
Thirst	2%	<1%	<1%

* Data combined from studies conducted in post-surgical patients recovering in an ICU setting.

Dexmedetomidine Hydrochloride for Injection is not recommended in children. Three preliminary studies were conducted, two in 42 neonates between 28 to 44 weeks of gestational age and one in 175 children between 1 month to <17 years of age, all in an intensive care setting for up to 24 hours. The safety profile in pediatrics was generally consistent with the underlying disease conditions, the other medications used in this patient group, and similar to that observed in adults. The most frequent treatment emergent adverse events in neonates between 28 to 44 weeks of gestational age were anger (6/42, 14.3%) and hypokalemia (3/42, 7.1%). For children between 1 month to <17 years of age, the most frequent treatment emergent adverse events were hypokalemia (14/175, 8.0%), pyrexia (12/175, 6.9%), hypotension (11/175, 6.3%) and agitation (9/175, 5.1%). Among these events reported in pediatric patients, the events of anger in neonates and hypokalemia in older children occur with greater frequency in pediatrics than in adults.

Intensive Care Unit Sedation of longer duration

Adverse event information is derived from studies using dexmedetomidine hydrochloride or active control administered as continuous infusion for maintenance of sedation in the Intensive Care Units in three studies that included adult patients from medical, surgical and trauma intensive care units. The mean total dexmedetomidine hydrochloride dose was 53.6 mcg/kg with a mean infusion rate per hour of 0.76 mcg/kg/hr (standard deviation = 0.36 mcg/kg/h). The mean duration of dexmedetomidine hydrochloride infusion was 65.5 hours (standard deviation = 59.70 hours). The majority of patients (68.6%, 506/737) received dexmedetomidine hydrochloride for 72 hours or less, with 26.7% (197/737) for 24 hours or less. The dexmedetomidine hydrochloride population was between 18 to 97 years of age, 49.5% ≥65 years of age, 59% male and 91.3% Caucasian.

Treatment-emergent adverse events are provided in Table 2 and reflect incidence rates for dexmedetomidine hydrochloride and active control groups. The most frequent dexmedetomidine hydrochloride adverse events were hypotension and bradycardia, consistent with alpha$_2$-adrenergic agonist physiologic effects (see WARNINGS AND PRECAUTIONS).

Table 2: Treatment-Emergent Adverse Events Occurring in >2% of Dexmedetomidine Hydrochloride Patients in Long-Term Intensive Care Unit Sedation Studies[1]

Preferred Term	Active Control 1 N=247	Active Control 2 N=372	Dexmedetomidine Hydrochloride N=737
Hypertension	15%	33%	32%
Hypertension Requiring Intervention	12%	20%	17%
Hypotension	11%	27%	31%
Hypotension Requiring Intervention	11%	14%	17%
Tachycardia	11%	32%	26%
Tachycardia Requiring Intervention	6%	6%	7%
Bradycardia	10%	13%	25%
Bradycardia Requiring Intervention	5%	1%	6%
Agitation	11%	13%	10%
Atrial fibrillation	12%	10%	8%
Anxiety	8%	3%	7%
Hypokalemia	2%	7%	7%
Nausea	4%	2%	6%
Pyrexia	2%	6%	5%
Diarrhea	5%	3%	4%
Constipation	1%	5%	4%
Anemia	2%	5%	4%
Hypoglycemia	1%	3%	4%
Delirium	7%	6%	4%
Insomnia	1%	2%	4%
Pneumonia	2%	4%	4%
Vomiting	2%	3%	4%
Hyperglycemia	0%	2%	4%
Pleural effusion	11%	3%	3%
Respiratory failure	5%	3%	3%
Withdrawal syndrome	3%	2%	3%
Supraventricular tachycardia	4%	2%	3%
Acute respiratory distress syndrome	3%	1%	2%
Sepsis	1%	2%	2%
Endotracheal intubation complication	3%	2%	2%

[1] Patients could receive concomitant analgesics or sedatives during treatment as clinically required.

Conscious Sedation

Adverse event information is derived from the two trials for conscious sedation in which 318 adult patients received dexmedetomidine hydrochloride. Midazolam was used as the rescue medication for patients on dexmedetomidine hydrochloride or placebo. The mean total dose was 1.6 mcg/kg (range: 0.5 to 6.7), mean dose per hour was 1.3 mcg/kg/hr (range: 0.3 to 6.1) and the mean duration of infusion of 1.5 hours (range: 0.1 to 6.2). The population was between 18 to 93 years of age, 30% > 65 years of age, 52% male and 61% Caucasian.

Treatment-emergent adverse events occurring at an incidence of >2% are provided in Table 3. The most frequent adverse events were hypotension, bradycardia, and dry mouth. 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 hydrochloride and comparator groups in both studies.

