Direction for Use
B. Braun Melsungen AG, 34209 Melsungen, Germany

Dexmedetomidine B. Braun 100 micrograms/ml
concentrate for solution for infusion

1 NAME OF THE MEDICINAL PRODUCT

Dexmedetomidine B. Braun 100 micrograms/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of concentrate contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine.

Each ampoule of 2 ml contains dexmedetomidine hydrochloride equivalent to 200 micrograms of dexmedetomidine.

Each ampoule of 4 ml contains dexmedetomidine hydrochloride equivalent to 400 micrograms of dexmedetomidine.

Each ampoule of 10 ml contains dexmedetomidine hydrochloride equivalent to 1000 micrograms of dexmedetomidine.

The concentration of the final solution after dilution should be 4 micrograms/ml

Excipients with known effect:

Each ampoule of 10 ml contains 35.4 mg of sodium.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The concentrate is a clear, colourless solution, pH 4.5 – 7.0

4 CLINICAL PARTICULARS

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. Dexmedetomidine should be administered by continuous infusion not to exceed 24 hours.

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

Procedural Sedation

For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

4.2 Posology and method of administration

Dosing Guidelines

- Dexmedetomidine B. Braun dosing should be individualized and titrated to desired clinical response.
- Dexmedetomidine B. Braun is not indicated for infusions lasting longer than 24 hours.
- Dexmedetomidine B. Braun should be administered using a controlled infusion device.

For sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting

For hospital use only. Dexmedetomidine B. Braun should be administered by healthcare professionals skilled in the management of patients requiring intensive care.

Posology

Initiation of Intensive Care Unit Sedation

For adult patients, a loading infusion of 1.0 mcg/kg over 10 minutes may be used. A dose reduction should be considered for patients over 65 years of age and adult patients with impaired hepatic function.

Maintenance of Intensive Care Unit Sedation

A maintenance infusion of 0.2 to 0.7 micrograms/kg/hr may be used, and may then be adjusted stepwise within the dose range in order to achieve the desired level of sedation, depending on the patient's response. A dose reduction should be considered for patients over 65 years of age and adult patients with impaired hepatic function. Dexmedetomidine B. Braun dosing should be individualized and titrated to desired clinical response.

For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

Initiation of Procedural Sedation

A loading infusion of 1.0 microgram/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 micrograms/kg given over 10 minutes may be suitable. For patients over 65 years of age, a loading infusion of 0.5 micrograms/kg over 10 minutes can be given. A dose reduction should be considered for adult patients with impaired hepatic function.

For awake fiberoptic intubation in adult patients: a loading infusion of one mcg/kg over 10 minutes.

Maintenance of Procedural Sedation

The maintenance infusion is generally initiated at 0.6 microgram/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/hour. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. For awake fiberoptic intubation in adult patients, a maintenance infusion of 0.7 mcg/kg/hr is recommended until the endotracheal tube is secured. A dose reduction should be considered for patients over 65 years of age and adult patients with impaired hepatic function.

Dosage adjustments:

Due to possible pharmacodynamic interactions, a reduction in dosage of Dexmedetomidine B. Braun or other concomitant anesthetics, sedatives, hypnotics or opioids may be required when co-administered.

Dosage reductions may need to be considered for adult patients with hepatic impairment, and geriatric patients.

Special populations

Elderly

Elderly patients over 65 years of age appear to have an increased risk for hypotension (see section 4.4). A dose reduction should be considered.

- Intensive Care Unit Sedation:

A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200 patients were 75 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of Dexmedetomidine. Therefore, a dose reduction may be considered in patients over 65 years of age.

- Procedural Sedation:

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

Renal impairment

No dose adjustment is required for patients with renal impairment.

Hepatic impairment

Dexmedetomidine is metabolised in the liver and should be used with caution in patients with hepatic impairment. A reduced maintenance dose may be considered (see sections 4.4 and 5.2).

Paediatric population

Safety and efficacy have not been established for Procedural or ICU Sedation in pediatric patients. One assessor-blinded trial in pediatric patients and two open-label studies in neonates were conducted to assess efficacy for ICU sedation. These studies did not meet their primary efficacy endpoints and the safety data submitted were insufficient to fully characterize the safety profile of Dexmedetomidine for this patient population. One open-label study conducted in pediatric patients for procedural sedation also did not meet its efficacy endpoint.

Additional safety data from pediatric patients became available following completion of an open-label ICU sedation study (Japan). In the Japan ICU study, the safety profile of Dexmedetomidine was generally similar to that of adults, although increased frequencies of adverse events of bradycardia, hypotension, and respiratory depression were seen. Therefore, Dexmedetomidine is not recommended in this population.

Method of administration

Intravenous use.

Dexmedetomidine B. Braun must be administered only as a diluted intravenous infusion using a controlled infusion device. Dexmedetomidine B. Braun should be administered only by persons skilled in the management of patients in the intensive care or operating room setting. Due to the known pharmacological effects of Dexmedetomidine B. Braun, patients should be continuously monitored while receiving Dexmedetomidine B. Braun. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- Advanced heart block (grade 2 or 3) unless paced
- Uncontrolled hypotension
- Acute cerebrovascular conditions

4.4 Special warnings and precautions for use

Monitoring

Dexmedetomidine B. Braun is intended for use in an intensive care setting, operating room and during diagnostic procedures. The use in other environments is not recommended. All patients should have continuous cardiac monitoring during Dexmedetomidine B. Braun infusion. Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea (see section 4.8).

