SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PREXODIN 200 mcg/2 mL Concentrate for Solution for IV Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each 1 mL of the solution contains 118.2 micrograms of dexmedetomidine hydrochloride, equivalent to 100 micrograms of dexmedetomidine; each 2 mL contains 236.4 micrograms of dexmedetomidine hydrochloride, equivalent to 200 micrograms of dexmedetomidine.

Excipients with known effect:

Sodium chloride.....9 mg/mL
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Colorless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PREXODIN is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.

- In this group of patients, PREXODIN is not indicated for infusions lasting longer than 24 hours. For sedation of adult intensive care unit patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to a Richmond Agitation-Sedation Scale (RASS) 0 to -3),
- For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation (e.g. procedural/awake sedation).

4.2 Posology and method of administration

Posology/frequency and duration of administration:

<u>In intensive care units;</u>

- **For sedation of adult patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to a Richmond Agitation-Sedation Scale (RASS) 0 to -3)**
- **For sedation of initially intubated and mechanically ventilated patients during treatment:**

PREXODIN is for hospital use only and should be administered in intensive care settings by healthcare professionals specialized in the following areas.

Posology
For patients already intubated and under sedation, transitioning to dexmedetomidine can begin with an initial infusion rate of 0.7 micrograms/kg/hour. This dose can then be adjusted incrementally within the range of 0.2–1.4 micrograms/kg/hour, based on the patient's response, to achieve the desired level of sedation. A lower initial infusion rate should be considered for physically frail patients. Dexmedetomidine is highly potent and should be administered at an infusion rate per hour. A new steady-state sedation level may take up to an hour to be achieved following dose adjustment.

Maximum Dose
The maximum dose of 1.4 micrograms/kg/hour should not be exceeded. Patients who do not achieve adequate sedation at this maximum dose should be transitioned to an alternative sedative agent.

Loading doses of PREXODIN are not recommended, as they have been associated with an increase in adverse reactions during intensive care sedation. If needed, propofol or midazolam may be administered until the clinical effects of PREXODIN are achieved.

Duration
There is no experience with dexmedetomidine use for durations exceeding 14 days. The use of PREXODIN beyond this period should be regularly re-evaluated.

PREXODIN dosage should be individualized and titrated to the desired clinical effect.

For sedation of non-intubated adult patients before and/or during diagnostic or surgical procedures requiring sedation (e.g., procedural/awake sedation);

PREXODIN should only be administered by healthcare professionals experienced in managing anesthesia for patients in the operating room or during diagnostic procedures. Patients must be continuously monitored for early signs of hypotension, hypertension, bradycardia, respiratory depression, airway obstruction, apnea, dyspnea, and/or oxygen desaturation by individuals not involved in the diagnostic or surgical procedure (see section 4.8).

Supplementary oxygen should be readily available and provided when necessary. Oxygen saturation must be monitored by pulse oximetry.

PREXODIN is administered as a loading infusion followed by a maintenance infusion during procedural sedation. Depending on the procedure, concurrent local anesthesia or analgesia may be needed to achieve the desired clinical effect. In painful procedures or when deeper sedation is required, additional analgesics or sedatives (e.g., opioids, midazolam, or propofol) are recommended. The pharmacokinetic distribution half-life of dexmedetomidine is estimated to

be approximately 6 minutes. This should be considered, along with the effects of other administered drugs, when determining the appropriate time required for titration to the desired clinical effect of dexmedetomidine.

Initiation of Procedural Sedation:
- A loading infusion of 1 microgram/kg over 10 minutes.

(For less invasive procedures, such as ophthalmic surgery, a loading infusion of 0.5 micrograms/kg over 10 minutes may be appropriate.)

Maintenance of Procedural Sedation:
- The maintenance infusion typically starts at 0.6–0.7 micrograms/kg/hour and is titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/hour. The maintenance infusion rate should be adjusted to reach the targeted sedation level.

Method of administration:
PREXODIN must be administered only as a diluted intravenous infusion using a controlled infusion device. See section 6.6 for instructions on diluting this medicinal product before use.

Additional information on special populations:
Renal Impairment:
Dose adjustment is not required for patients with renal impairment.

