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2 **HIGHLIGHTS OF PRESCRIBING INFORMATION**
3 **These highlights do not include all the information needed to use**
4 **dexmedetomidine hydrochloride safely and effectively. See full**
5 **prescribing information for Precedex.**
6
7 **Precedex (dexmedetomidine hydrochloride) injection**
8 **For intravenous infusion following dilution**
9 **Initial U.S. Approval: 1999**
10 -----**RECENT MAJOR CHANGES**-----
11 Dosage and Administration, Dosing Information (2.2) 09/2010
12 Dosage and Administration, Administration with Other Fluids (2.5) 09/2010
13 Warnings and Precautions (5) 09/2010
14 Adverse Reactions, Clinical Studies Experience (6.1) 09/2010
15 Use in Special Populations, Pregnancy (8.1) 09/2010
16 Clinical Pharmacology, Pharmacokinetics (12.3) 09/2010
17 Animal Toxicology and/or Pharmacology (13.2) 09/2010
18 Clinical Studies, Intensive Care Unit Sedation (14.1) 09/2010
19 -----**INDICATIONS AND USAGE**-----
20 Precedex is a relatively selective alpha₂-adrenergic agonist indicated for:
21 • Sedation of initially intubated and mechanically ventilated patients during
22 treatment in an intensive care setting. Administer Precedex by continuous
23 infusion not to exceed 24 hours. (1.1)
24 • Sedation of non-intubated patients prior to and/or during surgical and other
25 procedures. (1.2)
26 -----**DOSAGE AND ADMINISTRATION**-----
27 • Individualize and titrate Precedex dosing to desired clinical effect. (2.1)
28 • Administer Precedex using a controlled infusion device. (2.1)
29 • Dilute vial contents in 0.9% sodium chloride solution to achieve required
30 concentration (4 mcg/mL) prior to administration. (2.4)
31 For Intensive Care Unit Sedation: Generally initiate at one mcg/kg over 10
32 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. (2.2)
33 For Procedural Sedation: Generally initiate at one mcg/kg over 10 minutes,
34 followed by a maintenance infusion initiated at 0.6 mcg/kg/hr and titrated to
35 achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr.
36 Alternative doses recommended for patients over 65 years of age and awake
37 fiberoptic intubation patients. (2.2)
38
39 -----**DOSAGE FORMS AND STRENGTHS**-----
40 200 mcg/2 mL (100 mcg/mL) in a glass vial (3)

41 -----**CONTRAINDICATIONS**-----
42 None (4)
43 -----**WARNINGS AND PRECAUTIONS**-----
44 • Monitoring: Continuously monitor patients while receiving Precedex. (5.1)
45 • Bradycardia and sinus arrest: Have occurred in young healthy volunteers
46 with high vagal tone or with different routes of administration, e.g., rapid
47 intravenous or bolus administration. (5.2)
48 • Hypotension and bradycardia: May necessitate medical intervention. May
49 be more pronounced in patients with hypovolemia, diabetes mellitus, or
50 chronic hypertension, and in the elderly. Use with caution in patients with
51 advanced heart block or severe ventricular dysfunction. (5.2)
52 • Co-administration with other vasodilators or negative chronotropic agents:
53 Use with caution due to additive pharmacodynamic effects. (5.2)
54 • Transient hypertension: Observed primarily during the loading dose.
55 Consider reduction in loading infusion rate. (5.3)
56 • Arousability: Patients can become aroused/alert with stimulation; this
57 alone should not be considered as lack of efficacy (5.4)
58 • Prolonged exposure to dexmedetomidine beyond 24 hours may be
59 associated with tolerance and tachyphylaxis and a dose-related increase in
60 adverse events (5.6)
61 -----**ADVERSE REACTIONS**-----
62 • The most common adverse reactions (incidence greater than 2%) are
63 hypotension, bradycardia, and dry mouth. (6.1)
64 • Adverse reactions associated with infusions greater than 24 hours in
65 duration include ARDS, respiratory failure, and agitation. (6.1)
66
67 **To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc**
68 **at 1-888-441-4100 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**
69 -----**DRUG INTERACTIONS**-----
70 Anesthetics, sedatives, hypnotics, opioids: Enhancement of pharmacodynamic
71 effects. Reduction in dosage of Precedex or the concomitant medication may
72 be required. (7.1)
73 -----**USE IN SPECIFIC POPULATIONS**-----
74 • Geriatric patients: Dose reduction should be considered (2.2, 2.3, 5.1, 8.5)
75 • Hepatic impairment: Dose reduction should be considered (2.1, 2.2, 2.3,
76 5.6, 8.6)
77 • Pregnancy: Based on animal data, may cause fetal harm (8.1)
78 • Nursing Mothers: Caution should be exercised when administered to a
79 nursing woman (8.3)
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Revised: 09/2010

