PACKAGE INSERT

(For the use of a Registered Medical Practitioner or a Hospital or Laboratory only.)

DEXMECCORD Dexmedetomidine (as hydrochloride) Injection 100mcg/mL, 2mL vial

1 INDICATIONS AND USAGE

1.1 Intensive Care Unit Sedation

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

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

1.2 Procedural Sedation

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

- Dexmeccord dosing should be individualized and titrated to desired clinical response.
- Dexmeccord is not indicated for infusions lasting longer than 24 hours.
- Dexmeccord should be administered using a controlled infusion device.

2.2 Dosage Information

Table 1: Dosage Information

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Intensive Care Unit Sedation	**For adult patients:** a loading infusion of one mcg/kg over 10 minutes. **For patients over 65 years of age**: a dose reduction should be considered [*see Use in Specific Populations (8.5)*]. **For adult patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.5, 8.6, 8.7), Clinical Pharmacology (12.3)*].
Maintenance of Intensive Care Unit Sedation	**For adult patients:** a maintenance infusion of 0.2 to 0.7 mcg/kg/hour**.** The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation. **For patients over 65 years of age:** a dose reduction should be considered [*see Use in Specific Populations (8.5)*].

	For adult patients with impaired hepatic function: a dose reduction should be considered [*see Use in Specific Populations (8.5, 8.6, 8.7), Clinical Pharmacology (12.3)*].
Initiation of Procedural Sedation	**For adult patients:** a loading infusion of one mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable. **For awake fiberoptic intubation in adult patients:** a loading infusion of one mcg/kg over 10 minutes. **For patients over 65 years of age**: a loading infusion of 0.5 mcg/kg over 10 minutes [*see Use in Specific Populations (8.5)*]. **For patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.5, 8.6, 8.7), Clinical Pharmacology (12.3)*].
Maintenance of Procedural Sedation	**For adult patients:** the maintenance infusion is generally initiated at 0.6 mcg/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hour. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. **For awake fiberoptic intubation in adult patients:** a maintenance infusion of 0.7 mcg/kg/hour is recommended until the endotracheal tube is secured. **For patients over 65 years of age:** a dose reduction should be considered [*see Use in Specific Populations (8.5)*]. **For adult patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.5, 8.6, 8.7), Clinical Pharmacology (12.3)*].

2.3 Dosage Adjustment

Due to possible pharmacodynamic interactions, a reduction in dosage of Dexmeccord or other concomitant anesthetics, sedatives, hypnotics or opioids may be required when co-administered. *[see Drug Interactions (7.1)]*.

Dosage reductions may need to be considered for adult patients with hepatic impairment, and geriatric patients *[see Warnings and Precautions (5.7), Use in Specific Populations (8.5, 8.6, 8.7), Clinical Pharmacology (12.3)]*.

2.4 Preparation of Solution

Dexmeccord must be diluted in 0.9% sodium chloride solution 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 Dexmeccord.

To prepare the infusion, withdraw 2 mL of Dexmeccord and add to 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Shake gently to mix well.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.5 Administration with Other Fluids

Dexmeccord infusion should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established.

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

Dexmeccord has been shown to be compatible when administered with the following intravenous fluids and drugs:

- 0.9% sodium chloride in water
- 5% dextrose in water
- 20% mannitol
- Lactated Ringer's solution

2.6 Compatibility with Natural Rubber

Compatibility studies have demonstrated the potential for absorption of Dexmeccord to some types of natural rubber. Although Dexmeccord is dosed to effect, it is advisable to use administration components made with synthetic or coated natural rubber gaskets.

3 DOSAGE FORMS AND STRENGTHS

Dexmeccord Injection, 200 mcg/2 mL (100 mcg/mL) in a glass vial

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Drug Administration

Dexmeccord 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 Dexmeccord, patients should be continuously monitored while receiving Dexmeccord.

5.2 Hypotension, Bradycardia, and Sinus Arrest

Clinically significant episodes of bradycardia and sinus arrest have been reported with Dexmedetomidine 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 infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of Dexmedetomidine, increasing the rate of intravenous fluid administration, elevation of the lower extremities, and use of pressor agents. Because Dexmedetomidine 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-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

Caution should be exercised when administering Dexmedetomidine to patients with advanced heart block and/or severe ventricular dysfunction. Because Dexmedetomidine 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 could have an additive pharmacodynamic effect and should be administered with caution.