Hepatic Impairment:
Since PREXODIN is metabolized in the liver, it should be used with caution in patients with hepatic impairment. A reduced maintenance dose may be considered (see sections 4.4 and 5.2).

Pediatric Population:
The safety and efficacy of dexmedetomidine in children aged 0 to 18 years have not been established. Available data are described in sections 4.8, 5.1, and 5.2, but no dosage recommendations can be made.

Geriatric Population:
Dose adjustment is generally not required for elderly patients (see section 5.2). However, elderly patients appear to be at an increased risk of hypotension (see section 4.4). Limited data from procedural sedation do not indicate a clear dose relationship for this risk.

4.3 Contraindications
- Hypersensitivity to dexmedetomidine hydrochloride or any of the excipients,
- Advanced heart block (grade 2 or 3), in the absence of a pacemaker,
- Uncontrolled hypotension,

- Acute cerebrovascular conditions.

4.4 Special warnings and precautions for use

Monitoring

PREXODIN is intended for use in intensive care settings, operating rooms, and during diagnostic procedures. Its use in other settings is not recommended. Continuous cardiac monitoring is required for all patients during PREXODIN infusion. In non-intubated patients, respiratory monitoring is necessary due to the risk of respiratory depression and, in some cases, apnea (see section 4.8).

The recovery time following dexmedetomidine administration has been reported to be approximately one hour. When used in outpatient settings, close monitoring should continue for at least one hour (or longer depending on the patient's condition), and medical supervision should be maintained for an additional hour to ensure patient safety.

General Precautions

PREXODIN should not be administered as a bolus dose, and a loading dose is not recommended in the Intensive Care Unit (ICU). Therefore, healthcare providers should be prepared to use an alternative sedative, particularly for the acute control of agitation or during procedures, especially in the initial hours of treatment. If a rapid increase in sedation level is required during procedural sedation, a small bolus of another sedative may be used.

Some patients receiving dexmedetomidine may be observed as alert and responsive to stimulation. This alone should not be interpreted as a lack of drug efficacy in the absence of other clinical signs and symptoms.

Dexmedetomidine does not typically cause deep sedation, and patients can be easily awakened. Therefore, it is not suitable for patients who cannot tolerate this effect profile, such as those requiring continuous deep sedation.

PREXODIN should not be used as an induction agent for general anesthesia for intubation or to provide sedation during the use of muscle relaxants.

Dexmedetomidine lacks the anticonvulsant effects of some other sedatives and, therefore, will not suppress underlying seizure activity.

Caution should be exercised when dexmedetomidine is used in combination with other sedatives or medications with cardiovascular effects, as additive effects may occur.

PREXODIN is not recommended for patient controlled sedation. Adequate data are not available.

When used in outpatient settings, patients should be monitored by their caregivers for some time. Patients should be advised to avoid driving, performing hazardous tasks, and, where possible, using other sedative agents (e.g., benzodiazepines, opioids, alcohol) that may have cumulative sedative effects, based on the observed effects of dexmedetomidine, the procedure, concomitant medications, patient age, and condition.

Caution is advised when administering dexmedetomidine to elderly patients. Patients over 65 years of age may be more prone to hypotension when dexmedetomidine, including a loading dose, is used for procedures. Dose reduction should be considered (see section 4.2).

Mortality in ICU patients ≤65 years old

In the SPICE III randomized controlled trial conducted on 3904 critically ill adult ICU patients, dexmedetomidine was compared as a primary sedative drug to other agents. Overall, there was no significant difference in 90-day mortality rates between the dexmedetomidine and comparator groups (both groups had a mortality rate of 29.1%). However, age-related differences in mortality were observed. Dexmedetomidine had a notable effect on patients aged ≤65 years compared to alternative sedative agents (hazard ratio 1.26; 95% CI 1.02–1.56). Although the mechanism is unclear, this age-related heterogeneity in mortality effect was most pronounced in patients admitted for reasons other than postoperative care. The effect became more significant as APACHE II scores increased and age decreased. These findings should be carefully considered when evaluating the anticipated clinical benefits of dexmedetomidine relative to alternative sedatives, particularly in younger patients.

