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

For intravenous use. Initial U.S. Approval: 1999

INDICATIONS AND USAGE -

- Dexmedetomidine Hydrochloride Injection is a relatively selective alpha2-adrenergic agonist indicated for:
- Sedation of non-intubated patients prior to and/or during surgical and other procedures. (1.1)
- DOSAGE AND ADMINISTRATION -Individualize and titrate Dexmedetomidine Hydrochloride
- Injection dosing to desired clinical effect. (2.1) Administer Dexmedetomidine Hydrochloride Injection using
- a controlled infusion device. (2.1)
- · Dilute the 200 mcg/2 mL (100 mcg/mL) vial contents in 0.9% sodium chloride solution to achieve required concentration (4 mcg/mL) prior to administration. (2.4)

For Adult Procedural Sedation: Generally initiate at one mcg/kg over 10 minutes, followed by a maintenance infrain 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. (2.2)

Alternative Doses: Recommended for patients over 65 years of age and awake fiberoptic intubation patients. (2.2)

- DOSAGE FORMS AND STRENGTHS Dexmedetomidine Hydrochloride Injection, 200 mcg (dexmedeto-

midine)/2 mL [100 mcg (dexmedetomidine)/mL] in a glass vial. To be used after dilution. (3)

- CONTRAINDICATIONS None. (4)

WARNINGS AND PRECAUTIONS -

- Monitoring: Continuously monitor patients while receiving Dexmedetomidine Hydrochloride Injection. (5.1)
- · Bradycardia and Sinus Arrest: Have occurred in young healthy volunteers with high vagal tone or with different routes of
- administration, e.g., rapid intravenous or bolus administration. (5.2)

FULL PRESCRIBING INFORMATION: CONTENTS*

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Dexmedetomidine

Hydrochloride

Injection

5 WARNINGS AND PRECAUTIONS

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FULL PRESCRIBING INFORMATION

- INDICATIONS AND USAGE 1.1
 - Procedural Sedation Dexmedetomidine Hydrochloride Injection is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.
- DOSAGE AND ADMINISTRATION 2

2.1

- Dosina Guidelines Dexmedetomidine Hydrochloride Injection dosing should be individualized and titrated to desired clinical response. Dexmedetomidine Hydrochloride Injection is not indi-
- cated for infusions lasting longer than 24 hours. Dexmedetomidine Hydrochloride Injection should be administered using a controlled infusion device
- 2.2 Dosage Information

Table 1: Dosage Information

INDICATION DOSAGE AND ADMINISTRATION Initiation of For adult patients: a loading infusion of Procedura one mcg/kg over 10 minutes. For less Sedation 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)1. For adult patients with impaired hepatic function: a dose reduction should be con-sidered [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]. Hypotension and Bradycardia: May necessitate medical intervention. May be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in the elderly. Use with caution in patients with advanced heart block or severe ventricular dysfunction. (5.2)

Co-administration with Other Vasodilators or Negative Chronotropic Agents: Use with caution due to additive phar-macodynamic effects. (5.2)

- Transient Hypertension: Observed primarily during the loading dose. Consider reduction in loading infusion rate. (5.3)
- Arousability: Patients can become aroused/alert with stimulation: this alone should not be considered as lack of efficacy. (5.4)
- Prolonged exposure to dexmedetomidine beyond 24 hours may be associated with tolerance and tachyphylaxis and a dose-related increase in adverse events. (5.6)

- ADVERSE REACTIONS -

The most common adverse reactions (incidence greater than 2%) are hypotension, bradycardia, and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

- DRUG INTERACTIONS

Anesthetics, Sedatives, Hypnotics, Opioids: Enhancement of pharmacodynamic effects. Reduction in dosage of Dexmedeto-midine Hydrochloride, Injection or the concomitant medication may be required. (7.1)

- USE IN SPECIFIC POPULATIONS -

- Geriatric Patients: Dose reduction should be considered. (2.2, 2.3. 5.1. 8.5)
- Hepatic Impairment: Dose reduction should be considered. (2.1, 2.2, 2.3, 5.7, 8.6)
- Pregnancy: Based on animal data, may cause fetal harm.
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3)

See 17 for PATIENT COUNSELING INFORMATION

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

Table 1: Dosage Information (cont'd)

