2.16 SUMMARY PRODUCT CHARACTERISTICS (SPC)

2.16 SUMMARY PRODUCT CHARACTERISTICS (SPC):

2.16.1 PRODUCT INFORMATION FOR HEALTH PROFESSIONALS:

<table>
<tr><td>1</td><td>Name of the Finished Medicinal Product:</td></tr>
<tr><td>1.1</td><td>Product Name:
Dexmedetomidine Hydrochloride Injection 100 mcg/ml</td></tr>
<tr><td>1.2</td><td>Strength : 100 mcg/ml</td></tr>
<tr><td>1.3</td><td>Pharmaceutical Form: Injection</td></tr>
<tr><td>2</td><td>Qualitative and Quantitative Compositions:</td></tr>
<tr><td></td><td>Qualitative Declaration:
Active component
INN Name: Dexmedetomidine Hydrochloride

Quantitative Declaration:
Each ml contains-:

Dexmedetomidine Hydrochloride
Equivalent to Dexmedetomidine....100mcg
Water for Injection BP.....Q.S.

<table>
<tr><th>Sr. No.</th><th>Content Name</th><th>Quality Standard</th><th>Qty per ml</th></tr>
<tr><td>1.</td><td>Dexmedetomidine Hydrochloride</td><td>IH</td><td>118.0 mcg</td></tr>
<tr><td>2.</td><td>Sodium Chloride</td><td>BP</td><td>9.0 mg</td></tr>
<tr><td>3.</td><td>Sodium Hydroxide</td><td>BP</td><td># q.s.</td></tr>
<tr><td>4.</td><td>Hydrochloric Acid</td><td>BP</td><td># q.s.</td></tr>
<tr><td>5.</td><td>Water For Injection</td><td>BP</td><td>q.s to 1.0 ml</td></tr>
</table>

118.0 mcg of Dexmedetomidine Hydrochloride is equivalent to 100.0 mcg Dexmedetomidine.
For pH adjustment only.
IH: In-house Specification
BP: British Pharmacopoeia</td></tr>
<tr><td>3</td><td>Pharmaceutical Form: Injection
Clear colourless liquid.</td></tr>
<tr><td>4</td><td>Clinical Particulars:</td></tr>
</table>

4.1 Therapeutic Indications:

- **Intensive care unit sedation:** Dexmedetomidine is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.
- **Procedural Sedation:** Dexmedetomidine is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

4.2 Posology and Method of Administration

Dexmedetomidine should be administered using a controlled infusion device.

Dexmedetomidine dosing should be individualized and titrated to the desired clinical effect.

Dexmedetomidine is not indicated for infusion lasting longer than 24 hours.

For adult patients, Dexmedetomidine is generally initiated with a loading infusion of 1(one) mcg/kg over 10mins, followed by 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.

Dexmedetomidine has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Dexmedetomidine prior to extubation provided the infusion does not exceed 24 hours.

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Intensive Unit Sedation	**For adult patients:** A loading infusion of one mcg/kg over 10 minutes. **Care for patients over 65 years of age:** A dose reduction should be considered. **For patients with impaired hepatic-function:** A dose reduction should be considered.
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. **For patients with impaired hepatic or renal function:** A dose reduction should be considered.

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Procedural Sedation	**For adult patients:** A loading infusion of one mcg/kg over 10 mins. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5mcg/kg given over 10 mins may be suitable. **For awake fiberoptic intubation patients:** A loading infusion of one mcg/kg over 10 mins. **For patients over 65 years of age:** A loading infusion of 0.5 mcg/kg over 10 mins. **For patients with impaired hepatic or renal function:** A dose reduction should be considered.
Maintenance of Procedural Sedation	**For adult patients:** The maintenance infusion is generally initiated at 0.6mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1mcg/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 0.7mcg/kg/hr is recommended until the endotracheal tube is secured.
	For patients over 65 years of age: A dose reduction should be considered. **For patients with impaired hepatic function or renal function :** A dose reduction should be considered.

Dilution Prior to Administration:

Dexmedetomidine must be diluted in 0.9% Sodium Chloride solution prior to administration.

Preparation of solution is the same, whether for the loading dose or maintenance infusion.

To prepare the infusion, withdraw 2 ml of Dexmedetomidine and add to 48 ml of 0.9% Sodium Chloride injection to a total 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.

Administration with Other Fluids:

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

4.3	**Contra-indications:** No specific information available.
4.4	**Special warning and precautions for use:** **Drug Administration**: Due to the known pharmacological effects of Dexmedetomidine Hydrochloride, it should be administered only by a person skilled in the management of patients in ICU or operating room setting and the patients should be continuously monitored. **Hypotension, Bradycardia, and Sinus Arrest:** Clinically significant episodes of bradycardia and sinus arrest have been associated with Dexmedetomidine Hydrochloride administration in young, healthy volunteers with high vagal tone or with different routes of administration, including rapid intravenous or bolus administration. Reports of hypotension and bradycardia have been associated with Dexmedetomidine Hydrochloride infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of Dexmedetomidine Hydrochloride, increasing the rate of IV fluid administration, elevation of the lower extremities, and use of pressor agents. Because Dexmedetomidine Hydrochloride has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (eg, atropine) should be considered to modify vagal tone. In clinical trials, atropine or glycopyrrolate were effective in the treatment of most episodes of Dexmedetomidine Hydrochloride -induced bradycardia. **Transient Hypertension:** Transient Hypertension has been observed primarily during the loading dose in associated with the initial peripheral vasoconstrictive effect of Dexmedetomidine. Treatment of transient hypertension has generally not been necessary, although reduction of the loading infusion rate may be desired. **Arousability:** Some patients receiving Dexmedetomidine 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. **Withdrawal** **Intensive Care Unit Sedation:** If Dexmedetomidine were to be administered for more than 24 hours and stopped abruptly, withdrawal symptoms similar to those reported for another alpha-2-adrenergic agent, clonidine may result. These symptoms include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

