**WARNINGs AND PRECAUTIONS**

Adverse reactions associated with infusions greater than 24 hours have been associated with tolerance (reduction in response after longer duration; a higher adjusted dose rate range in the Dexmedetomidine HCl group was observed in Studies 2 and 3). Tachycardia was defined in absolute terms as <40 bpm or in relative terms as ≤30% lower than pre-study drug infusion value. Bradycardia was defined in absolute terms as <40 bpm or in relative terms as ≤30% lower than pre-study drug infusion value. Anticholinergic agents (e.g., glycopyrrolate, atropine); and/or medications that depress sinus node function; administering pressor agents.

**ADVERSE REACTIONS**

The following adverse events occurred between 2 and 5% for dexmedetomidine HCl and Midazolam, respectively: renal failure acute peritonitis, noncardiac pulmonary edema, respiratory failure, interstitial lung disease, acute renal failure, acute liver failure, lactic acidosis, hepatic failure, acute respiratory distress syndrome, ventricular tachycardia, supraventricular tachycardia, myoclonus, and seizures. Adverse reactions that occurred at an incidence of greater than 2% of patients receiving dexmedetomidine HCl and at an incidence greater than placebo are detailed in Table 5. **Hypotension**

**DOSAGE FORMS AND STRENGTHS**

Dexmedetomidine Hydrochloride Injection is a central alpha-2 adrenergic agonist and is contraindicated in patients with a known hypersensitivity to any of its components. The drug should be used with caution in patients with a history of cardiovascular disease or who are undergoing surgical or other procedures. (1.2)

**INDICATIONS AND USAGE**

Dexmedetomidine Hydrochloride Injection (100 mcg/mL): [see Dosage and Administration (2.2)]

**ADVERSE EFFECTS**

For more invasive procedures or for prolonged ICU sedation, adjusted dosage regimen recommended loading infusions of 0.5 mcg/kg over 10 minutes. Consider dosage reduction for maintenance of procedure or ICU sedation because the mean total dose was 1.6 mcg/kg (range: 0.5 mcg/kg to 6.7 mcg/kg), mean dosage was 0.07 mcg/kg/hour (range: 0.01 mcg/kg/hour to 0.2 mcg/kg/hour).

**STORAGE**

Store at room temperature (approximately 20°C to 25°C) and protect from freezing. Do not exceed 50°C (122°F) or 15°C (59°F). Use from the time of product introduction to the end of the expiration date printed on the label. Do not shake. Do not freeze.

**CONTRAINdications**

Contraindicated in patients with a known hypersensitivity to any of its components. The drug should be used with caution in patients with a history of cardiovascular disease or who are undergoing surgical or other procedures. (1.2)

**MECHANISM OF ACTION**

The primary mechanism of action for dexmedetomidine HCl is to induce a sedative effect with dosages ranging from 0.2 mcg/kg/hour to 1 mcg/kg/hour. This effect is mediated through an interaction with the α2A-adrenergic receptor subtype, which is localized in the central nervous system (CNS). Dexmedetomidine HCl is a highly selective α2-adrenoceptor agonist with minimal activity at α1-adrenoceptors. The drug is eliminated rapidly by metabolism in the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme. The drug is metabolized by the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme.

**NONCLINICAL TOXICOLOGY**

Dose-related increases in plasma levels of lactate and pyruvate were observed in rats and dogs. The effects of the drug on the liver and kidneys were not evaluated in these species. The drug is not renally excreted. The drug is metabolized by the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme. The drug is metabolized by the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme.