5.3 Transient Hypertension

Transient hypertension has been observed primarily during the loading dose in association with the initial peripheral vasoconstrictive effects of Dexmedetomidine. Treatment of the transient hypertension has generally not been necessary, although reduction of the loading infusion rate may be desirable.

5.4 Arousability

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

5.5 Withdrawal

Intensive Care Unit Sedation

If Dexmedetomidine were to be administered for more than 24 hours and stopped abruptly, withdrawal symptoms similar to those reported for another alpha-2-adrenergic agent, clonidine, may result. These symptoms include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

Procedural Sedation

Withdrawal symptoms were not seen after discontinuation of short term infusions of Dexmedetomidine (<6 hours).

5.6 Hepatic Impairment

Since Dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function *[see Dosage and Administration (2.2)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

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

- Hypotension, bradycardia and sinus arrest *[see Warnings and Precautions (5.2)]*

- Transient hypertension *[see Warnings and Precautions (5.3)]*

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

Intensive Care Unit Sedation

Adverse reaction information is derived from the continuous infusion trials of Dexmedetomidine for sedation in the Intensive Care Unit setting in which 1007 adult patients received Dexmedetomidine. The mean total dose was 7.4 mcg/kg (range: 0.8 to 84.1), mean dose per hour was 0.5 mcg/kg/hr (range: 0.1 to 6.0) and the mean duration of infusion of 15.9 hours (range: 0.2 to 157.2). The population was between 17 to 88 years of age, 43% ≥ 65 years of age, 77% male and 93% Caucasian. Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 2. The most frequent adverse reactions were hypotension, bradycardia and dry mouth. *[see Warnings and Precautions (5.2)]*.

Table 2. Adverse Reactions With an Incidence >2%—Adult Intensive Care Unit Sedation Population

Body System/ Adverse Event	**All Dexmedetomidine N = 1007**	**Randomized Dexmedetomidine N = 798**	**Placebo N = 400**	**Propofol N = 188**
	n (%)	n (%)	n (%)	n (%)
Vascular disorders				
Hypotension	248 (25%)	191 (24%)	48 (12%)	25 (13%)
Hypertension	123 (12%)	101 (13%)	76 (19%)	7 (4%)
Gastrointestinal disorders				
Nausea.	90 (9%)	73 (9%)	36 (9%)	20 (11%)
Dry mouth	35 (4%)	22 (3%)	4 (1%)	1 (1%)
Vomiting	34 (3%)	26 (3%)	21 (5%)	6 (3%)
Cardiac disorders				
Bradycardia	52 (5%)	36 (5%)	10 (3%)	0
Atrial fibrillation	44 (4%)	37 (5%)	13 (3%)	14 (7%)
Tachycardia	20 (2%)	15 (2%)	17 (4%)	2 (1%)
Sinus tachycardia	6 (1%)	6 (1%)	2 (1%)	4 (2%)
Ventricular tachycardia	4 (0%)	4 (1%)	3 (1%)	9 (5%)
General disorders and administration site conditions	35 (4%)	31 (4%)	15 (4%)	8 (4%)
Pyrexia				

Hyperthermia	19 (2%)	16 (2%)	12 (3%)	0
Chills	17 (2%)	14 (2%)	13 (3%)	4 (2%)
Edema peripheral	4 (0%)	2 (0%)	2 (1%)	4 (2%)
Metabolism and nutrition disorders				
Hypovolemia	31 (3%)	22 (3%)	9 (2%)	9 (5%)
Hyperglycemia	17 (2%)	15 (2%)	7 (2%)	5 (3%)
Hypocalcemia	7 (1%)	7 (1%)	0	4 (2%)
Acidosis	6 (1%)	5 (1%)	4 (1%)	4 (2%)
Respiratory, thoracic and mediastinal disorders				
Atelectasis	29 (3%)	23 (3%)	13 (3%)	12 (6%)
Pleural effusion	23 (2%)	16 (2%)	4 (1%)	12 (6%)
Hypoxia	16 (2%)	13 (2%)	8 (2%)	5 (3%)
Pulmonary edema	9 (1%)	9 (1%)	3 (1%)	5 (3%)
Wheezing	4 (0%)	4 (1%)	1 (0%)	4 (2%)
Psychiatric disorders				
Agitation	20 (2%)	16 (2%)	11 (3%)	1 (1%)
Blood and lymphatic system disorders				
Anemia	19 (2%)	18 (2%)	7 (2%)	4 (2%)
Injury, poisoning and procedural complications				
Post-procedural hemorrhage	15 (2%)	13 (2%)	10 (3%)	7 (4%)
Investigations				
Urine output decreased	6 (1%)	6 (1%)	0	4 (2%)