	Procedural Sedation: Withdrawal symptoms were not seen after discontinuation of short term infusions of Dexmedetomidine (<6 hours). **Hepatic Impairment:** Since Dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.
4.5	**Interaction with other drugs, other forms of interactions:** **Anesthetics/Sedatives/Hypnotics/Opioids:** Co-administration of Dexmedetomidine with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil, and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when coadministered with Dexmedetomidine, a reduction in dosage of Dexmedetomidine on the concomitant anesthetic, sedative, hypnotic or opioid may be required. **Neuromuscular Blockers:** In one study of 10 healthy volunteers, administration of Dexmedetomidine for 45 minutes at a plasma concentration of 1 (one) ng/mL resulted in no clinically meaningful increases in the magnitude or neuromuscular blockade associated with rocuronium administration.
4.6	**Usage in pregnancy& Lactation** **Pregnancy** There are no adequate and well controlled studies in pregnant women. Dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. **Lactation** It is not known whether Dexmedetomidine Hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Dexmedetomidine Hydrochloride is administered to a nursing woman. **Labour and delivery:** The safety of Dexmedetomidine Hydrochloride during labour and delivery has not been studied. Therefore, Dexmedetomidine Hydrochloride is not recommended during labour and delivery, including cesarean section. **Paediatrics:** There have been no clinical studies to establish the safety and efficacy of Dexmedetomidine in pediatric patients below 18 years of age. Therefore, Dexmedetomidine should not be used in this population.

	Gariatrics: Dexmedetomidine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function. **Hepatic Impairment:** Since Dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.
4.7	**Effects on ability to drive and operate machine:** Not relevant
4.8	**Undesirable effects:** Overall, the most frequently observed treatment-emergent adverse events include hypotension, hypertension, nausea, bradycardia, fever, vomiting hypoxia, tachycardia and anemia **Vascular Disorders:** Hypotension, Hypertension, Hemorrhage **Gastrointestinal Disorders:** Nausea, Dry mouth, Abdominal pain, diarrhea, vomiting, nausea. **Cardiac Disorders:** Bradycardia, Atrial fibrillation, Tachycardia, Sinus tachycardia, Ventricular tachycardia, myocardial infarction, heart disorder **General Disorders and Administration Site Conditions:** Pyrexia, Hyperthermia, Chills, Edema peripheral **Metabolism and Nutrition Disorders:** Hypovolemia, Hyperglycemia, Hypocalcemia, Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, Hypoglycemia. **Respiratory, Thoracic and Mediastinal Disorders:** Atelectasis, Pleural effusion, Hypoxia, Pulmonary edema, Wheezing, Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion **Psychiatric Disorders:** Agitation **Blood and Lymphatic System Disorders:** Anemia **Injury, Poisoning and Procedural Complications:** Post-procedural hemorrhage **Investigations:** Urine output decreased **Body as a Whole:** Fever, hyperpyrexia, hypovolemia, light anesthesia, pain, rigors **Central and Peripheral Nervous System Disorders:** Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion **Liver and Biliary System Disorders:** Increased gamma-glutamyl transpepsidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase **Psychiatric Disorders:** Agitation, confusion, delirium, hallucination, illusion **Renal Disorders:** Blood urea nitrogen increased, oliguria **Skin and Appendages Disorders:** Increased sweating **Vision Disorders:** Photopsia, abnormal vision.

4.9	**Overdose :** The tolerability of Dexmedetomidine was noted in one study in which healthy subjects were administrated doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hr. the maximum blood concentration achieved in this study was approximately 13 times the upper boundary of the therapeutic range. The most notable effects observed in two subjects who achieved the highest doses were first degree AV block and second degree heart block. No hemodynamic compromise was noted with the AV block and the heart block resolved spontaneously within one minute.
5	**Pharmacological Properties:**
5.1	**Pharmacodynamics Properties:** **Pharmacotherapeutic Group (ATC Code) :** N05CM18 Dexmedetomidine, a highly selective and potent alpha2-adrenergic agonist, has a potentially useful role as a sedative agent. In a study in healthy volunteers (N=10), respiratory rate and oxygen saturation remained within normal limits and there was no evidence of respiratory depression when it was administered by IV infusion at doses within the recommended dose range (0.2-0.7 mcg/kg/hr).
5.2	**Pharmacokinetic Properties:** Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when administered by intravenous infusion for up to 24 hours. Following intravenous administration, Dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{½}$) of approximately 6 minutes; a terminal elimination half-life ($t_{1/2}$) of approximately 2 hours; and steady-state volume of distribution (Vss) of approximately 118 liters. Clearance is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg. The pharmacokinetic profile of Dexmedetomidine was not altered by age. There were no differences in the pharmacokinetics of Dexmedetomidine in young (18–40 years), middle age (41–65 years), and elderly (>65 years) subjects.