The time to recovery after the use of dexmedetomidine was reported to be approximately one hour. When used in an outpatient setting close monitoring should continue for at least one hour (or longer based on the patient condition), with medical supervision continued for at least one further hour to ensure the safety of the patient.

Arousability

Some patients receiving Dexmedetomidine B. Braun 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.

Hypotension, Bradycardia and Sinus Arrest

Dexmedetomidine reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension (see section5.1).

Clinically significant episodes of bradycardia and sinus arrest have been reported with Dexmedetomidine administration in young, healthy adult 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 B. Braun infusion. Some of these cases have resulted in fatalities. If medical intervention is required, treatment may include decreasing or stopping the infusion of Dexmedetomidine B. Braun, increasing the rate of intravenous fluid administration, elevation of the lower extremities, and use of pressor agents. Because Dexmedetomidine B. Braun 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 considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treatment of most episodes of Dexmedetomidine -induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

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

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

Transient Hypertension

Transient hypertension has been observed primarily during the loading dose in association with the peripheral vasoconstrictive effects of dexmedetomidine and a loading dose is not recommended in

ICU sedation. Treatment of hypertension has generally not been necessary but decreasing the continuous infusion rate may be advisable.

Withdrawal

Intensive Care Unit Sedation:

With administration up to 7 days, regardless of dose, 12 (5%) Dexmedetomidine adult subjects experienced at least 1 event related to withdrawal within the first 24 hours after discontinuing study drug and 7 (3%) Dexmedetomidine adult subjects experienced at least 1 event 24 to 48 hours after end of study drug. The most common events were nausea, vomiting, and agitation.

In adult subjects, 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 Dexmedetomidine supportive therapy is indicated.

Procedural Sedation:

In adult subjects, withdrawal symptoms were not seen after discontinuation of short-term infusions of Dexmedetomidine (<6 hours).

Patients with hepatic impairment

Since dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function

Other

Diabetes insipidus has been reported in association with dexmedetomidine treatment. If polyuria occurs, it is recommended to stop dexmedetomidine and check serum sodium level and urine osmolality.

Tolerance and Tachyphylaxis

Use of dexmedetomidine beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions

Hyperthermia or Pyrexia

Dexmedetomidine may induce hyperthermia or pyrexia, which may be resistant to traditional cooling methods, such as administration of cooled intravenous fluids and antipyretic medications. Discontinue Dexmedetomidine if drug-related hyperthermia or pyrexia is suspected and monitor patients until body temperature normalizes.

Risk of Mortality

Use of dexmedetomidine greater than 24 hours has been associated with an increased mortality in critically ill adult intensive care unit (ICU) patients 63.7 years of age and younger compared to usual care**.**

Special warnings / precautions regarding excipients

Dexmedetomidine B. Braun contains less than 1 mmol sodium (23 mg) per each ampoule of 2 ml and 4 ml, that is to say essentially **'**sodium-free**'**.

This medicinal product contains 35.4 mg sodium per each ampoule of 10 ml, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, including sedative, anaesthetic and cardiorespiratory effects. Specific studies have confirmed enhanced 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 or the concomitant anaesthetic, sedative, hypnotic or opioid may be required.

No clinically meaningful increases in the magnitude of neuromuscular blockade was observed during the administration of dexmedetomidine and rocuronium administration.

In vitro studies suggested that dexmedetomidine is metabolized by several cytochrome P450 enzymes CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19 with no apparent predominant pathways. Dexmedetomidine has shown strongest properties for inhibition of CYP2D6, CYP3A4 and CYP2B6. Use caution during concomitant administration of dexmedetomidine with other medicines metabolized by CYP2D6, CYP3A4 and CYP2B6 enzymes.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

Available data from published randomized controlled trials and case reports over several decades of use with intravenously administered dexmedetomidine during pregnancy have not identified a drug-associated risk of major birth defects and miscarriage; however, the reported exposures occurred after the first trimester. Dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Most of the available data are based on studies with exposures that occurred at the time of caesarean section delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. Available data indicate that dexmedetomidine crosses the placenta.

In animal reproduction studies, fetal toxicity that lower fetal viability and reduced live fetuses occurred with subcutaneous administration of dexmedetomidine to pregnant rats during organogenesis at doses 1.8 times the maximum recommended human dose (MRHD) of 17.8 mcg/kg/day.

Developmental toxicity (low pup weights and adult offspring weights, decreased F1 grip strength, increased early implantation loss and decreased viability of second-generation offspring) occurred when pregnant rats were subcutaneously administered dexmedetomidine at doses less than the clinical dose from late pregnancy through lactation and weaning (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Increased post-implantation losses and reduced live fetuses in the presence of maternal toxicity (i.e. decreased body weight) were noted in a rat embryo-fetal development study in which pregnant dams were administered subcutaneous doses of dexmedetomidine 200 mcg/kg/day (equivalent to 1.8 times the intravenous MRHD of 17.8 mcg/kg/day based on body surface area [BSA]) during the period of organogenesis (Gestation Day [GD] 6 to 15). No malformations were reported.