Cardiovascular Effects and Precautions

Dexmedetomidine reduces heart rate and blood pressure through central sympatholysis but can cause peripheral vasoconstriction at higher concentrations, leading to hypertension (see section 5.1). Therefore, it is unsuitable for patients with severe cardiovascular instability.

Caution is advised when administering dexmedetomidine to patients with pre-existing bradycardia. Limited data are available on the effects of dexmedetomidine in patients with a heart rate <60, requiring special attention. Bradycardia usually does not require treatment but has often responded to anticholinergic medications or dose reduction when necessary. Patients with high physical fitness and slow resting heart rates may be particularly sensitive to the bradycardic effects of alpha-2 receptor agonists. Cases of transient sinus arrest and cardiac arrest, often preceded by bradycardia or atrioventricular block, have been reported (see section 4.8).

The hypotensive effects of dexmedetomidine may be more significant in patients with pre-existing hypotension (especially those unresponsive to vasopressors), hypovolemia, chronic hypotension, severe ventricular dysfunction, or diminished functional reserve, such as the

elderly. Special care is required for these patients (see section 4.3). Hypotension typically does not require specific treatment, but users should be prepared to intervene with dose reduction, fluids, and/or vasoconstrictors if necessary.

Patients with impaired peripheral autonomic activity (e.g., due to spinal cord injury) may exhibit more pronounced hemodynamic changes upon initiating dexmedetomidine and should be treated cautiously.

Transient hypertension has been observed, particularly during the loading dose, associated with the peripheral vasoconstrictive effects of dexmedetomidine. Consequently, a loading dose is not recommended for ICU sedation. Treatment for hypertension is generally unnecessary but may be managed by reducing the continuous infusion rate if needed.

At higher concentrations, dexmedetomidine may cause local vasoconstriction, which could be more significant in patients with ischemic heart disease or severe cerebrovascular disease, requiring close monitoring. In patients who develop signs of myocardial or cerebral ischemia, dose reduction or discontinuation of the drug should be considered.

When used in combination with spinal or epidural anesthesia, dexmedetomidine may increase the risk of hypotension or bradycardia, necessitating caution.

Hepatic Impairment
In patients with severe liver insufficiency, careful monitoring is required, as overdose can result in reduced clearance of dexmedetomidine, increasing the risk of adverse reactions, excessive sedation, or prolonged effects.

Neurological Disorders
Experience with dexmedetomidine in severe neurological disorders such as head trauma or post-neurosurgery is limited. Special care should be taken in cases requiring deep sedation. Dexmedetomidine can reduce cerebral blood flow and intracranial pressure, so these factors should be considered when selecting a treatment.

Other
Alpha-2 agonists, including dexmedetomidine, are rarely associated with withdrawal syndrome after long-term use. If agitation and hypertension occur shortly after discontinuation, withdrawal should be considered.

Dexmedetomidine may induce hyperthermia, which can be resistant to traditional cooling methods. If unexplained fever occurs, dexmedetomidine therapy should be discontinued. It is not recommended for use in patients susceptible to malignant hyperthermia.

Diabetes insipidus has been reported in connection with dexmedetomidine therapy. If polyuria occurs, dexmedetomidine should be discontinued, and serum sodium levels and urine osmolality should be monitored.

Excipients
PREXODIN contains less than 1 mmol of sodium (23 mg) per vial, i.e. essentially "sodium-free."

4.5 Interaction with other medicinal products and other forms of interaction
Interactions studies have only been conducted in adults.

Anesthetics/Sedatives/Hypnotics/Opioids
Concurrent administration of dexmedetomidine with anesthetics, sedatives, hypnotics, and opioids may enhance their effects. Specific studies with sevoflurane, isoflurane, propofol, alfentanil, and midazolam have confirmed these effects. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil, or midazolam have been observed. However, due to potential pharmacodynamic effects, it may be necessary to reduce the dose of dexmedetomidine or the accompanying anesthetics, sedatives, hypnotics, or opioids when administered together.

Neuromuscular Blockers
In a study involving 10 healthy volunteers, the administration of dexmedetomidine at a plasma concentration of 1 ng/mL for 45 minutes did not result in any clinically significant increase in the magnitude of neuromuscular block associated with rocuronium administration.