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137 listed.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Intensive Care Unit Sedation

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

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

1.2 Procedural Sedation

Precedex 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

- Precedex dosing should be individualized and titrated to desired clinical response.
- Precedex is not indicated for infusions lasting longer than 24 hours
- Precedex 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	<p>For adult patients: a loading infusion of up to one mcg/kg over 10 minutes.</p> <p>For patients being converted from alternate sedative therapy: a loading dose may not be required [see <i>Dosage and Administration: Maintenance of Intensive Care Unit Sedation (2.2)</i>].</p> <p>For patients over 65 years of age: a dose reduction should be considered [see <i>Use in Specific Populations (8.5)</i>].</p> <p>For patients with impaired hepatic-function: a dose reduction should be considered [see <i>Use in Specific Populations (8.6), Clinical Pharmacology (12.3)</i>].</p>
Maintenance of Intensive Care Unit Sedation	<p>For adult patients: a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation.</p> <p>For patients over 65 years of age: a dose reduction should be considered [see <i>Use in Specific Populations (8.5)</i>].</p> <p>For patients with impaired hepatic function: a dose reduction should be considered [see <i>Use in Specific Populations (8.6), Clinical Pharmacology (12.3)</i>].</p>

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<p>Initiation of Procedural Sedation</p>	<p>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.</p> <p>For awake fiberoptic intubation patients: a loading infusion of one mcg/kg over 10 minutes.</p> <p>For patients over 65 years of age: a loading infusion of 0.5 mcg/kg over 10 minutes [<i>see Use in Specific Populations (8.5)</i>].</p> <p>For patients with impaired hepatic function: a dose reduction should be considered [<i>see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)</i>].</p>
<p>Maintenance of Procedural Sedation</p>	<p>For adult patients: the maintenance infusion 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.</p> <p>For awake fiberoptic intubation patients: a maintenance infusion of 0.7 mcg/kg/hr is recommended until the endotracheal tube is secured.</p> <p>For patients over 65 years of age: a dose reduction should be considered [<i>see Use in Specific Populations (8.5)</i>].</p> <p>For patients with impaired hepatic function: a dose reduction should be considered [<i>see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)</i>].</p>

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2.3 Dosage Adjustment

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

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Dosage reductions may need to be considered for patients with hepatic impairment, and geriatric patients [*see Warnings and Precautions (5.6), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

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2.4 Preparation of Solution

175

Precedex 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.

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Strict aseptic technique must always be maintained during handling of Precedex.

179

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

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

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2.5 Administration with Other Fluids

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

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

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193

Precedex has been shown to be compatible when administered with the following intravenous fluids:

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- 0.9% sodium chloride in water
- 5% dextrose in water

196

- 197 • 20% mannitol
- 198 • Lactated Ringer's solution
- 199 • 100 mg/mL magnesium sulfate solution
- 200 • 0.3% potassium chloride solution

201

202 **2.6 Compatibility with Natural Rubber**

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

206

207 **3 DOSAGE FORMS AND STRENGTHS**

208 200 mcg/2 mL (100 mcg/mL) in a glass vial

209

210 **4 CONTRAINDICATIONS**

211 None

212

213 **5 WARNINGS AND PRECAUTIONS**

214

215 **5.1 Drug Administration**

216 Precedex should be administered only by persons skilled in the management of patients in the intensive care or
217 operating room setting. Due to the known pharmacological effects of Precedex, patients should be continuously
218 monitored while receiving Precedex.

219

220 **5.2 Hypotension, Bradycardia, and Sinus Arrest**

221 Clinically significant episodes of bradycardia and sinus arrest have been reported with Precedex administration
222 in young, healthy volunteers with high vagal tone or with different routes of administration including rapid
223 intravenous or bolus administration.

224

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

233

234 Caution should be exercised when administering Precedex to patients with advanced heart block and/or severe
235 ventricular dysfunction. Because Precedex decreases sympathetic nervous system activity, hypotension and/or
236 bradycardia may be expected to be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic
237 hypertension and in elderly patients.

238

239 In clinical trials where other vasodilators or negative chronotropic agents were co-administered with Precedex
240 an additive pharmacodynamic effect was not observed. Nonetheless, caution should be used when such agents
241 are administered concomitantly with Precedex.