Procedural Sedation

Adverse reaction information is derived from the two trials for procedural sedation in which 318 patients received Dexmedetomidine. 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 reactions occurring at an incidence of >2% are provided in Table 3. The most frequent adverse reactions were hypotension, bradycardia, and dry mouth [see Warnings and Precautions (5.2)]. Prespecified 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 and comparator groups in both studies.

Table 3. Adverse Reactions With an Incidence > 2%— Procedural Sedation Population

Body System/ Adverse Event	**Dexmedetomidine 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 beats per minute or ≤30% lower than pre-study drug infusion value.

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

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

[6] Hypoxia was defined in absolute and relative terms as SpO2 < 90% or 10% decrease from baseline

6.2 Postmarketing Experience

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

Table 4: Adverse Reactions Experienced During Post-approval Use of Dexmedetomidine

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 transpepsidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase
Metabolic and Nutritional Disorders	Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, hypoglycemia
Psychiatric Disorders	Agitation, confusion, delirium, hallucination, illusion
Red Blood Cell Disorders	Anemia
Renal Disorders	Blood urea nitrogen increased, oliguria
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

7 DRUG INTERACTIONS

7.1 Anesthetics, Sedatives, Hypnotics, Opioids

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

7.2 Neuromuscular Blockers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: 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/m^2 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/m^2 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/m2 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.
There are no adequate and well-controlled studies in pregnant women. Dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

8.2 Labor and Delivery
The safety of Dexmedetomidine during labor and delivery has not been studied. Therefore, Dexmedetomidine is not recommended during labor and delivery including cesarean section deliveries.

8.3 Nursing Mothers
It is not known whether Dexmedetomidine is excreted in human milk. Radio-labeled Dexmedetomidine administered subcutaneously to lactating female rats was excreted in milk. Because many drugs are excreted in human milk, caution should be exercised when Dexmedetomidine is administered to a nursing woman.

8.4 Pediatric Use
There have been no clinical studies to establish the safety and efficacy of Dexmedetomidine in pediatric patients below 18 years of age. Therefore, Dexmedetomidine should not be used in this population.

8.5 Geriatric Use
Dexmedetomidine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. 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 729 patients in the clinical studies were 65 years of age and over. A total of 200 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 *[see Warnings and Precautions (5.2)]*. Therefore a dose reduction may be considered in patients over 65 years of age *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

Procedural 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-treated patients 65 years or older (72%) and 75 years or older (74%) as compared to patients <65 years (47%). 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.

8.6 Hepatic Impairment

Since Dexmedetomidine clearance decreases with increasing severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Dexmeccord (dexmedetomidine hydrochloride) is not a controlled substance.

9.2 Dependence

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

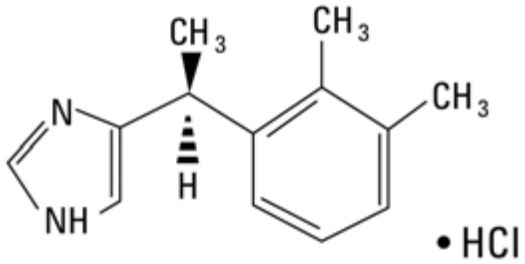
10 OVERDOSAGE

The tolerability of Dexmedetomidine was studied in one study in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hr. The maximum blood concentration achieved in this study was approximately 13 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.

Five adult patients received an overdose of Dexmedetomidine in the intensive care unit sedation studies. Two of these patients had no symptoms reported; one patient received a 2 mcg/kg loading dose over 10 minutes (twice the recommended loading dose) and one patient received a maintenance infusion of 0.8 mcg/kg/hr. 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 (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

11 DESCRIPTION

Dexmeccord (dexmedetomidine hydrochloride) injection concentrate is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine hydrochloride has a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2 \cdot HCl$ and the structural formula is:



Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Dexmeccord is supplied as a clear, colorless, solution with a pH of 4.5 to 7.0. Each mL contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg (0.1mg) of dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexmedetomidine 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 alpha$_1$ and alpha$_2$ activity is observed following slow intravenous infusion of high doses (≥ 1000 mcg/kg) or with rapid intravenous administration.