Table 3: Adverse Events with an Incidence > 2% - Conscious Sedation Adult Population

Body System/ Adverse Event	**Dexmedetomidine Hydrochloride N = 318**	**Placebo N = 113**
	n (%)	n (%)
Vascular disorders		
Hypotension[1]	173 (54%)	34 (30%)
Hypertension[2]	41 (13%)	27 (24%)
Respiratory, thoracic and mediastinal disorders		
Respiratory depression[5]	117 (37%)	36 (32%)
Hypoxia[6]	7 (2%)	3 (3%)
Bradypnea	5 (2%)	5 (4%)
Cardiac disorders		
Bradycardia[3]	45 (14%)	4 (4%)
Tachycardia[4]	17 (5%)	19 (17%)
Gastrointestinal disorders		
Nausea	10 (3%)	2 (2%)
Dry mouth	8 (3%)	1 (1%)

[1] Hypotension was defined in absolute and relative terms as Systolic blood pressure of <80 mmHg or ≤30% lower than pre-study drug infusion value, or Diastolic blood pressure of <50 mmHg

[2] Hypertension was defined in absolute and relative terms as Systolic blood pressure >180 mmHg or ≥30% higher than pre-study drug infusion value or Diastolic blood pressure of >100 mmHg.

[3] Bradycardia was defined in absolute and relative terms as <40 bpm or ≤30% lower than pre-study drug infusion value.

[4] Tachycardia was defined in absolute and relative terms as >120 bpm or ≥30% greater than pre-study drug infusion value.

[5] Respiratory Depression was defined in absolute and relative terms as respiratory rate (RR) <8 bpm or >25% decrease from baseline

[6] Hypoxia was defined in absolute and relative terms as SpO_2 < 90% or 10% decrease from baseline

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post approval use of dexmedetomidine hydrochloride. 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 hydrochloride during post approval use of the drug.

Table 4: Adverse Events Experienced During Post approval Use of Dexmedetomidine Hydrochloride

Body System	Preferred Term
Body as a Whole	Fever, hyperpyrexia, hypovolemia, light anesthesia, pain, rigors
Cardiovascular Disorders, General	Blood pressure fluctuation, heart disorder, hypertension, hypotension, myocardial infarction
Central and Peripheral Nervous System Disorders	Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion
Gastrointestinal System Disorders	Abdominal pain, diarrhea, vomiting, nausea
Heart Rate and Rhythm Disorders	Arrhythmia, ventricular arrhythmia, bradycardia, hypoxia, atrioventricular block, cardiac arrest, extrasystoles, atrial fibrillation, heart block, t wave inversion, tachycardia, supraventricular tachycardia, ventricular tachycardia
Liver and Biliary System Disorders	Increased gamma-glutamyl transpeptidase, hepatic function abnormal, hyperbilirubinemia, increased alanine transaminase, increased aspartate aminotransferase
Metabolic and Nutritional Disorders	Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, hypoglycemia, hypernatremia
Psychiatric Disorders	Agitation, confusion, delirium, hallucination, illusion
Red Blood Cell Disorders	Anemia
Renal disorders	Blood urea nitrogen increased, oliguria, polyuria (See also WARNINGS AND PRECAUTIONS, Renal)
Respiratory System Disorders	Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vascular disorders	Hemorrhage
Vision Disorders	Photopsia, abnormal vision

DRUG INTERACTIONS

Drug-Drug Interactions

Anesthetics, sedatives, hypnotics, opioids
Co-administration of dexmedetomidine hydrochloride with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed enhanced effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine hydrochloride and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with dexmedetomidine hydrochloride, a reduction in dosage of dexmedetomidine hydrochloride or the concomitant anesthetic, sedative, hypnotic or opioid may be required.

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

Drugs with cardiovascular activities

Dexmedetomidine hydrochloride is known to be associated with hypotension and bradycardia, especially during its initial use. However, it may also be associated with a transient or paradoxical hypertension which may occur during the initial use and maintenance use. Concomitant medications acting on the cardiovascular system should be reviewed, in addition to reducing the dexmedetomidine dose and/or using a vasodilator.

Cytochrome P-450
In vitro studies in human liver microsomes demonstrated no evidence of cytochrome P450 mediated drug interactions that are likely to be of clinical relevance.

DOSAGE AND ADMINISTRATION

Dosing Considerations
- Dexmedetomidine Hydrochloride for Injection should be used only in facilities adequately staffed and equipped for anesthesia, resuscitation, and cardiovascular monitoring.
- Dexmedetomidine Hydrochloride for Injection should not be generally used for a duration longer than 24 hours. Its continued use beyond 24 hours should be determined based on careful assessment of the patient's conditions.
- Dexmedetomidine Hydrochloride for Injection should be administered using a controlled infusion device with adequate precision.

Recommended Dose and Dosage Adjustment

Intensive Care Unit Sedation

Initiation

- Dexmedetomidine Hydrochloride for Injection is used for adult patients already intubated and sedated in an intensive care setting.
- An assessment of the level of sedation and the need for Dexmedetomidine Hydrochloride for Injection should precede the initiation of dexmedetomidine hydrochloride for Injection.
- For patients being converted from alternate sedative therapy, a loading dose is generally not necessary. Dexmedetomidine Hydrochloride for Injection may be initiated with a loading infusion of up to 1 mcg/kg over 20 minutes, if needed.

