1	HICHI ICHTS OF PRESCOIRING INFORMATION	41	CONTRAINDICATIONS
∠ 3	These highlights do not include all the information needed to use	42	None (4)
4	dexmedetomidine hydrochloride safely and effectively. See full	12	WADNINGS AND DDECAUTIONS
5	prescribing information for Precedex.	43 44	Monitoring: Continuously monitor nations while receiving Dreadow. (5.1)
6	I mage and a second sec	45	 Bradycardia and sinus arrest: Have occurred in young healthy volunteers
7	Precedex (dexmedetomidine hydrochloride) injection	46	with high vagal tone or with different routes of administration e.g. ranid
8	For intravenous infusion following dilution	47	intravenous or bolus administration. (5.2)
9	Initial U.S. Approval: 1999	48	Hypotension and bradycardia: May necessitate medical intervention. May
10	DECENT MAJOD CHANCES	49	be more pronounced in patients with hypovolemia, diabetes mellitus, or
11	Desage and Administration Desing Information (2.2)	50	chronic hypertension, and in the elderly. Use with caution in patients with
12	Dosage and Administration, Dosing information (2.2) 09/2010	51	advanced heart block or severe ventricular dysfunction. (5.2)
13	Warnings and Precautions (5) 09/2010	52	• Co-administration with other vasodilators or negative chronotropic agents:
14	Adverse Reactions, Clinical Studies Experience (6.1) 09/2010	53	Use with caution due to additive pharmacodynamic effects. (5.2)
15	Use in Special Populations, Pregnancy (8.1) 09/2010	54	• Transient hypertension: Observed primarily during the loading dose.
16	Clinical Pharmacology, Pharmacokinetics (12.3) 09/2010	55	Consider reduction in loading infusion rate. (5.3)
17	Animal Toxicology and/or Pharmacology (13.2) 09/2010	56	• Arousability: Patients can become aroused/alert with stimulation; this
18	Clinical Studies, Intensive Care Unit Sedation (14.1) 09/2010	5/	alone should not be considered as lack of efficacy (5.4)
10	BIDICI TIONG AND UCA OF	28 50	• Prolonged exposure to dexmedetomidine beyond 24 hours may be
20	INDICATIONS AND USAGE	59	associated with tolerance and tachyphylaxis and a dose-related increase in $\frac{1}{2}$
20	Precedex is a relatively selective alpha $_2$ -adrenergic agonist indicated for:	00	adverse events (5.6)
$\frac{21}{22}$	• Sedation of initially initialed and mechanically ventilated patients during	61	ADVERSE REACTIONS
$\frac{22}{23}$	infusion not to exceed 24 hours (1.1)	62	• The most common adverse reactions (incidence greater than 2%) are
$\frac{23}{24}$	 Sedation of non-intubated nations prior to and/or during surgical and other 	63	hypotension, bradycardia, and dry mouth. (6.1)
25	procedures (1.2)	64	· Adverse reactions associated with infusions greater than 24 hours in
20	Procedures. (1.2)	65	duration include ARDS, respiratory failure, and agitation. (6.1)
26	DOSAGE AND ADMINISTRATION	66	/
27	• Individualize and titrate Precedex dosing to desired clinical effect. (2.1)	67	To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc
28	• Administer Precedex using a controlled infusion device. (2.1)	68	at 1-888-441-4100 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
29	• Dilute vial contents in 0.9% sodium chloride solution to achieve required	60	DRUC INTEDACTIONS
30	concentration (4 mcg/mL) prior to administration. (2.4)	70	Anesthetics, sedatives, hypotics, opioids; Enhancement of pharmacodynamic
31		71	effects. Reduction in dosage of Precedex or the concomitant medication may
32	For Intensive Care Unit Sedation: Generally initiate at one mcg/kg over 10	$\frac{72}{72}$	be required (7.1)
22	minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. (2.2)	, _	be required. (7.1)
25	For Procedural Sedation: Generally initiate at one mcg/kg over 10 minutes,	73	USE IN SPECIFIC POPULATIONS
36	achieve desired alinical effect with desea ranging from 0.2 to 1 mag/kg/hr	74	• Geriatric patients: Dose reduction should be considered (2.2, 2.3, 5.1, 8.5)
37	Alternative desired children effect with doses langing from 0.2 to 1 mcg/kg/m.	75	• Hepatic impairment: Dose reduction should be considered (2.1, 2.2, 2.3,
38	<u>Alternative doses</u> recommended for patients over 05 years of age and awake fiberontic intubation patients (2.2)	76	5.6, 8.6)
50	nocroptic introdución partents. (2.2)	77	• Pregnancy: Based on animal data, may cause fetal harm (8.1)
39	DOSAGE FORMS AND STRENGTHS	78	• Nursing Mothers: Caution should be exercised when administered to a
40	200 mcg/2 mL (100 mcg/mL) in a glass vial (3)	/9 80	nursing woman (8.3)
		81	Revised: 09/2010
82		01	Revised. 07/2010
83			
84	FULL PRESCRIBING INFORMATION: CONTENTS*	116	8.5 Geriatric Use
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141	FULL PRESCRIBING INFORMATION		
142			
143	1	INDICATIONS AND USAGE	
144	1.1	Intensive Care Unit Sedation	
145		Precedex [®] is indicated for sedation of initially intubated and mechanically ventilated patients during treatment	
146		in an intensive care setting. Precedex should be administered by continuous infusion not to exceed 24 hours.	
147			
148		Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during	
149		extubation, and post-extubation. It is not necessary to discontinue Precedex prior to extubation.	
150			
151	1.2	Procedural Sedation	
152		Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.	
153			
154	2	DOSAGE AND ADMINISTRATION	
155			
156	2.1	Dosing Guidelines	
157			
158		 Precedex dosing should be individualized and titrated to desired clinical response. 	
159		Precedex is not indicated for infusions lasting longer than 24 hours	
160		Precedex should be administered using a controlled infusion device.	
161			
162	2 2.2 Dosage Information		
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Table 1: Dosage Information