Cytochrome P450
In vitro studies indicate that dexmedetomidine is metabolized by several cytochrome P450 enzymes, including CYP2A6, CYP1A2, CYP2E1, CYP2D6, and CYP2C19, without a predominant pathway. Dexmedetomidine exhibits strong inhibitory properties on CYP2D6, CYP3A4, and CYP2B6.

In vitro studies on human liver microsomal incubations have examined the inhibition of CYP enzymes, including CYP2B6, by dexmedetomidine. These studies suggest a potential for in vivo interactions between dexmedetomidine and substrates with predominant CYP2B6 metabolism.

Induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4 by dexmedetomidine has been observed *in vitro*, and while the possibility of induction *in vivo* cannot be excluded. The clinical significance is unknown. However, caution is recommended when dexmedetomidine is used concomitantly with drugs metabolized by CYP2D6, CYP3A4, or CYP2B6.

In an interaction study, the interaction between dexmedetomidine and esmolol was considered reasonable. However, in patients taking other medications that may cause similar effects (e.g., beta-blockers), an increased risk of hypotensive and bradycardic effects should be considered.

Additional information on special populations:
Pediatric Population:
Since interaction studies have only been conducted in adults, there is no available information regarding the pediatric population.

4.6 Fertility, pregnancy and lactation
General principles
Pregnancy category "C".

Women of childbearing potential / Contraception
Women of childbearing potential should use appropriate contraception.

Pregnancy
There are no sufficient or well-controlled studies regarding the use of dexmedetomidine in pregnant women.

Animal studies have shown reproductive toxicity (see section 5.3). The potential risk to humans is unknown.

PREXODIN should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexmedetomidine.

Lactation
It is unknown whether dexmedetomidine hydrochloride is excreted in human breast milk. Dexmedetomidine is excreted in human milk, however levels will be below the limit of detection by 24 hours following treatment discontinuation. A risk to infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue dexmedetomidine therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
In a rat fertility study, dexmedetomidine had no effect on male or female fertility. There is no available data on fertility in humans.

4.7 Effects on ability to drive and use machines

Patients should be told that their ability to perform activities requiring mental alertness, such as driving motor vehicles or operating dangerous machinery, or signing legal documents, may be impaired for a period of time after sedation.

4.8 Undesirable effects

Summary of Safety Profile

Sedation of Adult ICU Patients

In intensive care settings, the most commonly reported adverse reactions with dexmedetomidine include hypotension, hypertension and bradycardia, occurring in approximately 25%, 15% and 13% of patients respectively.

Hypotension and bradycardia are also the most common serious adverse reactions associated with dexmedetomidine, occurring in approximately 1.7% and 0.9% of randomized intensive care unit (ICU) patients, respectively.

Procedural/Awake Sedation

The most common adverse reactions during procedural sedation with dexmedetomidine(the protocols of phase III studies included predefined thresholds for reporting changes in blood pressure, respiratory rate, and heart rate as adverse events) are listed below:

- Hypotension (55% in the dexmedetomidine group vs. 30% in the placebo group receiving rescue midazolam and fentanyl)
- Respiratory depression (38% in the dexmedetomidine group vs. 35% in the placebo group receiving rescue midazolam and fentanyl)
- Bradycardia (14% in the dexmedetomidine group vs. 4% in the placebo group receiving rescue midazolam and fentanyl)

Adverse reactions are listed according to the MedDRA System Organ Class (SOC). Within each SOC, reactions are organized by frequency categories, presented in decreasing order of severity. Frequencies are defined as follows: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from available data).

Endocrine Disorders

Not known : Diabetes insipidus

Metabolism and Nutrition Disorders

Common : Hyperglycemia, hypoglycemia
Uncommon : Metabolic acidosis, hypoalbuminemia

Psychiatric Disorders

Common : Agitation

Uncommon : Hallucinations

Cardiac Disorders
Very common : Bradycardia[1,2]
Common : Myocardial ischemia or infarction, tachycardia
Uncommon : Atrioventricular block[1], decreased cardiac output, cardiac arrest[1]

Vascular Disorders
Very common : Hypotension[1,2], hypertension[1,2]

Respiratory, Thoracic, and Mediastinal Disorders
Very common : Respiratory depression[2,3]
Uncommon : Dyspnea, apnea

Gastrointestinal Disorders
Common : Nausea[2], vomiting, dry mouth[2]
Uncommon : Abdominal distension

General Disorders and Administration Site Conditions
Common : Withdrawal syndrome, hyperthermia
Uncommon : Drug ineffectiveness, thirst

[1] See the section on Description of selected adverse reactions.