No malformations or embryo-fetal toxicity were noted in a rabbit embryo-fetal development study in which pregnant does were administered dexmedetomidine intravenously at doses of up to 96 mcg/kg/day (approximately half the human exposure at the MRHD based on AUC) during the period of organogenesis (GD 6 to 18).

Reduced pup and adult offspring birth weights, and grip strength were reported in a rat developmental toxicology study in which pregnant females were administered dexmedetomidine subcutaneously at doses of 8 mcg/kg/day (0.07 times the MRHD based on BSA) during late pregnancy through lactation and weaning (GD 16 to postnatal day [PND] 25). Decreased viability of second generation offspring

and an increase in early implantation loss along with delayed motor development occurred in the 32 mcg/kg/day group (equivalent to less than the clinical dose based on BSA) when first generation offspring were allowed to mate. This study limited dosing to hard palate closure (GD 15 to 18) through weaning instead of dosing from implantation (GD 6 to 7) to weaning (PND 21).

In a study in the pregnant rat, placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously.Labor and Delivery

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

Lactation

Risk Summary

Available published literature reports the presence of dexmedetomidine in human milk following intravenous administration (see Data). There is no information regarding the effects of dexmedetomidine on the breastfed infant or the effects on milk production. Advise women to monitor the breastfed infant for irritability. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Dexmedetomidine and any potential adverse effects on the breastfed infant from Dexmedetomidine or from the underlying condition.

Data

In two published clinical studies, a total of 14 women were given intravenous dexmedetomidine 6 mcg/kg/hour for 10 minutes after delivery followed by continuous infusion of 0.2-0.7 mcg/kg/hour. Breast milk and maternal blood samples were collected at 0, 6, 12, and 24 hours after discontinuation of dexmedetomidine. Plasma and milk dexmedetomidine concentrations were detectable up to 6 hours in most subjects, up to 12 hours in one subject

and undetectable in all at 24 hours. The milk-to-plasma ratio from single paired maternal milk and plasma concentrations at each time point ranged from 0.53 to 0.95. The relative infant dose was estimated to range from 0.02 to 0.098%.Fertility

Fertility in male or female rats was not affected after daily subcutaneous injections at doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m2 basis). Dexmedetomidine was dosed from 10 weeks prior to mating in males and 3 weeks prior to mating and during mating in females. No human data on fertility are available.

4.7 Effects on ability to drive and use machines

Dexmedetomidine B. Braun has major influence on the ability to drive and use machines.

Patients should be advised to refrain from driving or other hazardous tasks for a suitable period of time after receiving dexmedetomidine for procedural sedation.

4.8 Undesirable effects

The following clinically significant adverse reactions are described elsewhere in the labeling:

• Hypotension, bradycardia and sinus arrest

• Transient hypertension

Clinical Studies

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 the clinical trials of another drug and may not reflect the rates observed in practice.

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.

Intensive Care Unit Sedation

Adverse reaction information is derived from the continuous infusion trials of Dexmedetomidine for sedation in the Intensive Care Unit setting in which 1,007 adult patients received Dexmedetomidine. 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% ≥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)].

Table 2. Adverse Reactions with an Incidence >2% - Intensive Care Unit Sedation Population

Body System/ Adverse Event	**All Dexmedetomidine N = 1007**	**Randomized Dexmedetomidine N = 798**	**Placebo N = 400**	**Propofol N = 188**
	n (%)	n (%)	n (%)	n (%)
Vascular disorders				
Hypotension	248 (25%)	191 (24%)	48 (12%)	25 (13%)
Hypertension	123 (12%)	101 (13%)	76 (19%)	7 (4%)
Gastrointestinal disorders				
Nausea	90 (9%)	73 (9%)	36 (9%)	20 (11%)
Dry mouth	35 (4%)	22 (3%)	4 (1%)	1 (1%)
Vomiting	34 (3%)	26 (3%)	21 (5%)	6 (3%)
Cardiac disorders				
Bradycardia	52 (5%)	36 (5%)	10 (3%)	0
Atrial fibrillation	44 (4%)	37 (5%)	13 (3%)	14 (7%)
Tachycardia	20 (2%)	15 (2%)	17 (4%)	2 (1%)
Sinus tachycardia	6 (1%)	6 (1%)	2 (1%)	4 (2%)
Ventricular tachycardia	4 (0%)	4 (1%)	3 (1%)	9 (5%)
General disorders and administration site conditions				
Pyrexia	35 (4%)	31 (4%)	15 (4%)	8 (4%)
Hyperthermia	19 (2%)	16 (2%)	12 (3%)	0
Chills	17 (2%)	14 (2%)	13 (3%)	4 (2%)
Edema peripheral	4 (0%)	2 (0%)	2 (1%)	4 (2%)
Metabolism and nutrition disorders				
Hypovolemia	31 (3%)	22 (3%)	9 (2%)	9 (5%)
Hyperglycemia	17 (2%)	15 (2%)	7 (2%)	5 (3%)
Hypocalcemia	7 (1%)	7 (1%)	0	4 (2%)
Acidosis	6 (1%)	5 (1%)	4 (1%)	4 (2%)
Respiratory, thoracic and mediastinal disorders				
Atelectasis	29 (3%)	23 (3%)	13 (3%)	12 (6%)
Pleural effusion	23 (2%)	16 (2%)	4 (1%)	12 (6%)
Hypoxia	16 (2%)	13 (2%)	8 (2%)	5 (3%)
Pulmonary edema	9 (1%)	9 (1%)	3 (1%)	5 (3%)
Wheezing	4 (0%)	4 (1%)	1 (0%)	4 (2%)
Psychiatric disorders				
Agitation	20 (2%)	16 (2%)	11 (3%)	1 (1%)
Blood and lymphatic system disorders				
Anemia	19 (2%)	18 (2%)	7 (2%)	4 (2%)
Injury, poisoning and procedural complications				
Post-procedural hemorrhage	15 (2%)	13 (2%)	10 (3%)	7 (4%)
Investigations				
Urine output decreased	6 (1%)	6 (1%)	0	4 (2%)