- INDICATION DOSAGE AND ADMINISTRATION Maintenance For adult natients: 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 of Procedural to achieve the targeted level of sedation. For awake fiberontic 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 (8.6), Clinical Pharmacology (12.3)].
- 2.3 Dosage Adjustment

2.4

Due to possible pharmacodynamic interactions, a reduction in dosage of Dexmedetomidine Hydrochloride Injection 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

Withdrawal 5.5 Procedural Sedation In adult subjects, withdrawal symptoms were not seen

Arousahility

5.3

5.4

patients with hepatic impairment and geriatric patients [see Warnings and Precautions (5.7), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]. Preparation of Solution Strict aseptic technique must always be maintained during

handling of Dexmedetomidine Hydrochloride Injection.

Parenteral drug products should be inspected visually for

particulate matter and discoloration prior to administra-

tion, whenever solution and container permit

5.6

signs and symptoms

Tolerance and Tachyphylaxis Use of dexmedetomidine beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions *[see Adverse Reactions*] (6,1)]

after discontinuation of short-term infusions of Dexme detomidine Hydrochloride Injection (<6 hours).

5.7

Dexmedetomidine Hydrochloride Injection, 200 mca/2 mL

(100 mcg/mL) must be diluted with 0.9% sodium chloride

niection to achieve required concentration (4 mcg/ml)

prior to administration. Preparation of solutions is the

same, whether for the loading dose or maintenance

To prepare the infusion, withdraw 2 mL of Dexmedeto

midine Hydrochloride Injection and add to 48 mL of

0.9% sodium chloride injection to a total of 50 mL. Shake

Dexmedetomidine Hydrochloride Injection infusion should not be co-administered through the same intravenous

catheter with blood or plasma because physical compat

Dexmedetomidine Hydrochloride Injection has been shown

to be incompatible when administered with the following drugs: amphotericin B, diazepam.

Dexmedetomidine Hydrochloride Injection has been shown

to be compatible when administered with the following

Compatibility studies have demonstrated the potential for

absorption of Dexmedetomidine Hydrochloride Injection to some types of natural rubber. Although Dexmedetomidine

Hydrochloride Injection is dosed to effect, it is advisable

to use administration components made with synthetic or coated natural rubber gaskets.

(dexmedetomidine Hydrochloride Injection, 200 mcg (dexmedetomidine)/2 mL [100 mcg (dexmedetomidine)/mL] in a glass vial. To be used after dilution.

Dexmedetomidine Hydrochloride Injection should be

administered only by persons skilled in the management of patients in the operating room setting. Due to the known pharmacological effects of Dexmedetomidine Hydrochlo-

ride Injection, patients should be continuously monitored

while receiving Dexmedetomidine Hydrochloride Injection

Clinically significant episodes of bradycardia and sinus arrest have been reported with Dexmedetomidine Hydro-

chloride Injection administration in young, healthy adult volunteers with high vagal tone or with different routes

of administration including rapid intravenous or bolus

Reports of hypotension and bradycardia have been

associated with Dexmedetomidine Hydrochloride Injection infusion. Some of these cases have resulted in fatalities.

If medical intervention is required, treatment may include decreasing or stopping the infusion of Dexmedetomidine

Hydrochloride Injection, increasing the rate of intravenous fluid administration, elevation of the lower extremities,

and use of pressor agents. Because Dexmedetomidine Hydrochloride Injection has the potential to augment

bradvcardia induced by vagal stimuli, clinicians should

be prepared to intervene. The intravenous administration

so anticholinergic agents (e.g., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treat-

ment of most episodes of Dexmedetomidine Hydrochlo-ride Injection-induced bradycardia. However, in some

patients with significant cardiovascular dysfunction, more

Caution should be exercised when administering

Dexmedetomidine Hydrochloride Injection to patients with

advanced heart block and/or severe ventricular dysfunc-tion. Because Dexmedetomidine Hydrochloride Injection

decreases sympathetic nervous system activity, hypoten-sion and/or bradycardia may be expected to be more

pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension and in elderly patients.