[2] Adverse reactions observed also in procedural sedation studies.

[3] In ICU sedation studies, "common" incidence.

Description of selected adverse reactions

Clinically significant hypotension or bradycardia should be treated as described in section 4.4.

In patients treated with dexmedetomidine who are relatively healthy and not in an intensive care unit, bradycardia has sometimes led to sinus arrest or pause.

Symptoms responded to leg raising and anticholinergics like atropine or glycopyrrolate. In isolated cases, bradycardia progressed to periods of asystole in patients with pre-existing bradycardia. Also cases of cardiac arrest, often preceded by bradycardia or atrioventricular block, have been reported.

Hypertension has been associated with the use of a loading dose and this reaction can be reduced by avoiding such a loading dose or by decreasing the infusion rate of the loading dose.

Additional Information for Special Populations:

Pediatric Population:

The majority of the patients were postoperative, postnatal infants >1 month old, evaluated for treatment in the intensive care unit for up to 24 hours, and showed a safety profile similar to adults. Data on neonates (28–44 weeks gestation) is very limited and restricted to maintenance doses of <0.2 micrograms/kg/hour. Literature reports a single case of hypothermic bradycardia in a neonate.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms

Several overdose cases of dexmedetomidine have been reported in both clinical studies and post-marketing data. The reported highest infusion rates of dexmedetomidine in these cases have reached up to 60 mcg/kg/h for 36 minutes and 30 mcg/kg/h for 15 minutes in a 20 month–old child and in an adult, respectively. The most commonly reported adverse reactions associated with overdose were bradycardia, hypotension, oversedation, drowsiness, and cardiac arrest.

Management

In overdose situations accompanied by clinical symptoms, the dexmedetomidine infusion should be reduced or discontinued. The expected effects are primarily cardiovascular and should be treated as required by the clinical condition (see section 4.4). At high concentration hypertension may be more prominent than hypotension. In clinical studies, sinus arrest cases spontaneously returned to baseline or responded to atropine and glycopyrrolate treatment. In isolated severe overdose cases resulting in cardiac arrest, resuscitation was required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action:

Dexmedetomidine is a selective alpha-2 receptor 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.

Sedation in Adult ICU (Intensive Care Unit) Patients

In placebo-controlled studies conducted with a postoperative ICU population previously intubated and sedated with midazolam or propofol, dexmedetomidine significantly reduced the need for both rescue sedatives (midazolam or propofol) and opioids during sedation periods lasting up to 24 hours. Most patients in the dexmedetomidine group did not require additional sedative treatment. Patients could be successfully extubated without the need to stop the dexmedetomidine infusion. Studies outside the ICU showed that dexmedetomidine could be safely administered to patients without endotracheal intubation, provided adequate monitoring was ensured.

In a medical and ICU population requiring mild to moderate sedation (RASS 0 to -3) for up to 14 days, dexmedetomidine was similar to midazolam (ratio 1.07; 95% CI 0.971, 1.176) and propofol (ratio 1; 95% CI 0.922, 1.075) in terms of the time spent within the target sedation range. Compared to midazolam, dexmedetomidine reduced the duration of mechanical ventilation and shortened the time to extubation compared to both midazolam and propofol. Patients treated with dexmedetomidine were easier to awaken, more cooperative, and able to communicate better, whether or not they experienced pain. In patients treated with dexmedetomidine, hypotension and bradycardia occurred more frequently compared to those treated with midazolam, while tachycardia was less frequent. Compared to patients treated with propofol, tachycardia was more common, while hypotension was similar. A study measuring delirium using the CAM-ICU scale showed that delirium was reduced in the dexmedetomidine group compared to midazolam, and delirium-related adverse effects were lower compared to propofol. Patients who were discontinued from treatment due to insufficient sedation were switched to propofol or midazolam. The risk of insufficient sedation increased in patients who had difficulty achieving sedation with standard treatments just before transitioning.