242

243 **5.3 Transient Hypertension**

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

247

248 **5.4 Arousability**

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

251

252 **5.5 Withdrawal**

253 Intensive Care Unit Sedation

254 With administration up to 7 days, regardless of dose, 12 (5%) Precedex subjects experienced at least 1 event
255 related to withdrawal within the first 24 hours after discontinuing study drug and 7 (3%) Precedex subjects

256 experienced at least 1 event 24 to 48 hours after end of study drug. The most common events were nausea,
257 vomiting, and agitation.
258 Tachycardia and hypertension requiring intervention in the 48 hours following study drug discontinuation
259 occurred at frequencies of <5%. If tachycardia and/or hypertension occurs after discontinuation of Precedex
260 supportive therapy is indicated.

261 Procedural Sedation

262 Withdrawal symptoms were not seen after discontinuation of short term infusions of Precedex (<6 hours).
263
264

265 **5.6 Tolerance and Tachyphylaxis**

266 Use of dexmedetomidine beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-
267 related increase in adverse reactions [see Adverse Reactions (6.1)].
268

269 **5.7 Hepatic Impairment**

270 Since Precedex clearance decreases with severity of hepatic impairment, dose reduction should be considered in
271 patients with impaired hepatic function [see *Dosage and Administration (2.2)*].
272

273 **6 ADVERSE REACTIONS**

274 **6.1 Clinical Studies Experience**

275 Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the
276 clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect
277 the rates observed in practice.
278

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

- 281 • Hypotension, bradycardia and sinus arrest [see *Warnings and Precautions (5.2)*]
 - 282 • Transient hypertension [see *Warnings and Precautions (5.3)*]
- 283

284 Most common treatment-emergent adverse reactions, occurring in greater than 2% of patients in both Intensive Care
285 Unit and procedural sedation studies include hypotension, bradycardia and dry mouth.
286

287 Intensive Care Unit Sedation

288 Adverse reaction information is derived from the continuous infusion trials of Precedex for sedation in the Intensive
289 Care Unit setting in which 1007 patients received Precedex. The mean total dose was 7.4 mcg/kg (range: 0.8 to
290 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
291 (range: 0.2 to 157.2). The population was between 17 to 88 years of age, 43% \geq 65 years of age, 77% male and 93%
292 Caucasian. Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 2. The
293 most frequent adverse reactions were hypotension, bradycardia and dry mouth. [see *Warnings and Precautions*
294 (5.2)].
295

296

297 **Table 2. Adverse Reactions With an Incidence > 2%— Intensive Care Unit Sedation Population < 24 hours***

Adverse Event	All Precedex (N=1007) (%)	Randomized Precedex (N=798) (%)	Placebo (N=400) (%)	Propofol (N=188) (%)
Hypotension	25%	24%	12%	13%
Hypertension	12%	13%	19%	4%
Nausea	9%	9%	9%	11%
Bradycardia	5%	5%	3%	0
Atrial fibrillation	4%	5%	3%	7%
Pyrexia	4%	4%	4%	4%
Dry mouth	4%	3%	1%	1%
Vomiting	3%	3%	5%	3%
Hypovolemia	3%	3%	2%	5%
Atelectasis	3%	3%	3%	6%
Pleural effusion	2%	2%	1%	6%
Agitation	2%	2%	3%	1%
Tachycardia	2%	2%	4%	1%
Anemia	2%	2%	2%	2%
Hyperthermia	2%	2%	3%	0
Chills	2%	2%	3%	2%
Hyperglycemia	2%	2%	2%	3%
Hypoxia	2%	2%	2%	3%
Post-procedural hemorrhage	2%	2%	3%	4%
Pulmonary edema	1%	1%	1%	3%
Hypocalcemia	1%	1%	0	2%
Acidosis	1%	1%	1%	2%
Urine output decreased	1%	1%	0	2%
Sinus tachycardia	1%	1%	1%	2%
Ventricular tachycardia	<1%	1%	1%	5%
Wheezing	<1%	1%	0	2%
Edema peripheral	<1%	0	1%	2%

298 * 26 subjects in the all Precedex group and 10 subjects in the randomized Precedex group had exposure for
299 greater than 24 hours.
300

301 Adverse reaction information was also derived from the placebo-controlled, continuous infusion trials of Precedex
302 for sedation in the surgical intensive care unit setting in which 387 patients received Precedex for less than 24 hours.
303 The most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea,
304 bradycardia, fever, vomiting, hypoxia, tachycardia and anemia (see Table 3).
305