Adverse reaction information was also derived from the placebo-controlled, continuous infusion trials of Dexmedetomidine for sedation in the surgical intensive care unit setting in which 387 adult

patients received Dexmedetomidine for less than 24 hours. The most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia (see Table 3).

Table 3. Treatment-Emergent Adverse Events Occurring in >1% of All Dexmedetomidine-Treated Adult Patients in the Randomized Placebo-Controlled Continuous Infusion <24 Hours ICU Sedation Studies

Adverse Event	Randomized Dexmedetomidine (N = 387)	Placebo (N = 379)
Hypotension	28%	13%
Hypertension	16%	18%
Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial Fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Hemorrhage	3%	4%
Anemia	3%	2%
Dry Mouth	3%	1%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycemia	2%	2%
Acidosis	2%	2%
Pleural Effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

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

Table 4. Key Treatment-Emergent Adverse Events Occurring in Dexmedetomidine- or Midazolam-Treated Adult Patients in the Randomized Active Comparator Continuous Infusion Long-Term Intensive Care Unit Sedation Study

Adverse Event	Dexmedetomidine (N = 244)	Midazolam (N = 122)
Hypotension1	56%	56%
Hypotension Requiring Intervention	28%	27%
Bradycardia2	42%	19%
Bradycardia Requiring Intervention	5%	1%
Systolic Hypertension3	28%	42%

Tachycardia4	25%	44%
Tachycardia Requiring Intervention	10%	10%
Diastolic Hypertension3	12%	15%
Hypertension3	11%	15%
Hypertension Requiring Intervention†	19%	30%
Hypokalemia	9%	13%
Pyrexia	7%	2%
Agitation	7%	6%
Hyperglycemia	7%	2%
Constipation	6%	6%
Hypoglycemia	5%	6%
Respiratory Failure	5%	3%
Renal Failure Acute	2%	1%
Acute Respiratory Distress Syndrome	2%	1%
Generalized Edema	2%	6%
Hypomagnesemia	1%	7%

† Includes any type of hypertension.
1 Hypotension was defined in absolute terms as Systolic blood pressure of <80 mmHg or Diastolic blood pressure of <50 mmHg or in relative terms as ≤30% lower than pre-study drug infusion value.
2 Bradycardia was defined in absolute terms as <40 bpm or in relative terms as ≤30% lower than pre-study drug infusion value.
3 Hypertension was defined in absolute terms as Systolic blood pressure >180 mmHg or Diastolic blood pressure of >100 mmHg or in relative terms as ≥30% higher than pre-study drug infusion value.
4 Tachycardia was defined in absolute terms as >120 bpm or in relative terms as ≥30% greater than pre-study drug infusion value.

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

Table 5. Number (%) of Adult Subjects Who Had a Dose-Related Increase in Treatment Emergent Adverse Events by Maintenance Adjusted Dose Rate Range in the Dexmedetomidine Group

	Dexmedetomidine (mcg/kg/hr)		
Adverse Event	**≤0.7* (N = 95)**	**>0.7 to ≤1.1* (N = 78)**	**>1.1* (N = 71)**
Constipation	6%	5%	14%
Agitation	5%	8%	14%
Anxiety	5%	5%	9%
Edema Peripheral	3%	5%	7%
Atrial Fibrillation	2%	4%	9%
Respiratory Failure	2%	6%	10%
Acute Respiratory Distress Syndrome	1%	3%	9%

* Average maintenance dose over the entire study drug administration.

Procedural Sedation
Adverse reaction information is derived from the two trials for procedural sedation [see Clinical Studies (14.2)] in which 318 adult patients received Dexmedetomidine. The mean total dose was 1.6 mcg/kg (range: 0.5 to 6.7), mean dose per hour was 1.3 mcg/kg/hr (range: 0.3 to 6.1) and the mean duration of infusion of 1.5 hours (range: 0.1 to 6.2). The population was between 18 to 93 years of age, ASA I-IV, 30% ≥65 years of age, 52% male and 61% Caucasian.

Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 6. The

most frequent adverse reactions were hypotension, bradycardia, and dry mouth [see Warnings and Precautions (5.2)]. Pre-specified criteria for the vital signs to be reported as adverse reactions are footnoted below the table. The decrease in respiratory rate and hypoxia was similar between Dexmedetomidine and comparator groups in both studies.