In a dose-controlled intensive care unit study conducted with a predominantly postoperative population aged 1 month to <17 years, pediatric efficacy was observed. Approximately 50% of patients treated with dexmedetomidine did not require additional midazolam for rescue sedation during a median treatment duration of 20.3 hours, which did not exceed 24 hours. Data for treatment durations longer than 24 hours are not available. Data in neonates (28-44 weeks gestation) are very limited and restricted to low doses (<0.2 mcg/kg/hour) (see sections 4.4 and 5.2). Neonates may be particularly sensitive to the bradycardic effects of PREXODIN in the presence of hypothermia and conditions where cardiac output is dependent on heart rate.

In double-blind, comparator-controlled intensive care unit studies, the incidence of cortisol suppression in patients treated with dexmedetomidine (n=778) was 0.5%, compared to 0% in those treated with either midazolam (n=338) or propofol (n=275). This event was reported as mild in 1 patient and moderate in 3 patients.

Procedural/Awake Sedation

The efficacy and safety of dexmedetomidine for sedation of non-intubated patients before and/or during surgical and diagnostic procedures were evaluated in two randomized, double-blind, placebo-controlled, multicenter clinical trials.

▪ In Study 1, patients undergoing elective surgeries/procedures with monitored anesthesia care and local/regional anesthesia were randomized to receive a 10-minute loading infusion of 1 mcg/kg (n=129) or 0.5 mcg/kg (n=134) dexmedetomidine or placebo (normal saline; n=63), followed by a maintenance infusion starting at 0.6 mcg/kg/hour.

The maintenance infusion of the study drug could be titrated between 0.2 mcg/kg/hour and 1 mcg/kg/hour.

The proportion of patients who reached the target sedation level (Observer's Assessment of Awareness/Sedation Scale ≤4) without the need for rescue midazolam was 54% in the 1 mcg/kg dexmedetomidine group, 40% in the 0.5 mcg/kg dexmedetomidine group, and 3% in the placebo group.

The risk difference in the proportion of patients who did not require rescue midazolam was 48% (95% CI: 37%-57%) in the 1 mcg/kg dexmedetomidine group and 40% (95% CI: 28%-48%) in the 0.5 mcg/kg dexmedetomidine group, compared to placebo.

The median (range) dose of rescue midazolam was 1.5 (0.5-7) mg in the 1 mcg/kg dexmedetomidine group, 2 (0.5-8) mg in the 0.5 mcg/kg dexmedetomidine group, and 4 (0.5-14) mg in the placebo group.

The difference in the mean dose of rescue midazolam, compared to placebo, was -3.1 mg (95% CI: -3.8 to -2.5) in the 1 mcg/kg dexmedetomidine group and -2.7 mg (95% CI: -3.3 to -2.1) in the 0.5 mcg/kg dexmedetomidine group, favoring dexmedetomidine.

The median time to the first dose of rescue midazolam was 114 minutes in the 1 mcg/kg dexmedetomidine group, 40 minutes in the 0.5 mcg/kg dexmedetomidine group, and 20 minutes in the placebo group.

▪ In Study 2, patients undergoing awake fiberoptic intubation with topical anesthesia were randomized to receive a 10-minute loading infusion of 1 mcg/kg dexmedetomidine (n=55) or placebo (normal saline; n=50), followed by a fixed maintenance infusion of 0.7 mcg/kg/hour.

To maintain a Ramsay Sedation Scale ≥2, 53% of patients receiving dexmedetomidine did not require rescue midazolam, compared to 14% of those receiving placebo.

The risk difference in the proportion of patients not requiring rescue midazolam was 43% (95% CI: 23% - 57%) in favor of dexmedetomidine.

The average dose of rescue midazolam was 1.1 mg in the dexmedetomidine group and 2.8 mg in the placebo group. The difference in the average dose of rescue midazolam was -1.8 mg (95% CI: -2.7 - -0.86), favoring dexmedetomidine.