In clinical trials where other vasodilators or negative chro-

notropic agents were co-administered with Dexmedetomi-dine Hydrochloride Injection an additive pharmacodynamic

effect was not observed. Nonetheless, caution should be

used when such agents are administered concomitantly

Transient hypertension has been observed primarily during the loading dose in association with the initial peripheral vasoconstrictive effects of Dexmedetomidine Hydrochlo-

ride Injection. Treatment of the transient hypertension has generally not been necessary, although reduction of the

Some patients receiving Dexmedetomidine Hydrochloride

Injection 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 clinica

with Dexmedetomidine Hydrochloride Injection

loading infusion rate may be desirable

Transient Hypertension

advanced resuscitative measures were required

Hypotension, Bradycardia, and Sinus Arrest

aently to mix well.

2.5

2.6

3

Λ

5

5.1

5.2

Administration with Other Fluids

ibility has not been established

ntravenous fluids:
 0.9% sodium chloride in water

Lactated Ringer's solution
100 mg/mL magnesium sulfate solution

0.3% potassium chloride solution

Compatibility with Natural Rubber

DOSAGE FORMS AND STRENGTHS

WARNINGS AND PRECAUTIONS

CONTRAINDICATIONS

Drug Administration

administration

5% dextrose in water

20% mannitol

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

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

Hydrochloride Injection (cont'd)

System Organ Class

General Disorders and

Hepatobiliary Disorders

Administration Site Conditions

Investigations

Metabolism and

Nervous System

Renal and Urinary

Psychiatric Disorders

Respiratory, Thoracic and Mediastinal

Skin and Subcutaneous

Surgical and Medical

Vascular Disorders

DRUG INTERACTIONS

Neuromuscular Blockers

USE IN SPECIFIC POPULATIONS

Tissue Disorders

Procedures

7

7.1

7.2

8

8.1

Pregnancy

Disorders

Disorders

Disorders

Nutrition Disorders

Gastrointestinal

Disorders

Preferred Term

nausea, vomiting

pyrexia, thirst

Abdominal pain, diarrhea,

Chills, hyperpyrexia, pain,

Hepatic function abnormal

Alanine aminotransferase

aminotransferase increased, blood alkaline

phosphatase increased, blood urea increased,

transferase increased

electrocardiogram QT

Acidosis, hyperkalemia,

Convulsion. dizziness.

Agitation, confusional

state, delirium, hallucination, illusion

Apnea, bronchospasm,

dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion,

Blood pressure fluctuation

hemorrhage, hypertension

espiratory acidosis

Hyperhidrosis

hypotension

Anesthetics, Sedatives, Hypnotics, Opioids Co-administration of Dexmedetomidine Hydrochloride

Injection 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 Hydrochloride Injection and isoflurane, propofol, alfentanil and midazolam have been demon-

strated. However, due to possible pharmacodynamic interactions, when co-administered with Dexmedetomidine

Hydrochloride Injection, a reduction in dosage of Deyme

detomidine Hydrochloride Injection or the concomitant

anesthetic, sedative, hypnotic or opioid may be required.

In one study of 10 healthy adult volunteers, administration of Dexmedetomidine Hydrochloride Injection for 45 minutes

at a plasma concentration of one ng/mL resulted in no clini-cally meaningful increases in the magnitude of neuromus-

cular blockade associated with rocuronium administration

Pregnancy Category C Pregnancy Category C There are no adequate and well-controlled studies of Dexmedetornidine Hydrochloride Injection use in pregnant women. In an *in vitro* human placenta study, placental transfer of dexmedetomidine occurred. In a study in the pregnant rat, placental transfer of dexmedetomidine was

observed when radiolabeled dexmedetomidine was admin-istered subcutaneously. Thus, fetal exposure should be

expected in humans, and Dexmedetomidine Hydrochloride Injection should be used during pregnancy only if the

potential benefits justify the potential risk to the fetus.