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
	Dexmedetomidine 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

* Presented as harmonic mean and pseudo standard deviation.
# Avg C_{ss} = Average steady-state concentration of Dexmedetomidine. (2.5–9 hour samples for 12 hour infusion and 2.5–18 hour samples for 24 hour infusions).

Distribution:

The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of Dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects. The potential for protein binding displacement of Dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored in vitro, and negligible changes in the plasma protein binding of Dexmedetomidine were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by Dexmedetomidine was explored in vitro and none of these compounds appeared to be significantly displaced by Dexmedetomidine.

Metabolism:

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

	Elimination: A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following intravenous administration of radiolabeled Dexmedetomidine, was recovered in the urine and 4% in the feces. No unchanged Dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated that products of N-glucuronidation accounted for approximately 34% of the cumulative urinary excretion.
5.3	**Pre-clinical Safety Data:** Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.
6	**Pharmaceuticals Particulars:**
6.1	**List of Excipients:** Sodium Chloride BP Sodium Hydroxide BP Hydrochloric Acid BP Water For Injection BP
6.2	**Incompatibilities:** **Administration with Other Fluids:** Dexmedetomidine infusion should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established. Dexmedetomidine has been shown to be incompatible when administered with the following drugs: Amphotericin B, Diazepam. **Dexmedetomidine has been shown to be compatible when administered with the following intravenous fluids and drugs :** 0.9% sodium chloride in water, 5% dextrose in water, 20% Mannitol, Alfentanil Hydrochloride, Amikacin Sulfate, Aminophylline, Amiodarone Hydrochloride, Ampicillin Sodium, Ampicillin Sodium-Sulbactam Sodium, Atracurium Besylate, Atropine Sulfate, Azithromycin, Aztreonam, Bretylium Tosylate, Bumetanide, Butorphanol Tartrate, Calcium Gluconate, Cefazolin Sodium, Cefepime Hydrochloride, Cefoperazone Sodium, Cefotaxime Sodium, Cefotetan Sodium, Cefoxitin Sodium, Ceftazidime, Ceftizoxime Sodium, Ceftriaxone Sodium, Cefuroxime Sodium, Chlorpromazine Hydrochloride, Cimetidine Hydrochloride, Ciprofloxacin, Cisatracurium Besylate, Clindamycin Phosphate, Dexamethasone Sodium Phosphate, Digoxin, Diltiazem Hydrochloride, Diphenhydramine Hydrochloride, Dobutamine Hydrochloride, Dolasetron Mesylate, Dopamine Hydrochloride, Doxycycline Hyclate, Droperidol, Enalaprilat, Ephedrine Hydrochloride, Epinephrine Hydrochloride, Erythromycin Lactobionate, Esmolol, Etomidate, Famotidine, Fenoldopam Mesylate, Fentanyl Citrate, Fluconazole, Furosemide, Gatifloxacin, Gentamicin Sulfate, Glycopyrrolate Bromide, Granisetron Hydrochloride, Haloperidol Lactate, Heparin Sodium, Hydrocortisone Sodium Succinate, Hydromorphone Hydrochloride, Hydroxyzine Hydrochloride, Inamrinone Lactate,

	Isoproterenol Hydrochloride, Ketorolac Tromethamine, Labetalol, Lactated Ringer's Solution, Levofloxacin, Lidocaine Hydrochloride, Linezolid, Lorazepam, Magnesium Sulfate, Meperidine Hydrochloride, Methylprednisolone Sodium Succinate, Metoclopramide Hydrochloride, Metronidazole, Midazolam, Milrinone Lactate, Mivacurium Chloride, Morphine Sulfate, Nalbuphine Hydrochloride, Nitroglycerin, Norepinephrine Bitartrate, Ofloxacin,Ondansetron Hydrochloride, Pancuronium Bromide, Phenylephrine Hydrochloride, Piperacillin Sodium, Piperacillin Sodium-Tazobactam Sodium, Potassium Chloride, Procainamide Hydrochloride, Prochlorperazine Edisylate, Promethazine Hydrochloride, Propofol, Ranitidine Hydrochloride, Rapacuronium Bromide, Remifentanil Hydrochloride, Rocuronium Bromide, Sodium Bicarbonate, Sodium Nitroprusside,Succinylcholine, Sufentanil Citrate, Sulfamethoxazole-Trimethoprim, Theophylline, Thiopental Sodium, Ticarcillin Disodium, Ticarcillin Disodium-Clavulanate Potassium, Tobramycin Sulfate, Vancomycin Hydrochloride, Vecuronium Bromide, Verapamil Hydrochloride, and a plasma-substitute.
6.3	**Shelf Life:** 36 Months
6.4	**Special Precaution for Storage:** Store below 30^0C.
6.5	**Nature and Contents of Container:** Dexmedetomidine Hydrochloride Injection100mcg/ml is packed in a 2 ml amber ampoule with white ring.1 such ampoule in PVC tray is packed in carton along with the pack insert.
6.6	**Special Precautions for Disposal:** Not applicable
7	**Registrant:** **Marketing Authorization Holder:** **M/s PHILLIPS PHARMACEUTICALS (NIGERIA) LTD** Address : Afprint Industrial Estate, Plot 122-132, Apapa Oshodi Expressway Lagos. Country : Nigeria. Telephone : +234 806761764 Fax : --- E-mail : --- **Manufacturing Site Address:** **M/s THEMIS MEDICARE LIMITED** Sector 6A, Plot No. 16, 17 & 18, IIE, SIDCUL, Haridwar – 249 403, Uttarakhand, INDIA. Telephone: 91-1334-239321/22 Fax: 91-334-239217 E-mail: hwdgmtech@themismedicare.com
8	**Date of Revision of the Text:** Not Applicable
9	**Dosimetry (if applicable):** Not Applicable
10	**Instruction for preparations of Radiopharmaceutical (if applicable):** Not Applicable

