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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
32 For Intensive Care Unit Sedation: Generally initiate at one mcg/kg over 10
33 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. (2.2)
34 For Procedural Sedation: Generally initiate at one mcg/kg over 10 minutes,
35 followed by a maintenance infusion initiated at 0.6 mcg/kg/hr and titrated to
36 achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr.
37 Alternative doses recommended for patients over 65 years of age and awake
38 fiberoptic intubation patients. (2.2)

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>

Initiation of Procedural Sedation	<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>
Maintenance of Procedural Sedation	<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>

165

166

2.3 Dosage Adjustment

167

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)*].

168

169

170

171

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)*].

172

173

174

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.

176

177

178

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

179

180

181

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.

182

183

184

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

185

186

2.5 Administration with Other Fluids

187

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

188

189

190

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

191

192

193

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

194

195

- 0.9% sodium chloride in water

- 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

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
262 Procedural Sedation

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

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
275 **6.1 Clinical Studies Experience**

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

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

296

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