Maintenance

- Adult patients will generally require a maintenance infusion of 0.2 to 1.1 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the optimal level of sedation. Caution is advised when using doses higher than 0.7 mcg/kg/hr. Experience is limited at doses higher than 1.1 mcg/kg/hr. A dose higher than 1.4 mcg/kg/hr should not be attempted.
- Dexmedetomidine Hydrochloride for Injection use beyond 24 hours must be assessed individually. Patients must be assessed at regular intervals for the need to continuing sedation. The experience of dexmedetomidine hydrochloride longer than 4 days is limited.

- Another intravenous sedative (e.g. midazolam or propofol) may be added according to clinical assessment. Opioids or neuromuscular blocking agents may also be used, based on individual assessment.
- The need for Dexmedetomidine Hydrochloride for Injection continuous infusion post-extubation must be assessed individually. In post-surgical ICU patients exposed for <24 hours, the dose of Dexmedetomidine Hydrochloride for Injection should be reduced by half after extubation. In clinical studies, the mean time of continued infusion observed post-extubation in these post-surgical ICU patients was approximately 6.6 hours.
- A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic function and in patients over 65 years of age.

Conscious Sedation
- Based on the Ramsay and Observer's Assessment of Alertness/Sedation Scales, the loading infusion provides clinically effective onset of sedation 10 to 15 minutes after start of infusion.
- For use in Monitored Anesthesia Care, an adequate nerve block and/or local infiltration should be used.
- For Awake Fiberoptic Intubation, the upper airway should be topicalized with proper lidocaine formulations.

Initiation
For adult patients, Dexmedetomidine Hydrochloride for Injection is generally initiated with a loading infusion of 1 mcg/kg over 10 minutes.

For patients over 65 years of age or those undergoing less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg over 10 minutes may be suitable.

Maintenance
The maintenance infusion of Dexmedetomidine Hydrochloride for Injection is generally initiated at 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

Following the load in awake fiberoptic intubation, a fixed maintenance dose of 0.7 mcg/kg/hr is recommended until the endotracheal tube is secured.

Dosage Adjustment
Due to possible pharmacodynamic interactions, a reduction in dosage of dexmedetomidine hydrochloride or other concomitant anesthetics, sedatives, hypnotics or opioids may be required when co-administered.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic function and in patients over 65 years of age.

Administration

Dexmedetomidine Hydrochloride for Injection 100 mcg/mL (200 mcg/2 mL)

Dexmedetomidine Hydrochloride for Injection 100 mcg/mL must be diluted in 0.9% sodium chloride injection to achieve required concentration (4 mcg/mL) prior to administration. Preparation of solutions is the same, whether for the loading dose or maintenance infusion.

Strict aseptic technique must always be maintained during handling of Dexmedetomidine Hydrochloride for Injection.

To prepare the infusion, withdraw 2 mL of Dexmedetomidine Hydrochloride for Injection and add to 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Shake gently to mix well. The reconstituted solution is stable for 25 hours at room temperature (15 - 30°C).

Compatibility with Other Fluids
Dexmedetomidine Hydrochloride for Injection has been shown to be compatible when administered with the following intravenous fluids: Lactated Ringers, 5% Glucose in Water for Injection, 0.9% Sodium Chloride in Water for Injection and 20% Mannitol in Water for Injection.

Dexmedetomidine has been found to be compatible with water solutions of the following drugs when administered via Y-site injections: thiopental sodium, vecuronium bromide, pancuronium bromide, glycopyrrolate bromide, phenylephrine hydrochloride.

Parenteral drug products should be inspected visually for clarity, particulate matter, precipitate and discoloration prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate or discoloration or leakage should not be used. Discard unused portion.

Compatibility with Natural Rubber
Compatibility studies have demonstrated the potential for absorption of dexmedetomidine hydrochloride to some types of natural rubber. Although Dexmedetomidine Hydrochloride for Injection is dosed to effect, it is advisable to use administration components made with synthetic or coated natural rubber gaskets.

Incompatibilities
Dexmedetomidine hydrochloride infusion should not be co-administered through the same intravenous catheter with blood, serum, or plasma because physical compatibility has not been established.

Dexmedetomidine hydrochloride has been shown to be incompatible when administered with the following drugs: amphotericin B, diazepam.

OVERDOSAGE

The tolerability of dexmedetomidine hydrochloride was studied in one study in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 1.4 mcg/kg/hr. The maximum blood concentration achieved in this study was approximately 6 times the upper boundary of the therapeutic range. The most notable effects observed in two subjects

who achieved the highest doses were first degree atrioventricular block and second degree heart block. No hemodynamic compromise was noted with the atrioventricular block and the heart block resolved spontaneously within one minute.

Four adult patients received an overdose of dexmedetomidine hydrochloride in the intensive care unit sedation studies. One patient received a 2 mcg/kg loading dose over 10 minutes (twice the recommended loading dose). Two other patients who received a 2 mcg/kg loading dose over 10 minutes, experienced bradycardia and/or hypotension. One patient who received a loading bolus dose of undiluted dexmedetomidine hydrochloride (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

General

Dexmedetomidine hydrochloride is a relatively selective alpha$_2$-adrenergic agonist with sedative properties. Alpha$_2$ selectivity is observed in animals following slow intravenous infusion of low and medium doses (10–300 mcg/kg). Both alpha1 and alpha$_2$ activity is observed following slow intravenous infusion of high doses (≥1000 mcg/kg) or with rapid intravenous administration.