2.16.2 PATIENT INFORMATION LEAFLET

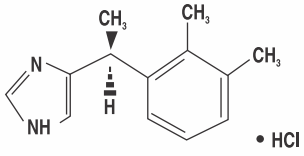
2.16.2 PATIENT INFORMATION LEAFLET - Not Applicable.

Pack Insert: Enclosed

For the use of Registered Medical Practitioner or a Hospital or a Laboratory only.

Dexmedetomidine Hydrochloride Injection

DESCRIPTION
Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine has a molecular weight of 236.7. The empirical formula is $C_{13}H_{16}N_2$ HCl and the structural formula is :



Each ml contains :
Dexmedetomidine Hydrochloride
equivalent to Dexmedetomidine ..... 100 mcg.
Water for Injection BP ..... Q.S.

CLINICAL PHARMACOLOGY
Dexmedetomidine, a highly selective and potent alpha$_2$-adrenergic agonist, has a potentially useful role as a sedative agent.

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

PHARMACOKINETICS
Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when administered by intravenous infusion for up to 24 hours.

Following intravenous administration, Dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{1/2}$) of approximately 6 minutes; a terminal elimination half-life (t1/2) of approximately 2 hours; and steady-state volume of distribution (Vss) of approximately 118 liters. Clearance is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

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

Mean ± SD Pharmacokinetic Parameters

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$t_{1/2}$, hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
CL, liter/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}, liter	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg C_{ss}#, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

* Presented as harmonic mean and pseudo standard deviation.
# Avg C_{ss} = Average steady-state concentration of Dexmedetomidine. (2.5–9 hour samples for 12 hour infusion and 2.5–18 hour samples for 24 hour infusions).

Distribution : The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of Dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects. The potential for protein binding displacement of Dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored in vitro, and negligible changes in the plasma protein binding of Dexmedetomidine were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by Dexmedetomidine was explored in vitro and none of these compounds appeared to be significantly displaced by Dexmedetomidine.

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

Elimination : A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following intravenous administration of radiolabeled Dexmedetomidine, was recovered in the urine and 4% in the feces. No unchanged Dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion.
Fractionation of the radioactivity excreted in urine demonstrated that products of N-glucuronidation accounted for approximately 34% of the cumulative urinary excretion.

INDICATIONS

Intensive care unit sedation : Dexmedetomidine is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.

Procedural Sedation : Dexmedetomidine is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

CONTRAINDICATIONS
No specific information available.

WARNINGS AND PRECAUTIONS

Drug Administration : Due to the known pharmacological effects of Dexmedetomidine HCL, it should be administered only by a person skilled in the management of patients in ICU or operating room setting and the patients should be continuously monitored.

Hypotension, Bradycardia, and Sinus Arrest : Clinically significant episodes of bradycardia and sinus arrest have been associated with Dexmedetomidine HCL administration in young, healthy volunteers with high vagal tone or with different routes of administration, including rapid intravenous or bolus administration.
Reports of hypotension and bradycardia have been associated with Dexmedetomidine HCL infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of Dexmedetomidine HCL, increasing the rate of IV fluid administration, elevation of the lower extremities, and use of pressor agents. Because Dexmedetomidine HCL has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (eg, atropine) should be considered to modify vagal tone. In clinical trials, atropine or glycopyrrolate were effective in the treatment of most episodes of Dexmedetomidine HCL -induced bradycardia.

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

Arousability : Some patients receiving Dexmedetomidine 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.

Withdrawal
Intensive Care Unit Sedation : If Dexmedetomidine were to be administered for more than 24 hours and stopped abruptly, withdrawal symptoms similar to those reported for another alpha-2-adrenergic agent, clonidine, may result. These symptoms include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

Procedural Sedation : Withdrawal symptoms were not seen after discontinuation of short term infusions of Dexmedetomidine (<6 hours).

Hepatic Impairment : Since Dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.

USE IN SPECIFIC POPULATION

Pregnancy : There are no adequate and well-controlled studies in pregnant women. Dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Lactation : It is not known whether Dexmedetomidine HCL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Dexmedetomidine HCL is administered to a nursing woman.

Labour and delivery : The safety of Dexmedetomidine HCL during labor and delivery has not been studied. Therefore, Dexmedetomidine HCL is not recommended during labor and delivery, including cesarean section

Paediatrics : There have been no clinical studies to establish the safety and efficacy of Dexmedetomidine in pediatric patients below 18 years of age. Therefore, Dexmedetomidine should not be used in this population.