Teratogenic effects were not observed in rats following subcutaneous administration of dexmedetomidine during the period of fetal organogenesis (from gesta-tion day 5 to 16) with doses up to 200 mcg/kg (rep-

resenting a dose approximately equal to the maximum

recommended human intravenous dose based on body surface area) or in rabbits following intravenous admin-

istration of dexmedetomidine during the period of fetal organogenesis (from gestation day 6 to 18) with doses

up to 96 mcg/kg (representing approximately half the human exposure at the maximum recommended dose

based on plasma area under the time-curve compari

son). However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live pups. was

observed in rats at a subcutaneous dose of 200 mcg/kg. The no-effect dose in rats was 20 mcg/kg (representing a

dose less than the maximum recommended human intra

venous dose based on a body surface area comparison)

In another reproductive toxicity study when dexmedetom

dine was administered subcutaneously to pregnant rats

at 8 and 32 mcg/kg (representing a dose less than the maximum recommended human intravenous dose based on a body surface area comparison) from gestation day 16

Additionally, when offspring of the 32 mcg/kg group were allowed to mate, elevated fetal and embryocidal toxicity

and delayed motor development was observed in second

generation offspring.

ight anesthesia

Oliguria, polvuria

headache, neuralgia, neuritis, speech disorder

hypoglycemia, hypovolemia hypernatremia

prolonaed

electrocardiogram T wave

inversion, gamma-glutamy

yperbilirubinemia

increased, aspartate

ADVERSE REACTIONS 6

Clinical Studies Experience Because clinical trials are conducted under widely varying 6.1 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 Hydrochloride Injection has been associated with the following serious adverse reactions Hypotension, bradycardia and sinus arrest [see Warn-ings 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 procedural sedation studies include hypotension, bradycardia and dry mouth

Procedural Sedation

Adverse reaction information is derived from the two trials for procedural sedation [see Clinical Studies (14.1). in which 318 adult patients received Dexmedetomidine Hydrochloride Injection. The mean total dose was Hydrochiofrade injection. Ine 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, 8.5 kJ-IV, 30% \geq 65 years of age, 52% male and 61% 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 Precau-tions (5.2)]. Pre-specified criteria for the vital signs to be reported as adverse reactions are footnoted below the table. The decrease in respiratory rate and hypoxia was similar between Dexmedetomidine Hydrochlo ride Injection and comparator groups in both studies

Table 2: Adverse Reactions with an Incidence

>2% — Procedural Sedation Population					
Adverse Event	Dexmedetomidine Hydrochloride Injection (N = 318) (%)	Placebo (N = 113) (%)			
Hypotension ¹	54%	30%			
Respiratory	070/	0.00%			
Depression ²	37%	32%			
Bradycardia ³	14%	4%			
Hypertension ⁴	13%	24%			
Tachycardia ⁵	5%	17%			
Nausea	3%	2%			
Dry Mouth	3%	1%			
Hypovia ⁶	2%	3%			

Bradypnea

Hypotension was defined in absolute and relative terms as Systolic blood pressure of $< 80 \text{ mmHg or} \le 30\%$ lower than pre-study drug infusion value, or Diastolic blood pressure of < 50 mmHg² Respiratory depression was defined in absolute and

2%

4%

relative terms as respiratory rate (RR) <8 beats per minute or > 25% decrease from baseline. ³ Bradycardia was defined in absolute and relative terms

as <40 beats per minute or \leq 30% lower than pre-study drug infusion value. ⁴ 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. Tachycardia was defined in absolute and relative terms

as >120 beats per minute or ≥30% greater than pre-

Hypoxia was defined in absolute and relative terms as

The following adverse reactions have been identified during post approval use of Dexmedetomidine Hydrochloride

Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always

nossible to reliably estimate their frequency or establish

Hypotension and bradycardia were the most common adverse reactions associated with the use of Dexmedeto-

midine Hydrochloride Injection during post approval use

Table 3: Adverse Reactions Experienced

During Post-approval Use of Dexmedetomidine Hydrochloride Injection

Preferred Term

Arrhythmia, atrial

fibrillation, atrioventricular block, bradycardia, cardiac

extrasystoles, myocardial

infarction, supraventricula

tachycardia, tachycardia,

ventricular arrhythmia.

ventricular tachycardia

Photopsia, visual

impairment

arrest, cardiac disorder

Anemia

 $SpO_2 < 90\%$ or 10% decrease from baseline

study drug infusion value.

Postmarketing Experience

of the drug

System Organ Class

Blood and Lymphatic

System Disorders

Cardiac Disorders

Eve Disorders

a causal relationship to drug exposure

6.2

8.2 Labor and Delivery The safety of Dexmedetomidine Hydrochloride Injection during labor and delivery has not been studied.