Table 6. Adverse Reactions with an Incidence >2% - Procedural Sedation Population

	Dexmedetomidine N = 318	**Placebo N = 113**
Body System/ Adverse Event	n (%)	n (%)
Vascular disorders		
Hypotension1	173 (54%)	34 (30%)
Hypertension2	41 (13%)	27 (24%)
Respiratory, thoracic and mediastinal disorders		
Respiratory depression5	117 (37%)	36 (32%)
Hypoxia6	7 (2%)	3 (3%)
Bradypnea	5 (2%)	5 (4%)
Cardiac disorders		
Bradycardia3	45 (14%)	4 (4%)
Tachycardia4	17 (5%)	19 (17%)
Gastrointestinal disorders		
Nausea	10 (3%)	2 (2%)
Dry mouth	8 (3%)	1 (1%)

1 Hypotension was defined in absolute and relative terms as Systolic blood pressure of <80 mmHg or ≤30% lower than pre-study drug infusion value, or Diastolic blood pressure of <50 mmHg.
2 Hypertension was defined in absolute and relative terms as Systolic blood pressure >180 mmHg or ≥30% higher than pre-study drug infusion value or Diastolic blood pressure of >100 mmHg.
3 Bradycardia was defined in absolute and relative terms as <40 beats per minute or ≤30% lower than pre-study drug infusion value.
4 Tachycardia was defined in absolute and relative terms as >120 beats per minute or ≥30% greater than pre-study drug infusion value.
5 Respiratory depression was defined in absolute and relative terms as respiratory rate (RR) <8 beats per minute or >25% decrease from baseline.
6 Hypoxia was defined in absolute and relative terms as SpO_2 <90% or 10% decrease from baseline.

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Dexmedetomidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hypotension and bradycardia were the most common adverse reactions associated with the use of Dexmedetomidine during post-approval use of the drug.

Table 7. Adverse Reactions Experienced During Post-Approval Use of Dexmedetomidine

Body System	**Preferred Term**
Body as a Whole	Fever, hyperpyrexia, hypovolemia, light anesthesia, pain, rigors
Cardiovascular Disorders, General	Blood pressure fluctuation, heart disorder, hypertension, hypotension, myocardial infarction
Central and Peripheral Nervous System Disorders	Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion
Gastrointestinal System Disorders	Abdominal pain, diarrhea, vomiting, nausea
Heart Rate and Rhythm Disorders	Arrhythmia, ventricular arrhythmia, bradycardia, hypoxia, Atrioventricular block, cardiac arrest, extrasystoles, atrial fibrillation, heart block, t

	wave inversion, tachycardia, supraventricular tachycardia, ventricular tachycardia
Liver and Biliary System Disorders	Increased gamma-glutamyl transpeptidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase
Metabolic and Nutritional Disorders	Disorders Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, hypoglycemia
Psychiatric Disorders	Agitation, confusion, delirium, hallucination, illusion
Red Blood Cell Disorders	Anemia
Renal Disorders	Blood urea nitrogen increased, oliguria
Respiratory System Disorders	Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vascular Disorders	Hemorrhage
Vision Disorders	Photopsia, abnormal vision

4.9 Drug Abuse, Dependence and Overdose

Dexmedetomidine is not a controlled substance.

Dependence

The dependence potential of Dexmedetomidine has not been studied in humans. However, since studies in rodents and primates have demonstrated that Dexmedetomidine exhibits pharmacologic actions similar to those of clonidine, it is possible that Dexmedetomidine may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation

Overdose

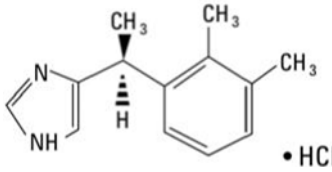
The tolerability of Dexmedetomidine was studied in one study in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hr. The maximum blood concentration achieved in this study was approximately 13 times the upper boundary of the therapeutic range.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

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

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives
ATC code: N05CM18

Dexmedetomidine B. Braun injection is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine B. Braun has a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2 \cdot HCl$ and the structural formula is:



Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Dexmedetomidine B. Braun is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each mL contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

Dexmedetomidine is a selective alpha-2 adrenoreceptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstricting effects prevail leading to an increase in systemic vascular resistance and blood pressure, while the bradycardic effect is further emphasised. Dexmedetomidine is relatively free from respiratory depressive effects when given as monotherapy to healthy subjects.

Alpha2 selectivity is observed in animals following slow intravenous infusion of low and medium doses (10-300 mcg/kg). Both alpha1 and alpha2 activity is observed following slow intravenous infusion of high doses (≥1,000 mcg/kg) or with rapid intravenous administration.

5.1 Pharmacodynamic properties

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 Dexmedetomidine was administered by intravenous infusion at doses within the recommended dose range (0.2 - 0.7 mcg/kg/hr).

5.2 Pharmacokinetic properties

The pharmacokinetics of dexmedetomidine has been assessed following short term IV administration in healthy volunteers and long term infusion in ICU population.

Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life (t1/2) 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.

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. Table 8 shows the main pharmacokinetic parameters when Dexmedetomidine was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 mcg/kg/hr (target plasma concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 mcg/kg/hr (target plasma concentration of 0.6 ng/mL) for 24 hours, and 0.70 mcg/kg/hr (target plasma concentration of 1.25 ng/mL) for 24 hours.