Geriatrics : Dexmedetomidine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function.

Hepatic Impairment : Since Dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.

DRUG INTERACTIONS

Anesthetics/Sedatives/Hypnotics/Opioids : Co-administration of Dexmedetomidine with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil, and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with Dexmedetomidine, a reduction in dosage of Dexmedetomidine on the concomitant anesthetic,sedative, hypnotic or opioid may be required.

Neuromuscular Blockers : In one study of 10 healthy volunteers, administration of Dexmedetomidine for 45 minutes at a plasma concentration of 1 (one) ng/mL resulted in no clinically meaningful increases in the magnitude or neuromuscular blockade associated with rocuronium administration.

ADVERSE EFFECTS

Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting hypoxia, tachycardia and anemia.

Vascular Disorders: Hypotension, Hypertension, Hemorrhage
Gastrointestinal Disorders: Nausea, Dry mouth, Abdominal pain, diarrhea, vomiting
Cardiac Disorders: Bradycardia, Atrial fibrillation, Tachycardia, Sinus tachycardia, Ventricular tachycardia, myocardial infarction, heart disorder
General Disorders and Administration Site Conditions: Pyrexia, Hyperthermia, Chills, Edema peripheral
Metabolism and Nutrition Disorders: Hypovolemia, Hyperglycemia, Hypocalcemia, Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, hypoglycemia
Respiratory, Thoracic and Mediastinal Disorders: Atelectasis, Pleural effusion, Hypoxia, Pulmonary edema, Wheezing, Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Psychiatric Disorders: Agitation
Blood and Lymphatic System Disorders: Anemia
Injury, Poisoning and Procedural Complications: Post-procedural hemorrhage
Investigations: Urine output decreased
Body as a Whole: Fever, hyperpyrexia, hypovolemia, light anesthesia, pain, rigors
Central and Peripheral Nervous System Disorders: Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion
Liver and Biliary System Disorders: Increased gamma-glutamyl transpepsidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase
Psychiatric Disorders: Agitation, confusion, delirium, hallucination, illusion
Renal Disorders: Blood urea nitrogen increased, oliguria
Skin and Appendages Disorders: Increased sweating
Vision Disorders: Photopsia, abnormal vision

DOSAGE AND ADMINISTRATION

Dexmedetomidine should be administered using a controlled infusion device.

Dexmedetomidine dosing should be individualized and titrated to the desired clinical effect.

Dexmedetomidine is not indicated for infusions lasting longer than 24 hours.

For adult patients, Dexmedetomidine is generally initiated with a loading infusion of 1 (one) mcg/kg over 10 minutes, followed by 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.
Dexmedetomidine has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Dexmedetomidine prior to extubation provided the infusion does not exceed 24 hours.

Dosage Information

Indication	Dosage and Administration
Initiation of Intensive Unit Sedation	**For adult patients:** a loading infusion of one mcg/kg over 10 minutes. **Care For patients over 65 years of age:** a dose reduction should be considered. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.
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. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.
Initiation of Procedural Sedation	**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. **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. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.
Maintenance of Procedural Sedation	**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. **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. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.

Dilution Prior to Administration : Dexmedetomidine must be diluted in 0.9% sodium chloride solution prior to administration.
Preparation of solution is the same, whether for the loading dose or maintenance infusion.
To prepare the infusion, withdraw 2 mL of Dexmedetomidine and add to 48 mL of 0.9% Sodium Chloride injection to a total 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.

Administration with Other Fluids : Dexmedetomidine infusion should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established. Dexmedetomidine has been shown to be incompatible when administered with the following drugs: amphotericin B, diazepam.

Dexmedetomidine has been shown to be compatible when administered with the following intravenous fluids and drugs : 0.9% sodium chloride in water, 5% dextrose in water, 20% mannitol, alfentanil hydrochloride, amikacin sulfate, aminophylline, amiodarone hydrochloride, ampicillin sodium, ampicillin sodium-sulbactam sodium, atracurium besylate, atropine sulfate, azithromycin, aztreonam, bretylium tosylate, bumetanide, butorphanol tartrate, calcium gluconate, cefazolin sodium, cefepime hydrochloride, cefoperazone sodium, cefotaxime sodium, cefotetan sodium, cefoxitin sodium, ceftazidime, ceftizoxime sodium, ceftriaxone sodium, cefuroxime sodium, chlorpromazine hydrochloride, cimetidine hydrochloride, ciprofloxacin, cisatracurium besylate, clindamycin phosphate, dexamethasone sodium phosphate, digoxin, diltiazem hydrochloride, diphenhydramine hydrochloride, dobutamine hydrochloride, dolasetron mesylate, dopamine hydrochloride, doxycycline hyclate, droperidol, enalaprilat, ephedrine hydrochloride, epinephrine hydrochloride, erythromycin lactobionate, esmolol, etomidate, famotidine, fenoldopam mesylate, fentanyl citrate, fluconazole, furosemide, gatifloxacin, gentamicin sulfate, glycopyrrolate bromide, granisetron hydrochloride, haloperidol lactate, heparin sodium, hydrocortisone sodium succinate, hydromorphone hydrochloride, hydroxyzine hydrochloride, inamrinone lactate, isoproterenol hydrochloride, ketorolac tromethamine, labetalol, lactated Ringer's solution, levofloxacin, lidocaine hydrochloride, linezolid, lorazepam, magnesium sulfate, meperidine hydrochloride, methylprednisolone sodium succinate, metoclopramide hydrochloride, metronidazole, midazolam, milrinone lactate, mivacurium chloride, morphine sulfate, nalbuphine hydrochloride, nitroglycerin, norepinephrine bitartrate, ofloxacin,ondansetron hydrochloride, pancuronium bromide, phenylephrine hydrochloride, piperacillin sodium, piperacillin sodium-tazobactam sodium, potassium chloride, procainamide hydrochloride, prochlorperazine edisylate, promethazine hydrochloride, propofol, ranitidine hydrochloride, rapacuronium bromide, remifentanil hydrochloride, rocuronium bromide, sodium bicarbonate, sodium nitroprusside, succinylcholine, sufentanil citrate, sulfamethoxazole-trimethoprim, theophylline, thiopental sodium, ticarcillin disodium, ticarcillin disodium-clavulanate potassium, tobramycin sulfate, vancomycin hydrochloride, vecuronium bromide, verapamil hydrochloride, and a plasma-substitute.