Nursing Mothers 8.3

It is not known whether Dexmedetomidine Hydrochloride Injection 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 b exercised when Dexmedetomidine Hydrochloride Injection is administered to a nursing woman

8.4 Pediatric Use

Safety and efficacy have not been established for Procedural Sedation in pediatric patients. The use of dexmedetomidine for procedural sedation in pediatric patients has not been evaluated

85 Geriatric Use Procedural Sedation

A total of 131 natients in the clinical studies were 65 years of age and over. A total of 47 patients were 75 years of ane and over. Hypotension occurred in a higher incidence in Dexmedetomidine Hydrochloride Injection-treated patients 65 years or older (72%) and 75 years or older (74%) as compared to patients < 65 vears (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 Hydrochloride Injection clearance decreases with increasing severity of hepatic impairment, dose reduction should be considered in natients with impaired hepatic function [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

DRUG ABUSE AND DEPENDENCE

Controlled Substance 9.1

Dexmedetomidine hydrochloride is not a controlled substance

9.3 Dependence

The dependence notential of Dexmedetomidine Hydrochloride Injection has not been studied in humans. However since studies in rodents and primates have demonstrated that Dexmedetomidine Hydrochloride Injection exhibits pharmacologic actions similar to those of clonidine, it is possible that Dexmedetomidine Hydrochloride Injection may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation [see Warnings and Precautions (5.5)1

OVERDOSAGE 10

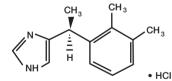
The tolerability of Dexmedetomidine Hydrochloride Injection was studied in one study in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mca/ka/hr. The maximum blood concentration achieved in this study was approximately 13 times the upper boundary 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

One patient who received a loading bolus dose of undiluted Dexmedetomidine Hydrochloride Injection (19.4 mcg/kg) had cardiac arrest from which he was successfull

DESCRIPTION

11

Dexmedetomidine Hydrochloride Injection 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-dimethylohenyl)ethyl]-1H-imidazole monohydrochloride, and the structural formula is:



C13H16N2 • HCI

Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a nKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Dexmedetomidine Hydrochloride Injection is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0.

M.W. 236.7

Each mL contains 118 mcg of dexmedetomidine hydro-chloride equivalent to 100 mcg (0.1 mg) of dexmedeto-midine, 9 mg of sodium chloride, 597 mcg of sodium acetate trihydrate and 27 mcg of glacial acetic acid in water The solution is preservative-free

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexmedetomidine Hydrochloride Injection is a relatively selective alpha₂-adrenergic agonist with sedative proper-ties. Alpha₂ selectivity is observed in animals following slow intravenous infusion of low and medium doses (10 to 300 mcg/kg). Both alpha1 and alpha2 activity is observed following slow intravenous infusion of high doses $(\geq 1,000 \text{ mcg/kg})$ or with rapid intravenous adminis-

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

Table 4: Mean ± SD Pharmacokinetic Parameters

Loading Infusion (min)/Total Infusion Duration (hrs)

	10 min/12 hrs	10 min/24 hrs	10 min/24 hrs	35 min/24 hrs		
	Dexmedetomidine Hydrochloride Injection Target Plasma Concentration (ng/mL) and Dose (mcg/kg/hr)					
Parameter	0.3/0.17	0.3/0.17	0.6/0.33	1.25/0.70		
t _{1/2} *, hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61		
CL, liter/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5		
V _{ss} , liter	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8		
Avg C _{ss} #, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20		

* Presented as harmonic mean and pseudo standard deviation.

Mean C_{ss} = Average steady-state concentration of Dexmedetomidine Hydrochloride Injection. The mean C_{ss} was calculated based on post-dose sampling from 2.5 to 9 hours samples for 12 hour infusion and post-dose sampling from 2.5 to 18 hours for 24 hour infusions

The loading doses for each of the above indicated groups were 0.5, 0.5, 1 and 2.2 mcg/kg, respectively.