In a study in healthy volunteers (N=10), respiratory rate and oxygen saturation remained within normal limits and there was no evidence of respiratory depression when dexmedetomidine hydrochloride was administered by intravenous infusion at doses within the prespecified dose range (0.2 – 0.7 mcg/kg/hr).

Clinical Pharmacology

Pharmacokinetics

Following intravenous administration, dexmedetomidine exhibits 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 is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when administered by intravenous infusion for up to 24 hours. Table 5 shows the main pharmacokinetic parameters when dexmedetomidine hydrochloride was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 mcg/kg/hr (target plasma concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 mcg/kg/hr (target plasma concentration of 0.6 ng/mL) for 24 hours, and 0.70 mcg/kg/hr (target plasma concentration of 1.25 ng/mL) for 24 hours.

Table 5: 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 Target 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 Css #, 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.
# Avg Css = Average steady-state concentration of dexmedetomidine. (2.5 − 9 hour samples for 12 hour infusion and 2.5 − 18 hour samples for 24 hour infusions).

Population pharmacokinetic analysis suggests similar pharmacokinetic behavior of dexmedetomidine with short (<24 hours) and long-term (> 24 hours) infusions, including the lack of accumulation of dexmedetomidine. Linear pharmacokinetics are observable in administration over the dose range of 0.2 mcg/kg/hr to 1.4 mcg/kg/hr, for all time periods. The values for clearance (CL), volume of distribution (V), and $t_{1/2}$ were 39.4 L/hr, 152 L, and 2.67 hours, respectively for infusion durations greater than 24 hours.

Distribution

The steady-state volume of distribution (V_{ss}) of dexmedetomidine is 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. Protein binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects.

The potential for protein binding displacement of dexmedetomidine by 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 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.

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 with a minor role of CYP1A2, CYP2E1,CYP2D6 AND CYP2C19) 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.

Elimination
The terminal elimination half-life ($t_{1/2}$) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39 L/h. 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.

Special Populations and Conditions

Pediatrics: The pharmacodynamics of dexmedetomidine hydrochloride was assessed in 134 patients in four clinical trials and reflect the patient disease conditions, the use of other agents in ICU, and effects of dexmedetomidine. The pharmacokinetic results from 96 patients age 1 month to <17 years in three clinical trials demonstrated that dexmedetomidine clearance increased with increasing age and weight-adjusted clearance decreased with increasing age with values from older children approaching those in adults. Pharmacokinetic results from 28 patients age 28 weeks gestational age to <1 month in one clinical trial demonstrated clearance and weight-adjusted clearance values similar to those of older children 6 to <17 years of age. The pharmacokinetic data indicate that weight-adjusted clearance is fastest in the 1 – 24 months group and decreases in the 2 – 17 years group. Dexmedetomidine Hydrochloride for Injection use is not recommended in children.

The use of dexmedetomidine hydrochloride for conscious sedation in pediatric patients has not been evaluated.

Geriatrics: The pharmacokinetic profile of dexmedetomidine hydrochloride was not altered by age. There were no differences in the pharmacokinetics of dexmedetomidine hydrochloride in young (18 − 40 years), middle age (41 − 65 years), and elderly (>65 years) subjects. However, in clinical trials an increased incidence of adverse events was observed in the elderly, and a dose reduction for both the loading and maintenance infusions should be considered in patients over 65 years of age (see DOSAGE AND ADMINISTRATION).

Gender: There was no observed difference in dexmedetomidine hydrochloride pharmacokinetics due to gender.

Hepatic Impairment: In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine hydrochloride 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. In clinical trials, an increased incidence of adverse events was observed in these patients, and a dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Renal Impairment: Dexmedetomidine hydrochloride pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL, and V_{ss}) were not significantly different in patients with severe renal impairment (creatinine clearance: <30 mL/min) compared to healthy subjects. Following infusion of dexmedetomidine hydrochloride for >24 hours, pharmacokinetic parameters for dexmedetomidine were similar from patients whose laboratory indicators suggest mild, moderate, severe or no renal impairment.

Concomitant Opioid Use: In Intensive Care Unit studies <24 hours, 41-44% of dexmedetomidine hydrochloride treated patients received no morphine sulfate for pain versus 15-19% in the placebo-treated patients.

In Intensive Care Unit studies, where patients received dexmedetomidine hydrochloride for longer than 24 hours, 21-22% of dexmedetomidine hydrochloride treated patients received no fentanyl for pain similar to active control (GABA-agonist or benzodiazepines) - treated patients.

In conscious sedation, 39.6-56.6% of dexmedetomidine hydrochloride treated patients received no fentanyl for pain versus 11.1% of placebo-treated patients.

Sedation of Longer Duration:
In three randomized double blind active controlled clinical trials in 1356 patients, continuous infusion of dexmedetomidine hydrochloride was evaluated in intensive care unit sedation of longer duration at maintenance doses between 0.2 and 1.4 mcg/kg/hr. Patients were from medical, surgical or trauma intensive care units; and they were initially intubated, and received mechanical ventilation. Dexmedetomidine hydrochloride use beyond 24 hours must be assessed individually (see DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

Store at 15 to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dexmedetomidine Hydrochloride for Injection is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution.