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

STORAGE
Store below 30°C.
Please keep away from children.

Parenteral products should be inspected visually for particulate matter and discolouration prior to administration.

SHELF LIFE
36 Months

PRESENTATION :-
Dexmedetomidine Hydrochloride injection is available in pack of 0.5 ml, 1 ml & 2 ml Ampoule.

NAFDAC Reg. No.:

Manufactured in India by :

THEMIS MEDICARE

THEMIS MEDICARE LIMITED
Sector 6A, Plot No. 16, 17 & 18, IIE,
SIDCUL, Haridwar-249 403, Uttarakhand.

HRD/6193/0817

Specification Box

Market : Export (Nigeria Phillips) | Item : Insert | New Code : HRD/6193/0817

Product Name : Dexmedetomidine HCL Inj. | For Ref. : HRD/4771/0815

Material : 60 GSM Maplitho Paper | Artist : Shrikant

Size : 192 x 230 mm, Folding Size : 48 x 28.75 mm (2V x 3H) | Varnish :

Location : Haridwar | TP :

Item Code : PP21DEXP0029 | Date : 21.08.2017, 09.10.2017

Color : Black

Prepared by Packaging Development	Approved by Packaging Development	Approved by RA	Approved by Marketing	Approved by Medical	Approved by Plant head	Approved by QA Head

Reason for change : For DRA Registration

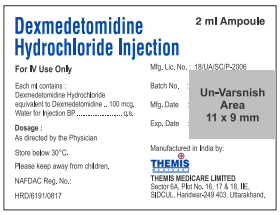
Path : D: \ Shrikant Artwork \ DRA \ Nigeria \ Nigeria Phillips \ Dexmedetomidine Inj. 2ml

1.1 ARTWORK AND LABEL OF THE COMMERCIAL PACK OF THE PRODUCT

- Label
- Carton
- Insert

Enclosed

Actual Size : 36 x 27 mm



Unwinding direction

Dexmedetomidine Hydrochloride Injection

2 ml Ampoule

For IV Use Only

Each ml contains :
Dexmedetomidine Hydrochloride
equivalent to Dexmedetomidine .. 100 mcg.
Water for Injection BP ..... q.s.

Dosage :
As directed by the Physician

Store below 30°C.

Please keep away from children.

NAFDAC Reg. No.:

HRD/6191/0817

Mfg. Lic. No. : 18/UA/SC/P-2006

Batch No. :

Mfg. Date :

Exp. Date :

Un-Varsnish Area 11 x 9 mm

Manufactured in India by:

THEMIS MEDICARE

THEMIS MEDICARE LIMITED
Sector 6A, Plot No. 16, 17 & 18, IIE,
SIDCUL, Haridwar-249 403, Uttarakhand.

400% of Actual Size

Specification Box

Market : Export (Nigeria Phillips) | Item : Label | New Code : HRD/6191/0817

Product Name : Dexmedetomidine HCL Inj. (2ml) | For Ref. : HRD/4819/1015

Material : 75 GSM Chromo Art Paper with Aqua Varnish, Sticker Label in Roll Form Un winding direction left to right

Size : 36 x 27 mm (LxH) | Varnish : Un-Varnish Zone for batch details

Location : Haridwar | TP :

Item Code : PP13DEXP0022 | Date : 21.08.2017, 11.09.2017, 09.10.2017

Color : Pantone 293 C Pantone 485 C Black

Prepared by Packaging Development	Approved by Packaging Development	Approved by RA	Approved by Marketing	Approved by Medical	Approved by Plant head	Approved by QA Head

Reason for change : For DRA Registration

Path : D: \ Shrikant Artwork \ DRA \ Nigeria \ Nigeria Phillips \ Dexmedetomidine 2ml

Specification Box

Market : Export (Nigeria Phillips)

Item : Carton

New Code : HRD/6192/0817

For Ref.: HRD/4818/1015

Product Name : Dexmedetomidine HCL Inj. (2ml)

Material : 300 GSM, ITC Cyber XL Board with Aqua Varnish

Artist: Shrikant

Size : 93 x 21 x 39 mm (LxWxH)

Varnish : Un-Varnish Zone for batch details

Location : Haridwar

TP :