Pharmacokinetics 12.3

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 (t1/2) 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 adminis-tered by intravenous infusion for up to 24 hours. Table 4 shows the main pharmacokinetic parameters when Dexmedetomidine Hydrochloride Injection was infused (after appropriate loading doses) at maintenance infusion (after appropriate loading objects) a mannerative motion 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

Dexmedetomidine pharmacokinetic parameters after Dexmedetomidine Hydrochloride Injection maintenance doses of 0.2 to 1.4 mcg/kg/hr for >24 hours were similar to the PK parameters after Dexmedetomidine Hydrochloride Injection maintenance dosing for < 24 hours in other studies. 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

Distribution

The steady-state volume of distribution (V_{cc}) of dexmedetomidine was approximately 118 liters. Dexmedeto midine 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 Hydrochloride Injection 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 dexme-detomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored in vitro, and negligible changes in the plasma protein binding of Dexmedetomidine Hydrochloride Injection were observed. The notential for protein binding displacement of phenytoin, warfarin, ibuprofer propranolol, theophylline and digoxin by Dexmedetomidine Hydrochloride Injection was explored in vitro and none of these compounds appeared to be significantly displaced by Dexmedetomidine Hydrochloride Injection

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 (medi-ated 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 esti-mated to be approximately 39 L/h. A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following intravenus admin-istration 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 excre-. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy-dexmedetomidine, the alucuronide o 3-hydroxy-dexmedetomidine, and 3-carboxylic acid-dexmedetomidine together represented approximately 14% of the dose in urine N-methylation of dexmedeto midine to form 3-hydroxy N-methyl dexmedetomidine 3-carboxy N-methyl dexmedetomidine and N-methy O-glucuronide dexmedetomidine accounted for approxi-mately 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 Hydrochloride Injection pharmacokinetics due to gender

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

Hepatic Impairment

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for Dexmedetomidine Hydrochloride Injection 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 Hydrochloride Injection 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 (5.7)] Renal Imnairment

Dexmedetomidine Hydrochloride Injection pharmacokinetics (Cmax, Tmax, AUC, t1/2, CL, and Vss) were not significantly different in natients with severe renal imnai (creatinine clearance: < 30 mL/min) compared to healthy suhiects

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 NONCLINICAL TOXICOLOGY

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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/m² basis) administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in females

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

CLINICAL STUDIES 14

The safety and efficacy of dexmedetomidine hydrochloride injection has been evaluated in two randomized, doubleblind, placebo-controlled multicenter clinical trials in 431 adult patients

14.1 Procedural Sedation

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

In Study 1, the sedative properties of Dexmedetomidine Hydrochloride Injection 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 5).

Patients were randomized to receive a loading infusion of either Dexmedetomidine Hydrochloride Injection 1 mcg/kg, Dexmedetomidine Hydrochloride Injection 0.5 mcg/kg, or placebo (normal saline) given over 10 minutes and followed

Table 5: 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)	

Table 6: 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 Hydrochloride Injection 0.5 mcg/kg	134	40	37 (27, 48)	1.4 (1.7)	-2.7 (-3.4, -2.0)
	Dexmedetomidine Hydrochloride Injection 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 Hydrochloride Injection 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

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 \leq 4. After achieving the desired level of sedation, a local or regional anesthetic block was performed. Demographic characteristics were similar between the Dexmedetomidine Hydrochloride Injection and comparator groups. Efficacy results showed that Dexmedetomidine Hydrochloride Injection was more effective than the comparator group when used to sedate non-intubated patients requiring monitored an care during surgical and other procedures (see Table 6)

In Study 2, the sedative properties of Dexmedetomidine Hydrochloride Injection 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 Patients were randomized to receive a loading infusion of Dexmedetomidine Hydrochlo ride Injection 1 mcg/kg or placebo (normal saline) given over 10 minutes and followed by a fixed maintenance infu-sion 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 Bamsay Sedation Scale > 2 Demographic characteristics were similar between th Dexmedetomidine Hydrochloride Injection and comparator groups. For efficacy results see Table 6.

HOW SUPPLIED/STORAGE AND HANDLING 16

Dexmedetomidine Hydrochloride Injection, is a clear, colorless solution available as:

Product No. 162102	NDC No. 63323-421-02	Strength 200 mcg (dexmedetomidine) per 2 mL (100 mcg (dexmedetomidine) per mL)	2 mL single dose vial, packaged in trays of 25.
		per me)	

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

The container closure is not made with natural rubber latex. Discard unused portion.

PATIENT COUNSELING INFORMATION

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Dexmedetomidine Hydrochloride 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 Dexmedetomiding Hydrochloride Injection and as clinically appropriate after discontinuation

• When Dexmedetomidine Hydrochloride 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.

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



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