Table 8. Mean ± SD Pharmacokinetic Parameters

Parameter	**Loading Infusion (min)/Total Infusion Duration (hrs)**			
	10 min/12 hrs	**10 min/24 hrs**	**10 min/24 hrs**	**35 min/24 hrs**
	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**

t1/2*, 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
Vss, liter	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg Css#, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

Abbreviations: t1/2 = half-life, CL = clearance, Vss = steady-state volume of distribution.
* Presented as harmonic mean and pseudo standard deviation.
# Mean Css = Average steady-state concentration of dexmedetomidine. The mean Css was calculated based on post-dose sampling from 2.5 − 9 hours samples for 12 hour infusion and post-dose sampling from 2.5 − 18 hours for 24 hour infusions.

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

Dexmedetomidine pharmacokinetic parameters after Dexmedetomidine maintenance doses of 0.2 to 1.4 mcg/kg/hr for >24 hours were similar to the pharmacokinetic (PK) parameters after Dexmedetomidine maintenance dosing for <24 hours in other studies. The values for clearance (CL), volume of distribution (V), and t1/2 were 39.4 L/hr, 152 L, and 2.67 hours, respectively.

Distribution

The steady-state volume of distribution (Vss) of dexmedetomidine is approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female subjects. 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.

Elimination

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 with a minor role of CYP1A2, CYP2E1, CYP2D6 and CYP2C19) 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-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronide.

Excretion

The terminal elimination half-life (t1/2) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39 L/h. 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. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxylic acid-dexmedetomidine together represented approximately 14% of the dose in urine. N-methylation of dexmedetomidine to form 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for approximately 18% of the dose in urine. The N-Methyl metabolite

itself was a minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have not been identified.

Special Populations

Male or Female Patients
No major pharmacokinetic differences have been observed based on gender.

Geriatric Patients
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.

Patients with Hepatic Impairment
In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine were lower than in healthy subjects. The mean clearance values for patients with mild, moderate, and severe hepatic impairment were 74%, 64% and 53% of those observed in the normal healthy subjects, respectively. The mean plasma clearance values of unbound dexmedetomidine for subjects with mild, moderate, and severe hepatic impairment were 59 %, 51 % and 32 % of those observed in the normal healthy subjects, respectively. Although dexmedetomidine is administered to effect, it may be necessary to consider initial/maintenance dose reduction in patients with hepatic impairment depending on the degree of impairment and the response.

Patients with Renal Impairment

The pharmacokinetics of dexmedetomidine (C_{max}, T_{max}, AUC, t1/2, CL, and V_{SS}) in subjects with severe renal impairment (creatinine clearance <30 ml/min) is not altered relative to healthy subjects.

Drug Interaction Studies

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

5.3 Preclinical safety data

Carcinogenesis

Animal carcinogenicity studies have not been performed with Dexmedetomidine.

Mutagenesis

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

Impairment of Fertility

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

Animal Toxicology and/or Pharmacology

There were no differences in the adrenocorticotropic hormone (ACTH)-stimulated cortisol response in dogs following a single dose of dexmedetomidine compared to saline control. However, after continuous subcutaneous infusions of dexmedetomidine at 3 mcg/kg/hr and 10 mcg/kg/hr for one week in dogs (exposures estimated to be within the clinical range), the ACTH-stimulated cortisol response was

diminished by approximately 27% and 40%, respectively, compared to saline-treated control animals indicating a dose-dependent adrenal suppression.

5.4 Clinical Studies

Sedation of adult ICU (Intensive Care Unit) patients

Two randomized, double-blind, parallel-group, placebo-controlled multicenter clinical trials included 754 adult patients being treated in a surgical intensive care unit. All patients were initially intubated and received mechanical ventilation. These trials evaluated the sedative properties of Dexmedetomidine by comparing the amount of rescue medication (midazolam in one trial and propofol in the second) required to achieve a specified level of sedation (using the standardized Ramsay Sedation Scale) between Dexmedetomidine and placebo from onset of treatment to extubation or to a total treatment duration of 24 hours. The Ramsay Level of Sedation Scale is displayed in Table 9.

Table 9. Ramsay Level of Sedation Scale

Clinical Score	Level of Sedation Achieved
6	Asleep, no response
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
3	Patient responds to commands
2	Patient cooperative, oriented, and tranquil
1	Patient anxious, agitated, or restless

In the first study, 175 adult patients were randomized to receive placebo and 178 to receive Dexmedetomidine by intravenous infusion at a dose of 0.4 mcg/kg/hr (with allowed adjustment between 0.2 and 0.7 mcg/kg/hr) following an initial loading infusion of one mcg/kg intravenous over 10 minutes. The study drug infusion rate was adjusted to maintain a Ramsay sedation score of ≥3. Patients were allowed to receive "rescue" midazolam as needed to augment the study drug infusion. In addition, morphine sulfate was administered for pain as needed. The primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to maintain sedation as specified while intubated. Patients randomized to placebo received significantly more midazolam than patients randomized to Dexmedetomidine (see Table 10).

A second prospective primary analysis assessed the sedative effects of Dexmedetomidine by comparing the percentage of patients who achieved a Ramsay sedation score of ≥3 during intubation without the use of additional rescue medication. A significantly greater percentage of patients in the Dexmedetomidine group maintained a Ramsay sedation score of ≥3 without receiving any midazolam rescue compared to the placebo group (see Table 10).