Item Code : PP09DEXP0028

Date : 21.08.2017, 11.09.2017

Color : Pantone Rhodamine Red C Pantone 293 C Pantone 485 C Black

Prepared by Packaging Development	Approved by Packaging Development	Approved by RA	Approved by Marketing	Approved by Medical	Approved by Plant head	Approved by QA Head

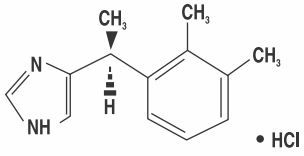
Reason for change : For DRA Registration

Path : D:\ Shrikant Artwork \ DRA \ Nigeria \ Nigeria Phillips \ Dexmedetomidine Inj. 2ml

For the use of Registered Medical Practitioner or a Hospital or a Laboratory only.

Dexmedetomidine Hydrochloride Injection

DESCRIPTION
Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine has a molecular weight of 236.7. The empirical formula is $C_{13}H_{16}N_2$ HCl and the structural formula is :



Each ml contains :
Dexmedetomidine Hydrochloride
equivalent to Dexmedetomidine ..... 100 mcg.
Water for Injection BP ..... Q.S.

CLINICAL PHARMACOLOGY
Dexmedetomidine, a highly selective and potent alpha$_2$-adrenergic agonist, has a potentially useful role as a sedative agent.

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

PHARMACOKINETICS
Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when administered by intravenous infusion for up to 24 hours.

Following intravenous administration, Dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{1/2}$) of approximately 6 minutes; a terminal elimination half-life (t1/2) of approximately 2 hours; and steady-state volume of distribution (Vss) of approximately 118 liters. Clearance is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

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

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
	Dexmedetomidine 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

* Presented as harmonic mean and pseudo standard deviation.
# Avg C_{ss} = Average steady-state concentration of Dexmedetomidine. (2.5–9 hour samples for 12 hour infusion and 2.5–18 hour samples for 24 hour infusions).

Distribution : The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of Dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects. The potential for protein binding displacement of Dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored in vitro, and negligible changes in the plasma protein binding of Dexmedetomidine were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by Dexmedetomidine was explored in vitro and none of these compounds appeared to be significantly displaced by Dexmedetomidine.

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

Elimination : A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following intravenous administration of radiolabeled Dexmedetomidine, was recovered in the urine and 4% in the feces. No unchanged Dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion.
Fractionation of the radioactivity excreted in urine demonstrated that products of N-glucuronidation accounted for approximately 34% of the cumulative urinary excretion.

INDICATIONS

Intensive care unit sedation : Dexmedetomidine is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.

Procedural Sedation : Dexmedetomidine is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

CONTRAINDICATIONS
No specific information available.

WARNINGS AND PRECAUTIONS

Drug Administration : Due to the known pharmacological effects of Dexmedetomidine HCL, it should be administered only by a person skilled in the management of patients in ICU or operating room setting and the patients should be continuously monitored.

Hypotension, Bradycardia, and Sinus Arrest : Clinically significant episodes of bradycardia and sinus arrest have been associated with Dexmedetomidine HCL administration in young, healthy volunteers with high vagal tone or with different routes of administration, including rapid intravenous or bolus administration.
Reports of hypotension and bradycardia have been associated with Dexmedetomidine HCL infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of Dexmedetomidine HCL, increasing the rate of IV fluid administration, elevation of the lower extremities, and use of pressor agents. Because Dexmedetomidine HCL has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (eg, atropine) should be considered to modify vagal tone. In clinical trials, atropine or glycopyrrolate were effective in the treatment of most episodes of Dexmedetomidine HCL -induced bradycardia.

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

Arousability : Some patients receiving Dexmedetomidine 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.

Withdrawal
Intensive Care Unit Sedation : If Dexmedetomidine were to be administered for more than 24 hours and stopped abruptly, withdrawal symptoms similar to those reported for another alpha-2-adrenergic agent, clonidine, may result. These symptoms include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

Procedural Sedation : Withdrawal symptoms were not seen after discontinuation of short term infusions of Dexmedetomidine (<6 hours).

Hepatic Impairment : Since Dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.

USE IN SPECIFIC POPULATION

Pregnancy : There are no adequate and well-controlled studies in pregnant women. Dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Lactation : It is not known whether Dexmedetomidine HCL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Dexmedetomidine HCL is administered to a nursing woman.

Labour and delivery : The safety of Dexmedetomidine HCL during labor and delivery has not been studied. Therefore, Dexmedetomidine HCL is not recommended during labor and delivery, including cesarean section

Paediatrics : There have been no clinical studies to establish the safety and efficacy of Dexmedetomidine in pediatric patients below 18 years of age. Therefore, Dexmedetomidine should not be used in this population.

Geriatrics : Dexmedetomidine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function.

Hepatic Impairment : Since Dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.

DRUG INTERACTIONS

Anesthetics/Sedatives/Hypnotics/Opioids : Co-administration of Dexmedetomidine with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil, and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with Dexmedetomidine, a reduction in dosage of Dexmedetomidine on the concomitant anesthetic,sedative, hypnotic or opioid may be required.

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ADVERSE EFFECTS

Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting hypoxia, tachycardia and anemia.