Table 3: Treatment-Emergent Adverse Events Occurring in >1% Of All Dexmedetomidine-Treated Patients in the Randomized Placebo-controlled Continuous Infusion <24 Hours ICU Sedation Studies		
Adverse Event	Randomized Dexmedetomidine (N=387)	Placebo (N=379)

Hypotension	28%	13%
Hypertension	16%	18%
Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial Fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Hemorrhage	3%	4%
Anemia	3%	2%
Dry Mouth	3%	1%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycemia	2%	2%
Acidosis	2%	2%
Pleural Effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

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

312

Table 4: Key Treatment-Emergent Adverse Events Occurring in Dexmedetomidine- or Midazolam-Treated Patients in the Randomized Active Comparator Continuous Infusion Long-Term Intensive Care Unit Sedation Study*		
Adverse Event	Dexmedetomidine (N=244)	Midazolam (N=122)
Hypotension ¹	56%	56%
Hypotension requiring intervention	28%	27%
Bradycardia ²	42%	19%
Bradycardia requiring intervention	5%	1%
Systolic Hypertension ³	28%	42%
Tachycardia ⁴	25%	44%
Tachycardia requiring intervention	10%	10%
Diastolic Hypertension ³	12%	15%
Hypertension ³	11%	15%
Hypertension requiring intervention [†]	19%	30%
Hypokalemia	9%	13%
Pyrexia	7%	2%
Agitation	7%	6%
Hyperglycemia	7%	2%
Constipation	6%	6%
Hypoglycemia	5%	6%
Respiratory Failure	5%	3%
Renal Failure Acute	2%	1%
Acute Respiratory Distress Syndrome	2%	1%
Generalized edema	2%	6%
Hypomagnesemia	1%	7%

313

[†]Includes any type of hypertension.

314

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

315

316

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

317

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

318

319

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

320

321

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

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323

324

Table 5. Number (%) of subjects who had a dose-related increase in Treatment Emergent Adverse Events by maintenance adjusted dose rate range in the Precedex group			
Adverse Event	Precedex mcg/kg/hr		
	≤ 0.7*	> 0.7 to ≤ 1.1*	> 1.1*
	N = 95	N = 78	N = 71
Constipation	6%	5%	14%
Agitation	5%	8%	14%
Anxiety	5%	5%	9%
Oedema peripheral	3%	5%	7%
Atrial fibrillation	2%	4%	9%
Respiratory failure	2%	6%	10%
Acute respiratory distress syndrome	1%	3%	9%

325 *Average maintenance dose over the entire study drug administration

326

327 Procedural Sedation

328 Adverse reaction information is derived from the two trials for procedural sedation in which 318 patients received
329 Precedex. 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:
330 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
331 years of age, 30% ≥ 65 years of age, 52% male and 61% Caucasian.

332 Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 3. The most frequent
333 adverse reactions were hypotension, bradycardia, and dry mouth [see *Warnings and Precautions (5.2)*]. Pre-
334 specified criteria for the vital signs to be reported as adverse reactions are footnoted below the table. The decrease in
335 respiratory rate and hypoxia was similar between Precedex and comparator groups in both studies.

336 **Table 6. Adverse Reactions With an Incidence > 2%— Procedural Sedation Population**

Adverse Event	Precedex N = 318 (%)	Placebo N = 113 (%)
Hypotension ¹	54%	30%
Respiratory depression ²	37%	32%
Bradycardia ³	14%	4%
Hypertension ⁴	13%	24%
Tachycardia ⁵	5%	17%
Nausea	3%	2%
Dry mouth	3%	1%
Hypoxia ⁶	2%	3%
Bradypnea	2%	4%

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

339 ² Respiratory depression was defined in absolute and relative terms as respiratory rate (RR)<8 beats per minute or
340 >25% decrease from baseline

341 ³ Bradycardia was defined in absolute and relative terms as <40 beats per minute or ≤30% lower than pre-study
342 drug infusion value.

343 ⁴ Hypertension was defined in absolute and relative terms as Systolic blood pressure >180 mmHg or ≥30% higher
344 than pre-study drug infusion value or diastolic blood pressure of >100 mmHg.

345 ⁵ Tachycardia was defined in absolute and relative terms as >120 beats per minute or ≥30% greater than pre-study
346 drug infusion value.