Each 1 mL of Dexmedetomidine Hydrochloride for Injection contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg dexmedetomidine and 9 mg of sodium chloride in Water for Injection. The solution is preservative-free and contains no additives or chemical stabilizers.

Dexmedetomidine Hydrochloride for Injection, 100 mcg/mL is available in 2 mL clear glass vials (200 mcg/2 mL). Vials are intended for single use only.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

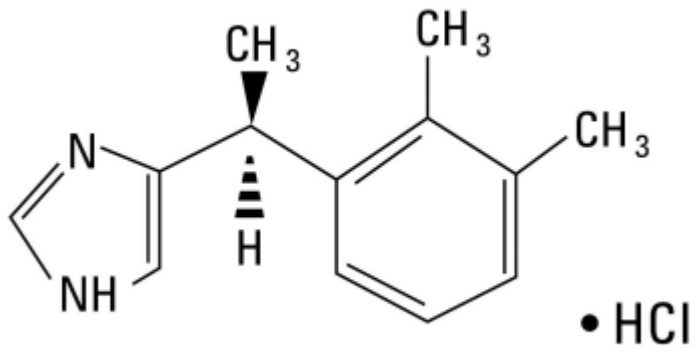
Proper name: dexmedetomidine hydrochloride

Chemical name: (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazolemonohydrochloride.

Molecular formula: $C_{13}H_{16}N_2 \cdot HCl$

Molecular mass: 236.7

Structural formula:



Physicochemical properties: Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1.

CLINICAL TRIALS

The safety and efficacy of dexmedetomidine hydrochloride has been evaluated in four randomized, double-blind, placebo- controlled multicenter clinical trials in 1185 patients.

Study results

Intensive Care Unit Sedation < 24 hours

Two randomized, double-blind, parallel-group, placebo-controlled multicenter clinical trials included 754 adult patients being treated in a surgical intensive care unit. All patients were initially intubated and received mechanical ventilation. These trials evaluated the sedative properties of dexmedetomidine hydrochloride by comparing the amount of rescue medication (midazolam in one trial and propofol in the second) required to achieve a specified level of sedation (using the standardized Ramsay sedation scale) between dexmedetomidine hydrochloride and placebo from onset of treatment to extubation or to a total treatment duration of 24 hours. The Ramsay Level of Sedation Scale is displayed in Table 6.

Table 6: Ramsay Sedation Scale

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

In the first study, 175 adult patients were randomized to receive placebo and 178 to receive dexmedetomidine hydrochloride by intravenous infusion at a dose of 0.4 mcg/kg/hr (with allowed adjustment between 0.2 and 0.7 mcg/kg/hr) following an initial loading infusion of one mcg/kg intravenous over 10 minutes. The study drug infusion rate was adjusted to maintain a Ramsay sedation score of ≥3. Patients were allowed to receive "rescue" midazolam as needed to augment the study drug infusion. In addition, morphine sulfate was administered for pain as needed.

The prospective primary analysis assessed the sedative effects of dexmedetomidine hydrochloride by comparing the percentage of patients who achieved a Ramsay sedation score of ≥ 3 during intubation without the use of additional rescue medication. A significantly greater percentage of patients in the dexmedetomidine hydrochloride group maintained a Ramsay sedation score of ≥ 3 without receiving any midazolam rescue compared to the placebo group (see Table 7).

Table 7: Midazolam use as rescue medication during intubation (ITT) Study One			
	Placebo N=175	Dexmedetomidine Hydrochloride N=178	p-value
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.
*Chi-square

In a second study, 198 adult patients were randomized to receive placebo and 203 to receive dexmedetomidine hydrochloride by intravenous infusion at a dose of 0.4 mcg/kg/hr (with allowed adjustment between 0.2 and 0.7 mcg/kg/hr) following an initial loading infusion of one mcg/kg intravenous over 10 minutes. The study drug infusion was adjusted to maintain a Ramsay sedation score of ≥3. Patients were allowed to receive "rescue" propofol as needed to augment the study drug infusion. In addition, morphine sulfate was administered as needed for pain.

A significantly greater percentage of patients in the dexmedetomidine hydrochloride group compared to the placebo group maintained a Ramsay sedation score of ≥ 3 without receiving any propofol rescue (see Table 8).

Table 8: Propofol use as rescue medication during intubation (ITT) Study Two			
	Placebo N=198	Dexmedetomidine Hydrochloride N=203	p-value
Categorized propofol use			
0 mg	47 (24%)	122 (60%)	<0.001*
0-50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

*Chi-square

Conscious Sedation

The safety and efficacy of dexmedetomidine hydrochloride for sedation of non-intubated adult patients prior to and/or during surgical and other procedures was evaluated in two randomized, double-blind, placebo-controlled multicenter clinical trials. Study 1 evaluated the sedative properties of dexmedetomidine hydrochloride in adult patients having a variety of elective surgeries/procedures performed under monitored anesthesia care. Study 2 evaluated dexmedetomidine hydrochloride in adult patients undergoing awake fiberoptic intubation prior to a surgical or diagnostic procedure.