Vascular Disorders: Hypotension, Hypertension, Hemorrhage
Gastrointestinal Disorders: Nausea, Dry mouth, Abdominal pain, diarrhea, vomiting
Cardiac Disorders: Bradycardia, Atrial fibrillation, Tachycardia, Sinus tachycardia, Ventricular tachycardia, myocardial infarction, heart disorder
General Disorders and Administration Site Conditions: Pyrexia, Hyperthermia, Chills, Edema peripheral
Metabolism and Nutrition Disorders: Hypovolemia, Hyperglycemia, Hypocalcemia, Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, hypoglycemia
Respiratory, Thoracic and Mediastinal Disorders: Atelectasis, Pleural effusion, Hypoxia, Pulmonary edema, Wheezing, Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Psychiatric Disorders: Agitation
Blood and Lymphatic System Disorders: Anemia
Injury, Poisoning and Procedural Complications: Post-procedural hemorrhage
Investigations: Urine output decreased
Body as a Whole: Fever, hyperpyrexia, hypovolemia, light anesthesia, pain, rigors
Central and Peripheral Nervous System Disorders: Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion
Liver and Biliary System Disorders: Increased gamma-glutamyl transpepsidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase
Psychiatric Disorders: Agitation, confusion, delirium, hallucination, illusion
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Skin and Appendages Disorders: Increased sweating
Vision Disorders: Photopsia, abnormal vision

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Initiation of Procedural Sedation	**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. **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. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.
Maintenance of Procedural Sedation	**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. **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. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.

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Preparation of solution is the same, whether for the loading dose or maintenance infusion.
To prepare the infusion, withdraw 2 mL of Dexmedetomidine and add to 48 mL of 0.9% Sodium Chloride injection to a total 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.

Administration with Other Fluids : Dexmedetomidine infusion should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established. Dexmedetomidine has been shown to be incompatible when administered with the following drugs: amphotericin B, diazepam.

Dexmedetomidine has been shown to be compatible when administered with the following intravenous fluids and drugs : 0.9% sodium chloride in water, 5% dextrose in water, 20% mannitol, alfentanil hydrochloride, amikacin sulfate, aminophylline, amiodarone hydrochloride, ampicillin sodium, ampicillin sodium-sulbactam sodium, atracurium besylate, atropine sulfate, azithromycin, aztreonam, bretylium tosylate, bumetanide, butorphanol tartrate, calcium gluconate, cefazolin sodium, cefepime hydrochloride, cefoperazone sodium, cefotaxime sodium, cefotetan sodium, cefoxitin sodium, ceftazidime, ceftizoxime sodium, ceftriaxone sodium, cefuroxime sodium, chlorpromazine hydrochloride, cimetidine hydrochloride, ciprofloxacin, cisatracurium besylate, clindamycin phosphate, dexamethasone sodium phosphate, digoxin, diltiazem hydrochloride, diphenhydramine hydrochloride, dobutamine hydrochloride, dolasetron mesylate, dopamine hydrochloride, doxycycline hyclate, droperidol, enalaprilat, ephedrine hydrochloride, epinephrine hydrochloride, erythromycin lactobionate, esmolol, etomidate, famotidine, fenoldopam mesylate, fentanyl citrate, fluconazole, furosemide, gatifloxacin, gentamicin sulfate, glycopyrrolate bromide, granisetron hydrochloride, haloperidol lactate, heparin sodium, hydrocortisone sodium succinate, hydromorphone hydrochloride, hydroxyzine hydrochloride, inamrinone lactate, isoproterenol hydrochloride, ketorolac tromethamine, labetalol, lactated Ringer's solution, levofloxacin, lidocaine hydrochloride, linezolid, lorazepam, magnesium sulfate, meperidine hydrochloride, methylprednisolone sodium succinate, metoclopramide hydrochloride, metronidazole, midazolam, milrinone lactate, mivacurium chloride, morphine sulfate, nalbuphine hydrochloride, nitroglycerin, norepinephrine bitartrate, ofloxacin,ondansetron hydrochloride, pancuronium bromide, phenylephrine hydrochloride, piperacillin sodium, piperacillin sodium-tazobactam sodium, potassium chloride, procainamide hydrochloride, prochlorperazine edisylate, promethazine hydrochloride, propofol, ranitidine hydrochloride, rapacuronium bromide, remifentanil hydrochloride, rocuronium bromide, sodium bicarbonate, sodium nitroprusside, succinylcholine, sufentanil citrate, sulfamethoxazole-trimethoprim, theophylline, thiopental sodium, ticarcillin disodium, ticarcillin disodium-clavulanate potassium, tobramycin sulfate, vancomycin hydrochloride, vecuronium bromide, verapamil hydrochloride, and a plasma-substitute.

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

STORAGE
Store below 30°C.
Please keep away from children.

Parenteral products should be inspected visually for particulate matter and discolouration prior to administration.

SHELF LIFE
36 Months

PRESENTATION :-
Dexmedetomidine Hydrochloride injection is available in pack of 0.5 ml, 1 ml & 2 ml Ampoule.

NAFDAC Reg. No.:

Manufactured in India by :

THEMIS MEDICARE

THEMIS MEDICARE LIMITED
Sector 6A, Plot No. 16, 17 & 18, IIE,
SIDCUL, Haridwar-249 403, Uttarakhand.

HRD/6193/0817