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Intensive Care Unit	For adult patients: a loading infusion of up to one mcg/kg over 10 minutes.
Sedation	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</i> (2.2)].
	For patients over 65 years of age: a dose reduction should be considered [see Use in Specific Populations (8.5)].
	For patients with impaired hepatic-function: a dose reduction should be considered [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].
Maintenance of Intensive Care Unit Sedation	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.
	For patients over 65 years of age: a dose reduction should be considered [see Use in Specific Populations (8.5)].
	For patients with impaired hepatic function: a dose reduction should be considered [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

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Initiation of Procedural 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 Sedation 0.5 mcg/kg given over 10 minutes may be suitable. For awake fiberoptic intubation patients: a loading infusion of one mcg/kg over 10 minutes. For patients over 65 years of age: a loading infusion of 0.5 mcg/kg over 10 minutes [see Use in Specific Populations (8.5)]. For patients with impaired hepatic function:: a dose reduction should be considered [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]. **Maintenance of Procedural** For adult patients: the maintenance infusion is generally initiated at Sedation 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. For awake fiberoptic intubation patients: a maintenance infusion of 0.7 mcg/kg/hr 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 patients with impaired hepatic function: a dose reduction should be considered [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

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2.3 Dosage Adjustment

167 Due to possible pharmacodynamic interactions, a reduction in dosage of Precedex or other concomitant 168 anesthetics, sedatives, hypnotics or opioids may be required when co-administered. [see Drug Interactions 169 (7.1)]. 170

171 Dosage reductions may need to be considered for patients with hepatic impairment, and geriatric patients [see 172 Warnings and Precautions (5.6), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

174 **2.4 Preparation of Solution**

- 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.
- 178 Strict aseptic technique must always be maintained during handling of Precedex.
- 180To prepare the infusion, withdraw 2 mL of Precedex and add to 48 mL of 0.9% sodium chloride injection to a181total of 50 mL. Shake gently to mix well.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to
 administration, whenever solution and container permit.

186 **2.5 Administration with Other Fluids**

- Precedex infusion should not be co-administered through the same intravenous catheter with blood or plasma
 because physical compatibility has not been established.
- Precedex has been shown to be incompatible when administered with the following drugs: amphotericin B, diazepam.
- 193 Precedex has been shown to be compatible when administered with the following intravenous fluids:
- 194 195

0.9% sodium chloride in water

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- 197 20% mannitol • 198 • Lactated Ringer's solution 199 100 mg/mL magnesium sulfate solution • 0.3% potassium chloride solution 200 • 201 202 2.6 Compatibility with Natural Rubber Compatibility studies have demonstrated the potential for absorption of Precedex to some types of natural 203 204 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 CONTRAINDICATIONS 4 211 None 212 WARNINGS AND PRECAUTIONS 213 5 214 215 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 required, treatment may include decreasing or stopping the infusion of Precedex, increasing the rate of 226 227 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 intervene. The intravenous administration of anticholinergic agents (e.g., glycopyrrolate, atropine) should be 229 230 considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treatment of most episodes of Precedex-induced bradycardia. However, in some patients with significant cardiovascular 231 232 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 bradycardia may be expected to be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic 236
- hypertension and in elderly patients.
- In clinical trials where other vasodilators or negative chronotropic agents were co-administered with Precedex
 an additive pharmacodynamic effect was not observed. Nonetheless, caution should be used when such agents
 are administered concomitantly with Precedex.

5.3 Transient Hypertension

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

5.4 Arousability

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

252 5.5 Withdrawal

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- 253Intensive Care Unit Sedation254With administration up to 7
 - With administration up to 7 days, regardless of dose, 12 (5%) Precedex subjects experienced at least 1 event

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

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

265 **5.6 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)].

5.7 Hepatic Impairment

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

- Use of Precedex has been associated with the following serious adverse reactions:
 - Hypotension, bradycardia and sinus arrest [see Warnings and Precautions (5.2)]
 - Transient hypertension [see Warnings and Precautions (5.3)]

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

287 Intensive Care Unit Sedation

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

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