5.2 Pharmacokinetic properties

General Characteristics

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

Distribution:

Dexmedetomidine follows a two-compartment distribution model. In healthy volunteers, it exhibits a rapid distribution phase with an estimated central distribution half-life ($t_{1/2\alpha}$) of approximately 6 minutes.

The estimated terminal elimination half-life ($t_{1/2}$) is around 1.9 to 2.5 hours (min 1.35, max 3.68 hours), and the estimated steady-state distribution volume (Vss) is approximately 1.16 to 2.16 L/kg (90 to 151 liters). Plasma clearance (Cl) has an average estimated value of 0.46 to 0.73 L/hr/kg (35.7 to 51.1 L/hr). These Vss and Cl estimates were based on an average body weight of 69 kg. In the ICU population, after more than 24 hours of infusion, the plasma pharmacokinetics of dexmedetomidine show similarity. The estimated pharmacokinetic parameters are: $t_{1/2}$ approximately 1.5 hours, Vss approximately 93 liters, and Cl approximately 43 L/hr. Dexmedetomidine's pharmacokinetics are linear within the 0.2 to 1.4 mcg/kg/hour dose range and do not accumulate during treatments lasting up to 14 days. Dexmedetomidine binds to plasma proteins by approximately 94%. The plasma protein binding is stable across a concentration range of 0.85 to 85 ng/ml.

Dexmedetomidine binds to both human serum albumin and alpha-1-acid glycoprotein, with serum albumin being the primary binding protein in plasma.

Biotransformation and Elimination:

Dexmedetomidine is eliminated through extensive metabolism in the liver. There are three main types of metabolic reactions: direct N-glucuronidation, direct N-methylation, and cytochrome P450 catalyzed oxidation. The most abundant circulating dexmedetomidine metabolites are two isomeric N-glucuronides. The metabolite H-1, N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide, is also the primary circulating product of dexmedetomidine biotransformation. Cytochrome P-450 catalyzes the formation of two minor metabolites in the circulation: 3-hydroxymethyl dexmedetomidine produced by hydroxylation at the 3-methyl group of dexmedetomidine, and H-3 produced by oxidation in the imidazole ring. Available data suggest that various CYP forms (CYP2A6, CYP1A2, CYP2E1, CYP2D6, and CYP2C19) mediate the formation of oxidized metabolites. These metabolites have negligible pharmacological activity.

Radioactively labeled dexmedetomidine intravenous administration showed that, nine days later, an average of 95% of the radioactivity was detected in urine and 4% in feces.

The main urinary metabolites consist of two isomeric N-glucuronides, which together account for approximately 34% of the dose, and N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide, which accounts for 14.51% of the dose. Minor metabolites, including dexmedetomidine carboxylic acid, 3-hydroxymethyl dexmedetomidine, and O-glucuronide, each accounted for between 1.11% and 7.66% of the dose. Less than 1% of the unchanged parent drug was recovered in urine. About 28% of the urinary metabolites are unidentified minor metabolites.

Characteristics in Patients

In Geriatric Patients:

The pharmacokinetic profile of PREXODIN does not change with age. There were no differences in the pharmacokinetics of dexmedetomidine in young (18-40 years), middle-aged (41-65 years), and elderly (>65 years) patients.

Renal impairment:

The pharmacokinetics of dexmedetomidine (C_{max}, T_{max}, AUC, $t_{1/2}$, CL, and V_{ss}) in patients with severe renal failure (creatinine clearance: <30 mL/min) were not significantly different when compared to healthy volunteers.

Hepatic impairment:

The plasma protein binding of dexmedetomidine was reduced in patients with liver failure compared to healthy volunteers. The average percentage of unbound dexmedetomidine in plasma ranged from 8.5% in healthy volunteers to 17.9% in patients with severe liver failure. In patients with varying degrees of liver failure (Child-Pugh class A, B, C), hepatic dexmedetomidine clearance was reduced and plasma elimination ($t_{1/2}$) was prolonged. The average plasma clearance values of unbound dexmedetomidine in volunteers with mild, moderate, and severe liver failure were 59%, 51%, and 32% of those observed in normal healthy volunteers, respectively. The average $t_{1/2}$ value in patients with mild, moderate, and severe liver failure was prolonged to 3.9, 5.4, and 7.4 hours, respectively. While dexmedetomidine is used for its effects, it may be necessary to consider a reduction in the initial/maintenance dose depending on the degree of liver failure and response in patients with liver failure.