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

348

349 **6.2 Postmarketing Experience**

350 The following adverse reactions have been identified during post approval use of Precedex. Because these
351 reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably
352 estimate their frequency or establish a causal relationship to drug exposure.

353

354 Hypotension and bradycardia were the most common adverse reactions associated with the use of Precedex
355 during post approval use of the drug.

356

Table 7: Adverse Reactions Experienced During Post-approval Use of Precedex	
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

357 **7 DRUG INTERACTIONS**

358

359 **7.1 Anesthetics, Sedatives, Hypnotics, Opioids**

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

366

367 **7.2 Neuromuscular Blockers**

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

371

372 **8 USE IN SPECIFIC POPULATIONS**

373

374 **8.1 Pregnancy**

375 **Pregnancy Category C:**

376 There are no adequate and well-controlled studies of Precedex use in pregnant women. In an in-vitro human
377 placenta study, placental transfer of dexmedetomidine occurred. In a study in the pregnant rat, placental transfer
378 of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously.
379 Thus, fetal exposure should be expected in humans, and Precedex should be used during pregnancy only if the
380 potential benefits justify the potential risk to the fetus.

381

382 Teratogenic effects were not observed in rats following subcutaneous administration of dexmedetomidine
383 during the period of fetal organogenesis (from gestation day 5 to 16) with doses up to 200 mcg/kg
384 (representing a dose approximately equal to the maximum recommended human intravenous dose based on
385 body surface area) or in rabbits following intravenous administration of dexmedetomidine during the period of
386 fetal organogenesis (from gestation day 6 to 18) with doses up to 96 mcg/kg (representing approximately half
387 the human exposure at the maximum recommended dose based on plasma area under the time-curve
388 comparison). However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live
389 pups, was observed in rats at a subcutaneous dose of 200 mcg/kg. The no-effect dose in rats was 20 mcg/kg
390 (representing a dose less than the maximum recommended human intravenous dose based on a body surface
391 area comparison). In another reproductive toxicity study when dexmedetomidine was administered
392 subcutaneously to pregnant rats at 8 and 32 mcg/kg (representing a dose less than the maximum recommended
393 human intravenous dose based on a body surface area comparison) from gestation day 16 through weaning,
394 lower offspring weights were observed. Additionally, when offspring of the 32 mcg/kg group were allowed to
395 mate, elevated fetal and embryocidal toxicity and delayed motor development was observed in second
396 generation offspring.

397

398 **8.2 Labor and Delivery**

399 The safety of Precedex during labor and delivery has not been studied.

400

401 **8.3 Nursing Mothers**

402 It is not known whether Precedex is excreted in human milk. Radio-labeled dexmedetomidine administered
403 subcutaneously to lactating female rats was excreted in milk. Because many drugs are excreted in human milk,
404 caution should be exercised when Precedex is administered to a nursing woman.

405

406 **8.4 Pediatric Use**

407 The efficacy, safety, and pharmacokinetics of Precedex in pediatric patients less than 18 years of age have not
408 been established. Therefore, Precedex should not be used in this population.

409

410 **8.5 Geriatric Use**

411 Intensive Care Unit Sedation

412 A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200 patients were 75
413 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and
414 hypotension was observed following administration of Precedex [see Warnings and Precautions (5.2)].

415 Therefore a dose reduction may be considered in patients over 65 years of age [see *Dosing and Administration*
416 (2.2) and *Clinical Pharmacology* (12.3)].

417

418 Procedural Sedation

419 A total of 131 patients in the clinical studies were 65 years of age and over. A total of 47 patients were 75 years
420 of age and over. Hypotension occurred in a higher incidence in Precedex-treated patients 65 years or older
421 (72%) and 75 years or older (74%) as compared to patients <65 years (47%). A reduced loading dose of 0.5
422 mcg/kg given over 10 minutes is recommended and a reduction in the maintenance infusion should be
423 considered for patients greater than 65 years of age.

424

425 **8.6 Hepatic Impairment**

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

429

430 **9 DRUG ABUSE AND DEPENDENCE**

431

432 **9.1 Controlled Substance**

433 Precedex (dexmedetomidine hydrochloride) is not a controlled substance.

434

435 **9.2 Dependence**

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

440

441 **10 OVERDOSAGE**

442 The tolerability of Precedex was studied in one study in which healthy subjects were administered doses at and
443 above the recommended dose of 0.2 to 0.7 mcg/kg/hr. The maximum blood concentration achieved in this study
444 was approximately 13 times the upper boundary of the therapeutic range. The most notable effects observed in
445 two subjects who achieved the highest doses were first degree atrioventricular block and second degree heart
446 block. No hemodynamic compromise was noted with the atrioventricular block and the heart block resolved
447 spontaneously within one minute.