12.2 Pharmacodynamics

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 was administered by intravenous infusion at doses within the recommended dose range (0.2 - 0.7 mcg/kg/hr).

12.3 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 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 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.
# 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).

Distribution

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

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

Geriatrics:
The pharmacokinetic profile of Dexmedetomidine was not altered by age. There were no differences in the pharmacokinetics of Dexmedetomidine in young (18 - 40 years), middle age (41 - 65 years), and elderly (>65 years) subjects.

Pediatrics:
The pharmacokinetic profile of Dexmedetomidine has not been studied in pediatric patients.

Hepatic Impairment:
In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for Dexmedetomidine 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.

Although Dexmedetomidine is dosed to effect, it may be necessary to consider dose reduction in subjects with hepatic impairment *[see Dosage and Administration (2.2), Warnings and Precautions (5.6)]*.

Renal Impairment:
Dexmedetomidine pharmacokinetics (Cmax, Tmax, AUC, t1/2, CL, and Vss) were not significantly different in patients with severe renal impairment (creatinine clearance: <30 mL/min) compared to healthy subjects.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal carcinogenicity studies have not been performed with dexmedetomidine.

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

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

13.2 Animal Toxicology and/or Pharmacology

Dexmedetomidine had no effect on adrenocorticotropic hormone-stimulated cortisol release in dogs after a single dose; however, after the subcutaneous infusion of Dexmedetomidine for one week, the cortisol response to adrenocorticotropic hormone was diminished by approximately 40%, indicating adrenal insufficiency.

14 CLINICAL STUDIES

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

14.1 Intensive Care Unit Sedation

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 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 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 Level of 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 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 primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to maintain sedation as specified while intubated. Patients randomized to placebo received significantly more midazolam than patients randomized to Dexmedetomidine (see Table 7).

A second prospective primary analysis assessed the sedative effects of Dexmedetomidine 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 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 N=178**	**p-value**
Mean Total Dose (mg) of Midazolam Standard deviation	19 mg 53 mg	5 mg 19 mg	0.0011*
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

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

In a second study, 198 adult patients were randomized to receive placebo and 203 to receive Dexmedetomidine 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. The primary outcome measure for this study was the total amount of rescue medication (propofol) needed to maintain sedation as specified while intubated.

Patients randomized to placebo received significantly more propofol than patients randomized to Dexmedetomidine (see Table 8).

A significantly greater percentage of patients in the Dexmedetomidine 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 N=203**	**p-value**
Mean total dose (mg) of Propofol Standard deviation	513 mg 782 mg	72 mg 249 mg	<0.0001*
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

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

In a controlled clinical trial, Dexmedetomidine was compared to midazolam for ICU sedation exceeding 24 hours duration. Dexmedetomidine was not shown to be superior to midazolam for the primary efficacy endpoint, the percent of time patients were adequately sedated (81% versus 81%). In addition, administration of Dexmedetomidine for longer than 24 hours was associated with tolerance, tachyphylaxis, and a dose-related increase in adverse events [*see Adverse Reactions (6.1)*].
In study 3005012, patients were sedated with propofol prior to randomization to either propofol (3005012) or dexmedetomidine.
In study 3005013, patients were sedated with midazolam prior to randomization to either midazolam (3005013) or dexmedetomidine.

3005012
The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 64.6 (60.0 to 69.1)% for subjects on dexmedetomidine and 64.7 (59.9 to 69.4)% for subjects on propofol. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. propofol (0.92) was above the predefined non-inferiority margin (>0.85), Dexmedetomidine was proven to be non-inferior to propofol in maintaining a target depth of sedation. The median duration of mechanical ventilation was 21 hours shorter in the dexmedetomidine group (96.5 hours) than in the propofol group (117.5 hours). The length of stay in the ICU from randomization to medically fit for discharge or transfer did not differ (p = 0.535) between groups. 72.5% of subjects in the dexmedetomidine group and 64.4% of subjects in the propofol group needed the first-line (i.e. midazolam boli) rescue treatment for inadequate sedation during the treatment period (p = 0.054). The total number of doses of the rescue treatment was 2495 and 1986 in the dexmedetomidine and propofol groups, respectively. The mean average dose (0.74 vs. 0.31 mg/h, p <0.001) and the mean total dose (32.9 vs. 22.8 mg, p = 0.024) of the first-line rescue treatment were higher in the dexmedetomidinegroup than in the propofol group. The first-line rescue treatment also started earlier in the dexmedetomidine group (median of 1.4 vs. 4.3 hours, p = 0.018). No differences between groups were observed in the use of second-line rescue