In Study 1, the sedative properties of dexmedetomidine hydrochloride were evaluated by comparing the percent of adult patients not requiring rescue midazolam to achieve a specified

level of sedation using the standardized Observer's Assessment of Alertness/Sedation Scale (Table 9).

Table 9: Observer's Assessment of Alertness/Sedation

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 a loading infusion of either dexmedetomidine hydrochloride 1 mcg/kg, 0.5 mcg/kg, or placebo (normal saline) given over 10 minutes and followed by a maintenance infusion started at 0.6 mcg/kg/hr. The maintenance infusion of study drug could be titrated from 0.2 mcg/kg/hr to 1 mcg/kg/hr to achieve the targeted sedation score (Observer's Assessment of Alertness/Sedation Scale ≤ 4). Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an Observer's Assessment of Alertness/Sedation Scale < 4. After achieving the desired level of sedation, a local or regional anesthetic block was performed. Demographic characteristics were similar between the dexmedetomidine hydrochloride and comparator groups.

Efficacy results showed that dexmedetomidine hydrochloride was more effective than the comparator group when used to sedate non-intubated patients requiring monitored anesthesia care during surgical and other procedures (see Table 10).

In Study 2 the sedative properties of dexmedetomidine hydrochloride were evaluated by comparing the percent of adult patients requiring rescue midazolam to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale score > 2 (Table 5). Patients were randomized to receive a loading infusion of dexmedetomidine hydrochloride of 1 mcg/kg or placebo (normal saline) given over 10 minutes and followed by a fixed maintenance infusion of 0.7 mcg/kg/hr. After achieving the desired level of sedation, topicalization of the airway was carried out with lidocaine formulations. Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain a Ramsay Sedation Scale > 2. Demographic characteristics were similar between the dexmedetomidine hydrochloride and comparator groups. For efficacy results see Table 10.

Table 10: Key Efficacy Results of Conscious Sedation Studies

Study	Treatment Arm	No. of Adult Patients Enrolled[a]	% Not Requiring midazolam rescue	Confidence[b] interval on the difference vs. placebo	Mean (SD) Total Dose (mg) of Rescue midazolam Required	Confidence[b] intervals of the mean rescue dose
Study 1	Dexmedetomidine Hydrochloride 0.5 mcg/kg	134	40	37 (27,48)	1.4 (1.7)	-2.7 (-3.4, -2.0)
	Dexmedetomidine Hydrochloride 1 mcg/kg	129	54	51 (40,62)	0.9 (1.5)	-3.1 (-3.8, -2.5)
	PBO	63	3	–	4.1 (3.0)	–
Study 2	Dexmedetomidine Hydrochloride 1 mcg/kg	55	53	39 (20,57)	1.1 (1.5)	-1.8 (-2.7, -0.9)
	PBO	50	14	–	2.9 (3.01)	–

Notes:

[a] Based on ITT population defined as all randomized and treated

[b] Normal approximation to the binomial with continuity correction.

DETAILED PHARMACOLOGY

Primary Pharmacodynamics

Dexmedetomidine administered subcutaneously (SC) in mice using the rotarod and traction tests indicated that it was a poor muscle-relaxant, and that it impaired motor coordination only at the clearly sedative doses of 0.01 and 0.1 mg/kg.

Secondary Pharmacodynamics

Dexmedetomidine administered subcutaneously in doses up to 0.3 mg/kg in fed rats demonstrated a significant, dose-dependent elevation of blood glucose levels, with negative correlation to plasma immunoreactive insulin levels. Insulin secretion was almost totally inhibited beginning at the 0.1 mg/kg dose. Dexmedetomidine did not show any effect on the level of free fatty acids.

Dexmedetomidine given intravenously is devoid of clear CNS activity up to 0.001 mg/kg in mice and rats; at higher doses (≥ 0.003 mg/kg), dexmedetomidine induced clear CNS depressant effects.

Pharmacokinetics

In beagle dogs, dexmedetomidine was rapidly eliminated following a 50 mcg/kg IV dose with a mean apparent $t_{1/2}$ of 0.68 hour; plasma elimination $t_{1/2}$ was slightly longer following intra-muscular (IM) dosing.

Rats administered an intravenous 20 mcg/kg dose of [^{3}H]dexmedetomidine showed drug-related radioactivity widely distributed throughout the body, with the highest mean concentrations in blood, plasma, and selected tissues occurring from 0.25 to 12 hours postdose.

[^{3}H]dexmedetomidine was extensively metabolized by rats. Less than 1% of the dose was excreted in the urine as the parent drug. Major urinary metabolites included the COOH, OH, G-OH, SO3OH, M-2, and M-5 metabolites. Levels of the SO3OH metabolite were greater in female urine than in male urine. Fecal patterns generally resembled those found in urine.

The metabolism of [^{3}H]dexmedetomidine in beagle dogs was similar to that observed in rats. Biliary excretion of [^{3}H]dexmedetomidine following IV and SC administration was studied in rats with an implanted bile-duct cannula; an average of 51.6% and 45.4% of the radioactive dose was recovered in rat bile 24 hours after IV and SC administration, respectively. Major biliary metabolites were the glucuronide of a hydroxylated metabolite (G-OH) and an unidentified conjugate, M-2. Unidentified metabolites represented 12% to 18% of the dose.