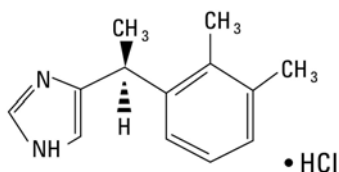
448

449 Five patients received an overdose of Precedex in the intensive care unit sedation studies. Two of these patients
450 had no symptoms reported; one patient received a 2 mcg/kg loading dose over 10 minutes (twice the
451 recommended loading dose) and one patient received a maintenance infusion of 0.8 mcg/kg/hr. Two other
452 patients who received a 2 mcg/kg loading dose over 10 minutes, experienced bradycardia and/or hypotension.
453 One patient who received a loading bolus dose of undiluted Precedex (19.4 mcg/kg), had cardiac arrest from
454 which he was successfully resuscitated.

455

456 **11 DESCRIPTION**

457 Precedex (dexmedetomidine hydrochloride) injection is a sterile, nonpyrogenic solution suitable for
458 intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of
459 medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole
460 monohydrochloride. Precedex has a molecular weight of 236.7 and the empirical formula is C₁₃H₁₆N₂ · HCl
461 and the structural formula is:



462

463 Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa
464 of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Precedex is supplied as a clear, colorless,
465 isotonic solution with a pH of 4.5 to 7.0. Each mL contains 118 mcg of dexmedetomidine hydrochloride

466 equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative-
467 free and contains no additives or chemical stabilizers.

468

469 **12 CLINICAL PHARMACOLOGY**

470

471 **12.1 Mechanism of Action**

472 Precedex is a relatively selective alpha₂-adrenergic agonist with sedative properties. Alpha₂ selectivity is
473 observed in animals following slow intravenous infusion of low and medium doses (10-300 mcg/kg). Both
474 alpha₁ and alpha₂ activity is observed following slow intravenous infusion of high doses (≥ 1000 mcg/kg) or
475 with rapid intravenous administration.

476

477 **12.2 Pharmacodynamics**

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

481

482 **12.3 Pharmacokinetics**

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

488

489 Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when
490 administered by intravenous infusion for up to 24 hours. Table 5 shows the main pharmacokinetic parameters
491 when Precedex was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 mcg/kg/hr
492 (target plasma concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 mcg/kg/hr (target plasma concentration of
493 0.6 ng/mL) for 24 hours, and 0.70 mcg/kg/hr (target plasma concentration of 1.25 ng/mL) for 24 hours.

494

Table 8. Mean ± SD Pharmacokinetic Parameters				
Parameter	Loading Infusion (min)/Total infusion duration (hrs)			
	10 min/12 hrs	10 min/24 hrs	10 min/24 hrs	35 min/24 hrs
	Precedex 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

495

* Presented as harmonic mean and pseudo standard deviation.

496

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

499

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

500

501 Dexmedetomidine pharmacokinetic parameters after Precedex maintenance doses of 0.2 to 1.4 mcg/kg/hr for
502 >24 hours were similar to the PK parameters after Precedex maintenance dosing for < 24 hours in other studies.
503 The values for clearance (CL), volume of distribution (V), and t_{1/2} were 39.4 L/hr, 152 L, and 2.67 hours,
504 respectively.

505

506 Distribution

507 The steady-state volume of distribution (V_{ss}) of dexmedetomidine was approximately 118 liters.
508 Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female subjects. The
509 average protein binding was 94% and was constant across the different plasma concentrations tested. Protein
510 binding was similar in males and females. The fraction of Precedex that was bound to plasma proteins was
511 significantly decreased in subjects with hepatic impairment compared to healthy subjects.

512

513 The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline,
514 digoxin and lidocaine was explored *in vitro*, and negligible changes in the plasma protein binding of Precedex
515 were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol,
516 theophylline and digoxin by Precedex was explored *in vitro* and none of these compounds appeared to be
517 significantly displaced by Precedex.