Table 10. Midazolam Use as Rescue Medication During Intubation (ITT)
Study One

	Placebo N=175	Dexmedetomidine N=178	p-value
Mean Total Dose (mg) of Midazolam	19 mg	5 mg	0.0011*
Standard deviation	53 mg	19 mg	
Categorized Midazolam Use			
0 mg	43 (25%)	108 (61%)	<0.001**
0-4 mg	34 (19%)	36 (20%)	
>4 mg	98 (56%)	34 (19%)	

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

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

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

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

Patients randomized to placebo received significantly more propofol than patients randomized to Dexmedetomidine (see Table 11).

A significantly greater percentage of patients in the Dexmedetomidine group compared to the placebo group maintained a Ramsay sedation score of ≥3 without receiving any propofol rescue (see Table 11).

Table 11. Propofol Use as Rescue Medication During Intubation (ITT)
Study Two

	Placebo N=198	**Dexmedetomidine N=203**	**p-value**
Mean Total Dose (mg) of Propofol Standard deviation	513 mg 782 mg	72 mg 249 mg	<0.0001*
Categorized Propofol Use			
0 mg	47 (24%)	122 (60%)	<0.001**
0-50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

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

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the Dexmedetomidine and placebo groups. On average, Dexmedetomidine-treated patients received less morphine sulfate for pain than placebo-treated patients (0.43 versus 0.89 mg/h). In addition, 41% (83 of 203 patients) of Dexmedetomidine patients received no morphine sulfate for pain versus 15% (30 of 198 patients) in the placebo group.

In a controlled clinical trial, Dexmedetomidine was compared to midazolam for ICU sedation exceeding 24 hours duration. Dexmedetomidine was not shown to be superior to midazolam for the primary efficacy endpoint, the percent of time patients were adequately sedated (81% versus 81%). In addition, administration of Dexmedetomidine for longer than 24 hours was associated with tolerance, tachyphylaxis, and a dose-related increase in adverse events [see Adverse Reactions (6.1)].

In study 3005012, patients were sedated with propofol prior to randomization to either propofol (3005012) or dexmedetomidine.

In study 3005013, patients were sedated with midazolam prior to randomization to either midazolam (3005013) or dexmedetomidine.

In both study 3005012 and 3005013, the loading dose was omitted in order to reduce the risk of occurrence of cardiovascular events at the start of treatment.

3005012

The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 64.6 (60.0 to 69.1)% for subjects on dexmedetomidine and 64.7 (59.9 to 69.4)% for subjects on propofol. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. propofol (0.92) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to propofol in maintaining a target depth of sedation. The median duration of mechanical ventilation was 21 hours shorter in the dexmedetomidine group (96.5 hours) than in the propofol group (117.5 hours).

The length of stay in the ICU from randomization to medically fit for discharge or transfer did not differ ($p = 0.535$) between groups.

72.5% of subjects in the dexmedetomidine group and 64.4% of subjects in the propofol group needed the first-line (i.e. midazolam boli) rescue treatment for inadequate sedation during the treatment period ($p = 0.054$). The total number of doses of the rescue treatment was 2495 and 1986 in the dexmedetomidine and propofol groups, respectively. The mean average dose (0.74 vs. 0.31 mg/h, $p < 0.001$) and the mean total dose (32.9 vs. 22.8 mg, $p = 0.024$) of the first-line rescue treatment were higher in the dexmedetomidine group than in the propofol group. The first-line rescue treatment also started earlier in the dexmedetomidine group (median of 1.4 vs. 4.3 hours, $p = 0.018$). No differences between groups were observed in the use of second-line rescue treatment (mostly fentanyl) during the study treatment period or in the total use of fentanyl during the study.

3005013

The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 60.7 (55.4 to 66.1)% for subjects on dexmedetomidine and 56.6 (51.2 to 61.9)% for subjects on midazolam. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. midazolam (0.97) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to midazolam in maintaining a target depth of sedation. The median duration of mechanical ventilation was 41 hours shorter in the dexmedetomidine group (123.0 hours) than in the midazolam group (164.0 hours).

The length of stay in the ICU from randomization to medically fit for discharge or transfer did not differ ($p = 0.269$) between groups.

A similar percentage of subjects in the dexmedetomidine group (43.8%) and midazolam group (45.4%) received the first-line (i.e. propofol boli) rescue treatment for inadequate sedation during the treatment period ($p = 0.720$). The total number of doses (1100 vs. 1008), the mean average total dose (5.00 vs. 3.59 mg/h, $p = 0.173$) and the mean total dose (360 vs. 299 mg, $p = 0.317$) of the first-line rescue treatment were similar in both groups. The median time to the first use (19.3 vs. 20.0 hours) was also similar ($p = 0.741$). No differences between groups were observed in the use of second-line rescue treatment (mostly fentanyl) during the study treatment period or in the total use of fentanyl during the study.

SPICE III Study

In a published randomized controlled trial (Sedation Practice in Intensive Care Evaluation (SPICE) III trial) of 3,904 critically ill adult ICU patients, dexmedetomidine was used as primary sedative and compared with usual care. In the study, exposure to dexmedetomidine was greater than 24 hours with a median duration of treatment of 2.56 days (interquartile range, 1.10 to 5.23). The administration of dexmedetomidine was continued as clinically required for up to 28 days after randomization.