treatment (mostly fentanyl) during the study treatment period or in the total use of fentanyl during the study.

3005013

The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 60.7 (55.4 to 66.1)% for subjects on dexmedetomidine and 56.6 (51.2 to 61.9)% for subjects on midazolam. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. midazolam (0.97) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to midazolam in maintaining a target depth of sedation. The median duration of mechanical ventilation was 41 hours shorter in the dexmedetomidine group (123.0 hours) than in the midazolam group (164.0 hours). The length of stay in the ICU from randomization to medically fit for discharge or transfer did not differ ($p = 0.269$) between groups. A similar percentage of subjects in the dexmedetomidine group (43.8%) and midazolam group (45.4%) received the first-line (i.e. propofol boli) rescue treatment for inadequate sedation during the treatment period ($p = 0.720$). The total number of doses (1100 vs. 1008), the mean average total dose (5.00 vs. 3.59 mg/h, $p = 0.173$) and the mean total dose (360 vs. 299 mg, $p = 0.317$) of the first-line rescue treatment were similar in both groups. The median time to the first use (19.3 vs. 20.0 hours) was also similar ($p = 0.741$). No differences between groups were observed in the use of second-line rescue treatment (mostly fentanyl) during the study treatment period or in the total use of fentanyl during the study.

14.2 Procedural Sedation

The safety and efficacy of Dexmedetomidine for sedation of non-intubated 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 in patients having a variety of elective surgeries/procedures performed under monitored anesthesia care. Study 2 evaluated Dexmedetomidine in patients undergoing awake fiberoptic intubation prior to a surgical or diagnostic procedure.

In Study 1, the sedative properties of Dexmedetomidine were evaluated by comparing the percent of patients not requiring rescue midazolam to achieve a specified level of sedation using the standardized Observer's Assessment of Alertness/Sedation Scale (see Table 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 1 mcg/kg, Dexmedetomidine 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 and comparator groups. Efficacy results showed that Dexmedetomidine 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 were evaluated by comparing the percent of patients requiring rescue midazolam to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale score ≥ 2 (Table 6). Patients were randomized to receive a loading infusion of Dexmedetomidine 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 occurred. 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 and comparator groups. For efficacy results see Table 10.

Table 10. Key Efficacy Results of Procedural Sedation Studies

Study	**Loading Infusion Treatment Arm**	**Number of 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 0.5 mcg/kg	134	40	37 (27,48)	1.4 (1.7)	-2.7 (-3.4, -2.0)
	Dexmedetomidine 1 mcg/kg	129	54	51 (40,62)	0.9 (1.5)	-3.1 (-3.8, -2.5)
	placebo	63	3	–	4.1 (3.0)	–
Study 2	Dexmedetomidine 1 mcg/kg	55	53	39 (20,57)	1.1 (1.5)	-1.8 (-2.7, -0.9)
	placebo	50	14	–	2.9 (3.0)	–

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Dexmeccord (dexmedetomidine hydrochloride) injection, Concentrate 200 mcg/2 mL (100 mcg/mL) is available in 2 mL clear glass vial. Vials are intended for single use only.

Do not store above 30°C. Protect from light.

17 SHELF LIFE

Unopened vial:
3 years

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.
From a microbiological point of view, the product should be used immediately.

18 PATIENT COUNSELING INFORMATION
Dexmeccord 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 Dexmeccord and as clinically appropriate after discontinuation.

- When Dexmeccord 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.

- Additionally, patients should be informed to report symptoms that may occur within 48 hours after the administration of Dexmeccord such as: weakness, confusion, excessive sweating, weight loss, abdominal pain, salt cravings, diarrhea, constipation, dizziness or light-headedness.

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Date of Revision of Package Insert
December 2020