**CLINICAL PHARMACOLOGY**

Dexmedetomidine HCl is a selective α2-adrenergic agonist. The drug is metabolized by the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme. The drug is metabolized by the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme. The drug is metabolized by the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme. The drug is metabolized by the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme. The drug is metabolized by the liver and is not renally excreted. The drug is metabolized by cytochrome P450 1A2, and as a result, may be affected by other drugs that inhibit this enzyme.
7.5.4. Drug Interaction: CYP2D6 Inhibitors

Clinical trials in 1185 adult patients have assessed the impact of CYP2D6 inhibitors on the pharmacokinetics of dexmedetomidine HCl. The maintenance infusion dose of dexmedetomidine HCl increased in patients treated concomitantly with certain CYP2D6 inhibitors, such as amiodarone, cimetidine, and ketoconazole. Other CYP2D6 inhibitors such as dextromethorphan, propoxyphene, and quinidine also increased the area under the curve (AUC) of dexmedetomidine HCl. However, no significant increase in the mean total plasma clearance of dexmedetomidine HCl was observed with the above inhibitors. The potential for protein binding displacement of other drugs highly bound to proteins (i.e., phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin), and negligible changes in the plasma protein binding of dexmedetidine were observed. The potential for protein binding displacement of other drugs highly bound to proteins (i.e., phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin) is of clinical relevance.

7.7.2. Laboratory Tests

In studies where the elimination of dexmedetomidine HCl was assessed, a higher incidence of bradycardia and hypotension was observed following administration of dexmedetomidine HCl to patients greater than 65 years of age. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of dexmedetomidine HCl.

8.6.4. Drug-Drug Interactions

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine HCl were similar to the PK parameters after dexmedetomidine HCl maintenance dosing for < 24 hours in other studies. The values for clearance are estimated to be approximately 39 L/hour.

9.3.11.4. Psychiatric Disorders

Table 11: Categorized Midazolam Use

<table>
<thead>
<tr>
<th>Categorized Midazolam Use</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Requiring Midazolam</td>
<td>73 (37%)</td>
<td>72 (37%)</td>
</tr>
<tr>
<td>≤5 mg</td>
<td>35 (18%)</td>
<td>34 (17%)</td>
</tr>
<tr>
<td>&gt;5 mg ≤10 mg</td>
<td>21 (11%)</td>
<td>21 (11%)</td>
</tr>
<tr>
<td>&gt;10 mg</td>
<td>11 (6%)</td>
<td>15 (8%)</td>
</tr>
</tbody>
</table>

9.3.14.1. Non-Clinical Toxicology

9.3.2. Mutagenesis

13.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

14.1. Contraindications

14.1.1. Use in Women of Childbearing Potential

15.3. Monographs

15.3.1. USP

16. Production Information

16.2. Item Description

17. Package Information

17.1. USP

18. Patient Information

18.1. General Information

18.1.1. Precautions

18.1.1.1. Elderly Patients

18.1.1.2. Patients with Hepatic Impairment

18.1.1.3. Patients with Renal Impairment

18.1.1.4. Patients with Cardiac Impairment

18.1.1.5. Patients with Obstetric and Neonatal Use

18.2. Indications

18.3. Administration and Dosage

18.3.1. Translumbar epidural

18.3.2. Intravenous

18.3.3. Sedation

18.4. Adverse Reactions

18.5. Toxicology

18.6. Overdose Management

18.7. Contraindications

18.8. Precautions

18.9. Warnings

18.10. Adverse Reactions

18.11. Overdosage Management

18.12. Contraindications

18.13. Precautions


18.15. Toxicology

18.16. Overdose Management

18.17. Contraindications

18.18. Precautions

18.19. Adverse Reactions

18.20. Toxicology

18.21. Overdose Management

18.22. Contraindications

18.23. Precautions

18.24. Adverse Reactions

18.25. Toxicology

18.26. Overdose Management

18.27. Contraindications

18.28. Precautions

18.29. Adverse Reactions

18.30. Toxicology

18.31. Overdose Management

18.32. Contraindications

18.33. Precautions

18.34. Adverse Reactions

18.35. Toxicology

18.36. Overdose Management

18.37. Contraindications

18.38. Precautions

18.39. Adverse Reactions

18.40. Toxicology

18.41. Overdose Management

18.42. Contraindications

18.43. Precautions

18.44. Adverse Reactions