There was no overall significant difference in the primary outcome of 90-day mortality between the dexmedetomidine and usual care group (mortality 29.1% in both groups). In exploratory subgroup analyses, dexmedetomidine was associated with a decreased mortality in patients with age greater than the median age of 63.7 years (risk difference -4.4; 95% confidence interval -8.7 to -0.1) compared to usual care. Conversely, dexmedetomidine was associated with an increased mortality in patients with age less than or equal to the median age of 63.7 years (risk difference 4.4; 95% confidence interval 0.8 to 7.9) compared to usual care.

The significance of these findings is unknown, but they should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in patients less than or equal to 63.7 years old. Dexmedetomidine is not indicated for use longer than 24 hours and therefore its administration should not exceed 24 hours [see Section (4.1)].

Procedural/awake sedation

The safety and efficacy of dexmedetomidine for sedation of non-intubated patients prior to and/or during surgical and diagnostic procedures was evaluated in two randomised, double-blind, placebo-controlled multicentre clinical trials.

Study 1 randomised patients undergoing elective surgeries/procedures under monitored anaesthesia care and local/regional anaesthesia to receive a loading infusion of dexmedetomidine either 1 µg/kg (n=129) or 0.5 µg/kg (n=134), or placebo (normal saline; n=63) given over 10 minutes and followed by a maintenance infusion started at 0.6 µg/kg/h. The maintenance infusion of study drug could be titrated from 0.2 µg/kg/h to 1 µg/kg/h. The proportion of patients that achieved the targeted sedation level (Observer's Assessment of Alertness/Sedation Scale ≤4) without need for rescue midazolam was 54% of the patients receiving dexmedetomidine 1 µg/kg and 40% of the patients receiving dexmedetomidine 0.5 µg/kg compared to 3% of patients receiving the placebo. The risk difference in proportion of subjects randomised to dexmedetomidine 1 µg/kg group and dexmedetomidine 0.5 µg/kg group not requiring rescue midazolam was 48% (95% CI: 37% - 57%) and 40% (95% CI: 28% - 48%), respectively compared placebo. The median (range) midazolam rescue dose was 1.5 (0.5-7.0) mg in the dexmedetomidine1.0 µg/kg group, 2.0 (0.5-8.0) mg in the dexmedetomidine 0.5 µg/kg group, and 4.0 (0.5-14.0) mg in the placebo group. The difference in means in dose of rescue midazolam in dexmedetomidine 1 µg/kg and dexmedetomidine 0.5 µg/kg group compared to placebo was -3.1 mg (95% CI: -3.8 - -2.5) and -2.7 mg (95% CI: -3.3 - -2.1), respectively favouring dexmedetomidine. The median time to first rescue dose was 114 minutes in the dexmedetomidine 1.0 µg/kg group, 40 minutes in the dexmedetomidine 0.5 µg/kg group, and 20 minutes in the placebo group.

Study 2 randomised patients undergoing awake fibreoptic intubation under topical anaesthesia to receive a loading infusion of dexmedetomidine 1 µg/kg (n=55) or placebo (normal saline) (n=50) given over 10 minutes and followed by a fixed maintenance infusion of 0.7 µg/kg/h. To maintain a Ramsay Sedation Scale ≥2 53% of the patients receiving dexmedetomidine did not require midazolam rescue vs. 14% of patients receiving placebo. The risk difference in proportion of subjects randomised to dexmedetomidine not requiring rescue midazolam was 43% (95% CI: 23% - 57%) compared placebo. The mean midazolam rescue dose was 1.1 mg in the dexmedetomidine group, and 2.8 mg in the placebo group. The difference in means in dose of rescue midazolam was -1.8 mg (95% CI: -2.7 - -0.86) favouring dexmedetomidine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Compatibility studies have shown potential for adsorption of dexmedetomidine to some types of natural rubber. Although dexmedetomidine is dosed to effect, it is advisable to use components with synthetic or coated natural rubber gaskets.

6.3 Shelf life

Unopened

3 years

After dilution

Do not refrigerate.

Chemical and physical in-use stability has been demonstrated for 48 hours at 25 °C .

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 30◦C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2, 4 or 10 ml colourless glass ampoules

Pack sizes

5 x 2 ml, 10 x 2 ml, 25 x 2 ml ampoules

4 x 4 ml, 10 x 4 ml ampoules

4 x 10 ml, 10 x 10 ml ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Containers are for single use only.

Preparation of solution

Dexmedetomidine B. Braun can be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection to achieve the required concentration of 4 micrograms/ml prior to administration. Strict aseptic technique must always be maintained during handling of Dexmedetomidine B. Braun. Please see below in tabulated form the volumes needed to prepare the infusion.

To achieve required concentration of 4 micrograms/ml:

Volume of Dexmedetomidine B. Braun concentrate for solution for infusion	Volume of diluent	Total volume of infusion
2 ml	48 ml	50 ml

4 ml	96 ml	100 ml
10 ml	240 ml	250 ml
20 ml	480 ml	500 ml

The solution should be shaken gently to mix well.

Before administration, the solution should be visually inspected to ensure it is clear and colourless. It should not be used if any particulate matter is observed.

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

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

Dexmedetomidine HCl has been shown to be compatible when administered with the following intravenous fluids and medicinal products:

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. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 REVISION DATE

05.2023

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