Lacteal excretion, tissue distribution, and placental transfer of radioactivity were studied in rats following administration of a 0.015 mg/kg SC dose of [^{3}H]dexmedetomidine. Radioactivity was distributed in maternal tissues and crossed the placenta to distribute in fetal tissues. Drug-related radioactivity was detected in the milk of dams at 0.5 hours and reached a maximum mean concentration at 4 hours. Thereafter, levels of radioactivity in milk decreased to non-detectable levels at 72 hours. The milk:plasma concentration ratio was less than 1 at all collection time points, indicating that radioactivity did not accumulate in the milk.

TOXICOLOGY

Acute Toxicity

The highest non-lethal dose by intravenous injects was 1000 mcg/kg in mice, rats and dogs in both sexes.

In a rat neurotoxicity study, Day 7 postnatal rat pups subcutaneously injected with dexmedetomidine hydrochloride (3 mcg/kg or 10 mcg/kg or 30 mcg/kg), did not produce significant degeneration in the limbic thalamic nuclei and limbic cortical regions compared to ketamine (20 mg/kg), which resulted in significant neuronal cell death and degeneration. This was determined by histological staining (silver, Fluoro-Jade B, and Caspase-3) to detect neuroapoptosis and neurodegeneration in postnatal rat pup brains.

Long-Term Toxicology

A two-week IV infusion study in adult dogs was performed to investigate the potential effect of dexmedetomidine on toxicologic, pathologic, and hormone secretion parameters. Dexmedetomidine at 50 or 100 mcg/kg/day was well-tolerated, with treatment-related effects (sedation, hypothermia (↓ 3-4°C)) reversed by the end of the recovery period. Dexmedetomidine increased cortisol secretion, decreased LH secretion in males, decreased TSH secretion, and at the 100 mcg/kg/day dose level, decreased ACTH-stimulated cortisol secretion.

Rats receiving dexmedetomidine by IV administration for four weeks at doses up to 160 mcg/kg/day showed sedation and piloerection occurring at all doses, with exophthalmos observed only at the highest dose. No deaths occurred. Based on the drug-related small decreases in thymus and body weights at 160 mcg/kg/day, the no-toxic-effect-dose (NTED) of dexmedetomidine was determined to be 40 mcg/kg/day.

Carcinogenicity
Animal carcinogenicity studies have not been performed with dexmedetomidine.

Genotoxicity
Dexmedetomidine was not found to be mutagenic in the *Ames Salmonella* and *E. coli* assays, L5178/tk+/- mouse lymphoma assay, *in vitro* human lymphocyte cytogenics assays, and *in vivo* mouse micronucleus assays. No structural or numerical chromosome aberrations were noted in the presence or absence of metabolic activation. Dexmedetomidine did not demonstrate clastogenic activity.

Reproductive Toxicology
Reproductive and developmental toxicity studies were performed with dexmedetomidine in rats and rabbits.

A fertility study (Segment I) in rats at doses up to 54 mcg/kg/day administered subcutaneously showed that the No-Observed-Adverse-Effect Level (NOAEL) for F0 males and females was 54 mcg/kg/day for fertility indices and 6 mcg/kg/day for systemic toxicity. The NOAEL for F1 development was considered to be at 6 mcg/kg/day.

In a prenatal monkey neurotoxicity study, infusion of dexmedetomidine hydrochloride to pregnant monkeys at doses up to 30 mcg/kg/hr (10X Human Equivalent Dose) for 12 hours did not induce neuroapoptosis in fetal monkey brains compared to controls. In the same study, infusion of ketamine at 20-50 mg/kg/hr for 12 hours to mothers resulted in significant neuroapoptosis in fetal monkey brains. This was determined by immunohistochemical staining for activated caspase 3 and TUNEL in fetal monkey brains.

Teratogenic effects were not observed following administration of dexmedetomidine at subcutaneous doses up to 200 mcg/kg in rats from day 5 to day 16 of gestation and intravenous doses up to 96 mcg/kg in rabbits from day 6 to day 18 of gestation. The dose in rats is approximately 2 times the maximum recommended human intravenous dose on a mcg/m2 basis. The exposure in rabbits is approximately equal to that in humans at the maximum recommended intravenous dose based on plasma area-under-the-curve values. However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live pups, was observed in rats at subcutaneous dose of 200 mcg/kg. The no-effect dose was 20 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). In another reproductive study when dexmedetomidine was administered subcutaneously to pregnant rats from gestation day 16 through nursing, it caused lower pup weights at 8 and 32 mcg/kg as well as fetal and embryocidal toxicity of second generation offspring at a dose of 32 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m2 basis). Dexmedetomidine also

produced delayed motor development in pups at a dose of 32 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). No such effects were observed at a dose of 2 mcg/kg (less than the maximum recommended intravenous dose on a mcg/m^2 basis). Placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously to pregnant rats.

In rabbits, the influence of dexmedetomidine on teratogenicity (Segment II) after IV administration in doses up to 96 mcg/kg/day was investigated. The NOAEL was 96 mcg/kg/day for maternal toxicity and 96 mcg/kg/day for F1 development. No higher dose was feasible. No teratogenicity was observed in any dose level tested.