518
519

Metabolism

520 Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine
521 excreted in urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450
522 mediated metabolism. The major metabolic pathways of dexmedetomidine are: direct N-glucuronidation to
523 inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6) of dexmedetomidine to generate
524 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxy-
525 dexmedetomidine; and N methylation of dexmedetomidine to generate 3-hydroxy N-methyl-dexmedetomidine,
526 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronide.
527

528

Elimination

529 The terminal elimination half-life ($t_{1/2}$) of dexmedetomidine is approximately 2 hours and clearance is estimated
530 to be approximately 39 L/h. A mass balance study demonstrated that after nine days an average of 95% of the
531 radioactivity, following intravenous administration of radiolabeled dexmedetomidine, was recovered in the
532 urine and 4% in the feces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of
533 the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the
534 radioactivity excreted in urine demonstrated that products of N-glucuronidation accounted for approximately
535 34% of the cumulative urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy-
536 dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxylic acid-dexmedetomidine
537 together represented approximately 14% of the dose in urine. N-methylation of dexmedetomidine to form 3
538 hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N methyl O glucuronide
539 dexmedetomidine accounted for approximately 18% of the dose in urine. The N Methyl metabolite itself was a
540 minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have
541 not been identified.

542

Gender:

543 There was no observed difference in Precedex pharmacokinetics due to gender.
544

545

Geriatrics:

546 The pharmacokinetic profile of Precedex was not altered by age. There were no differences in the
547 pharmacokinetics of Precedex in young (18 – 40 years), middle age (41 – 65 years), and elderly (>65 years)
548 subjects.
549

550

Pediatrics:

551 The pharmacokinetic profile of Precedex has not been studied in pediatric patients.
552

553

Hepatic Impairment:

554 In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for
555 Precedex were lower than in healthy subjects. The mean clearance values for patients with mild, moderate, and
556 severe hepatic impairment were 74%, 64% and 53% of those observed in the normal healthy subjects,
557 respectively. Mean clearances for free drug were 59%, 51% and 32% of those observed in the normal healthy
558 subjects, respectively.
559

560

561 Although Precedex is dosed to effect, it may be necessary to consider dose reduction in subjects with hepatic
562 impairment [*see Dosage and Administration (2.2), Warnings and Precautions (5.6)*]
563

564

Renal Impairment:

565 Precedex pharmacokinetics (C_{max} , T_{max} , AUC, $t_{1/2}$, CL, and VSS) were not significantly different in patients
566 with severe renal impairment (creatinine clearance: <30 mL/min) compared to healthy subjects.
567

568

Drug Interactions:

569 *In vitro* studies: *In vitro* studies in human liver microsomes demonstrated no evidence of cytochrome P450
570 mediated drug interactions that are likely to be of clinical relevance.
571

572 **13 NONCLINICAL TOXICOLOGY**

573
574 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

575 Animal carcinogenicity studies have not been performed with dexmedetomidine.

576
577 Dexmedetomidine was not mutagenic *in vitro*, in either the bacterial reverse mutation assay (E. coli and
578 Salmonella typhimurium) or the mammalian cell forward mutation assay (mouse lymphoma).
579 Dexmedetomidine was clastogenic in the *in vitro* human lymphocyte chromosome aberration test with, but not
580 without, rat S9 metabolic activation. In contrast, dexmedetomidine was not clastogenic in the *in vitro* human
581 lymphocyte chromosome aberration test with or without human S9 metabolic activation. Although
582 dexmedetomidine was clastogenic in an *in vivo* mouse micronucleus test in NMRI mice, there was no evidence
583 of clastogenicity in CD-1 mice.

584
585 Fertility in male or female rats was not affected after daily subcutaneous injections of dexmedetomidine at
586 doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m² basis)
587 administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in
588 females.

589
590 **13.2 Animal Toxicology and/or Pharmacology**

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

597
598 **14 CLINICAL STUDIES**

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

601
602 **14.1 Intensive Care Unit Sedation**

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

610

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

611
612 In the first study, 175 patients were randomized to receive placebo and 178 to receive Precedex by intravenous
613 infusion at a dose of 0.4 mcg/kg/hr (with allowed adjustment between 0.2 and 0.7 mcg/kg/hr) following an
614 initial loading infusion of one mcg/kg intravenous over 10 minutes. The study drug infusion rate was adjusted to
615 maintain a Ramsay sedation score of ≥ 3 . Patients were allowed to receive “rescue” midazolam as needed to
616 augment the study drug infusion. In addition, morphine sulfate was administered for pain as needed. The
617 primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to

618 maintain sedation as specified while intubated. Patients randomized to placebo received significantly more
619 midazolam than patients randomized to Precedex (see Table 8).
620

621 A second prospective primary analysis assessed the sedative effects of Precedex by comparing the percentage of
622 patients who achieved a Ramsay sedation score of ≥ 3 during intubation without the use of additional rescue
623 medication. A significantly greater percentage of patients in the Precedex group maintained a Ramsay sedation
624 score of ≥ 3 without receiving any midazolam rescue compared to the placebo group (see Table 8).
625