Prenatal and postnatal development (Segment III study) was examined in rats at doses up to 32 mcg/kg/day administered subcutaneously. The NOAEL was 8 mcg/kg/day for maternal toxicity and 2 mcg/kg/day for F1 development.

Local Tolerance Studies
A solution of dexmedetomidine was shown to be mildly irritating in rats when injected intramuscularly.

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PART III: CONSUMER INFORMATION

[Pr]dexmedeTOMidine Hydrochloride for Injection
100 mcg/mL dexmedetomidine (as dexmedetomidine hydrochloride**)**

This leaflet is part III of a three-part "Product Monograph" published when Dexmedetomidine Hydrochloride for Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Dexmedetomidine Hydrochloride for Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Dexmedetomidine Hydrochloride for Injection is used in adults:
- for continuous sedation (to keep you calm) after you arrive at the intensive care unit after your surgery under a general anesthesia
- for sedation when you receive certain surgical procedures under a local anesthesia or nerve block or when you are receiving a breathing tube while awake

What it does:
Dexmedetomidine Hydrochloride for Injection acts by activating a part of the brain which helps keep you calm.

When it should not be used:
You should not be given Dexmedetomidine Hydrochloride for Injection if you:
- are allergic to dexmedetomidine hydrochloride or to any nonmedicinal ingredient in the formulation.

What the medicinal ingredient is:
dexmedetomidine hydrochloride.

What the nonmedicinal ingredients are:
sodium chloride and water for injection. Dexmedetomidine Hydrochloride for Injection is preservative-free and contains no additives or other chemicals.

What dosage forms it comes in:
Dexmedetomidine Hydrochloride for Injection is available as:
- A solution containing 100 micrograms/mL of dexmedetomidine that will be further diluted into saline and given to you by intravenous infusion. The Dexmedetomidine Hydrochloride for Injection concentrate solution is available in a 2 mL glass vial.

WARNINGS AND PRECAUTIONS

Dexmedetomidine Hydrochloride for Injection should only be administered by healthcare professionals skilled in the management of patients in the intensive care unit or operating room setting.

BEFORE you are given Dexmedetomidine Hydrochloride for Injection talk to your doctor or nurse if you:
- have heart problems, including chronic high blood pressure
- have diabetes mellitus
- have liver problems
- have severe kidney problems
- are taking any other medicines
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating
- are older than 65 years of age
- are pregnant or think you might be pregnant
- are breastfeeding

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with Dexmedetomidine Hydrochloride for Injection include:
- anesthestic drugs such as: sevoflurane, isoflurane, propofol, alfentanil, and midazolam
- neuromuscular blockers such as rocuronium, cisatracurium
- heart medications

PROPER USE OF THIS MEDICATION

Usual Adult dose:
Dosage will be individualized and titrated to the desired clinical effect. You will be given a loading dose followed by a maintenance dose, specific for your body weight and the procedure you are undergoing. Your doctor will decide what the appropriate dose is for your specific case.

Your doctor and/or nurse will monitor blood pressure, heart rate and oxygen levels, both continuously during the infusion of Dexmedetomidine Hydrochloride for Injection and as clinically appropriate after discontinuation.

It is important that following the return of consciousness, you do not attempt to change position or rise from bed without assistance.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You should report symptoms that may occur within 48 hours after you are given Dexmedetomidine Hydrochloride for Injection such as: dry mouth, nausea, vomiting, or fever.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM	
After exposure to Dexmedetomidine Hydrochloride for Injection, you should contact your physician or anesthesia professional if you have any of the following reactions:	
Symptom / effect	
Common	
Hypotension (low blood pressure): dizziness, fainting, light-headedness	Call your doctor immediately or 911.
Hypertension (high blood pressure): headaches, vision disorders, nausea and vomiting	
Hyperglycemia (high blood sugar): irregular heartbeats, muscle weakness and generally feeling unwell	
Hypokalemia(low potassium blood level) : irregular heartbeats, muscle weakness and generally feeling unwell	
Bradycardia: slow heartbeat	
Tachycardia: fast heartbeat	
Hypoxia: blueish colouration to the skin, confusion, fast heartbeat, shortness of breath, sweating	
Uncommon	
Nervousness	Talk with your doctor.
Headaches	
Agitation	
Weakness	
Confusion	
Excessive sweating	
Weight loss	
Abdominal pain	
Salt cravings	
Diarrhea	
Constipation	
Dizziness/ Lightheadedness	
Anemia: fatigue, loss of energy, weakness, shortness of breath	
Respiratory difficulty	Call your doctor immediately or 911.

This is not a complete list of side effects. For any unexpected effects while taking Dexmedetomidine Hydrochloride for Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Dexmedetomidine Hydrochloride for Injection is stored between 15 to 30°C.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Dexmedetomidine Hydrochloride for Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html the manufacturer's website (https://www.sandoz.ca/en), or by calling the manufacturer, Sandoz Canada Inc., at 1-800-361-3062.

  or by written request at:
  110, rue de Lauzon
  Boucherville, (QC), Canada
  J4B 1E6

  or by e-mail at:
  medinfo@sandoz.com

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