Table 10: Midazolam use as rescue medication during intubation (ITT)			
Study One			
	Placebo N=175	Precedex N=178	p-value
Mean total dose (mg) of midazolam	19 mg	5 mg	0.0011*
Standard deviation	53 mg	19 mg	
Categorized midazolam use			
0 mg	43 (25%)	108 (61%)	<0.001**
0-4 mg	34 (19%)	36 (20%)	
>4 mg	98 (56%)	34 (19%)	

626 ITT (intent-to-treat) population includes all randomized patients.

627 *ANOVA model with treatment center. **Chi-square
628

629 A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the Precedex
630 and placebo groups. On average, Precedex-treated patients received less morphine sulfate for pain than placebo-
631 treated patients (0.47 versus 0.83 mg/h). In addition, 44% (79 of 178 patients) of Precedex patients received no
632 morphine sulfate for pain versus 19% (33 of 175 patients) in the placebo group.
633

634 In a second study, 198 patients were randomized to receive placebo and 203 to receive Precedex by intravenous
635 infusion at a dose of 0.4 mcg/kg/hr (with allowed adjustment between 0.2 and 0.7 mcg/kg/hr) following an
636 initial loading infusion of one mcg/kg intravenous over 10 minutes. The study drug infusion was adjusted to
637 maintain a Ramsay sedation score of ≥ 3 . Patients were allowed to receive “rescue” propofol as needed to
638 augment the study drug infusion. In addition, morphine sulfate was administered as needed for pain. The
639 primary outcome measure for this study was the total amount of rescue medication (propofol) needed to
640 maintain sedation as specified while intubated.
641

642 Patients randomized to placebo received significantly more propofol than patients randomized to Precedex (see
643 Table 9).
644

645 A significantly greater percentage of patients in the Precedex group compared to the placebo group maintained
646 a Ramsay sedation score of ≥ 3 without receiving any propofol rescue (see Table 9).

647

Table 11: Propofol use as rescue medication during intubation (ITT)			
Study Two			
	Placebo N=198	Precedex N=203	p-value
Mean total dose (mg) of propofol	513 mg	72 mg	<0.0001*
Standard deviation	782 mg	249 mg	
Categorized propofol use			
0 mg	47 (24%)	122 (60%)	<0.001**
0-50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

*ANOVA model with treatment center. **Chi-square

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A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the Precedex and placebo groups. On average, Precedex-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 Precedex patients received no morphine sulfate for pain versus 15% (30 of 198 patients) in the placebo group.

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660

In a controlled clinical trial, Precedex was compared to midazolam for ICU sedation exceeding 24 hours duration. Precedex 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 Precedex for longer than 24 hours was associated with tolerance, tachyphylaxis, and a dose-related increase in adverse events [see Adverse Reactions (6.1)].

661

14.2 Procedural Sedation

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

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673

In Study 1, the sedative properties of Precedex 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 (Table 10).

Table 12 Observer's Assessment of Alertness/Sedation

Assessment Categories				
<u>Responsiveness</u>	<u>Speech</u>	<u>Facial Expression</u>	<u>Eyes</u>	<u>Composite Score</u>
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)

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Patients were randomized to receive a loading infusion of either Precedex 1 mcg/kg, Precedex 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 \leq 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 Precedex and comparator groups. Efficacy results showed that Precedex 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 Precedex 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 \geq 2 (Table 6). Patients were randomized to receive a loading infusion of Precedex 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 an Ramsay Sedation Scale \geq 2. Demographic characteristics were similar between the Precedex and comparator groups. For efficacy results see Table 10.

693 **Table 13. 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	Precedex 0.5 mcg/kg	134	40	37 (27,48)	1.4 (1.7)	-2.7 (-3.4, -2.0)
	Precedex 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	Precedex 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)	–

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^aBased on ITT population defined as all randomized and treated patients.

^bNormal approximation to the binomial with continuity correction.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Store at controlled room temperature, 25°C (77°F) with excursions allowed from 15 to 30°C (59 to 86°F). [See USP.]

17 PATIENT COUNSELING INFORMATION

Precedex 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 Precedex and as clinically appropriate after discontinuation.

- When Precedex 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 Precedex such as: weakness,

714 confusion, excessive sweating, weight loss, abdominal pain, salt cravings,
715 diarrhea, constipation, dizziness or light-headedness.

716

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