Although the PREXODIN dose is adjusted based on the effect, dose reduction may be necessary in patients with liver failure (see section 4.2).

Gender:

No gender-related differences have been observed in the pharmacokinetics of dexmedetomidine.

Pediatric Population:
Data for neonates (28-44 weeks gestation) and children up to 17 years of age are limited. In children (1 month to 17 years), the half-life of dexmedetomidine was found to be similar to that observed in adults, but higher in neonates (<1 month). In the 1 month-6 years age group, the plasma clearance corrected for body weight was higher, but decreased in older children. In neonates (<1 month), the plasma clearance corrected for body weight was lower than in older age groups (0.9 L/hour/kg) due to immaturity. The available data are summarized in the table below:

		Average (%95 CI)	
Age	N	CL (l/hour/kg)	$t_{1/2}$ (hour)
< 1 month	28	0.93 (0.76; 1.14)	4.47 (3.81; 5.25)
1 to < 6 months	14	1.21 (0.99; 1.48)	2.05 (1.59; 2.65)
6 to < 12 months	15	1.11 (0.94; 1.31)	2.01 (1.81; 2.22)
12 to < 24 months	13	1.06 (0.87; 1.29)	1.97 (1.62; 2.39)
2 to < 6 years	26	1.11 (1; 1.23)	1.75 (1.57; 1.96)
6 to < 17 years	28	0.8 (0.69; 0.92)	2.03 (1.78; 2.31)

Linearity/non-linearity:
Dexmedetomidine exhibits linear pharmacokinetics when administered via intravenous infusion for up to 24 hours at a dose range of 0.2 to 0.7 micrograms/kg/hour.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.
In reproductive toxicity studies, dexmedetomidine did not affect male or female fertility in rats, and no teratogenic effects were observed in rats or rabbits. In the rabbit study, intravenous administration of the maximum dose of 96 mcg/kg/day caused effects similar to those clinically observed. In rats, subcutaneous administration of the maximum dose of 200 mcg/kg/day resulted in an increase in embryofetal death and reduced fetal body weight. These effects were associated with significant maternal toxicity. In the rat fertility study, a dose of 18 mcg/kg/day resulted in a decrease in fetal body weight, and delayed ossification was observed at a dose of 54 mcg/kg/day. The exposure levels observed in rats were below the clinical exposure range.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Water for injection

6.2 Incompatibilities

As physical incompatibility has not been established, PREXODIN infusion should not be administered together with blood or plasma in the same intravenous catheter.

The following drugs have been shown to be incompatible with PREXODIN:
Amphotericin B, diazepam

The following intravenous solutions have been shown to be compatible with PREXODIN:
- 0.9% sodium chloride in water

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

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.
PREXODIN solution diluted with 0.9% sodium chloride maintains its physical and chemical stability at room temperature below 25°C for 24 hours. From a microbiological point of view, the product should be used immediately. If not used immediately, the storage time and conditions prior to the use are the responsibility of the user (professional healthcare personnel).

6.5 Nature and contents of container

The primary packaging material consists of a 2 mL transparent Type I glass vial and a gray fluoropolymer-coated bromobutyl rubber stopper. The vials are sealed with white polypropylene caps and aluminum flip-off packaging material to ensure leak-proof properties. Each cardboard box contains five leak-proof vials and a package leaflet.

6.6 Special precautions for disposal and other handling

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

Aseptic techniques should always be followed when preparing PREXODIN.

PREXODIN should be visually inspected for particulate matter and color changes, under all conditions permitted by the solution and container.

Preparation Instructions:

PREXODIN injection, 200 micrograms/2 mL (100 mcg/mL)
PREXODIN should be diluted with 0.9% sodium chloride injection to achieve the required concentration (4 micrograms/mL) before administration. The preparation method for the solution is the same for both loading dose and maintenance infusion.

For preparing the infusion, draw 2 mL of PREXODIN infusion solution.
Add 48 mL of 0.9% sodium chloride to obtain a total of 50 mL.
Gently shake and mix thoroughly.
After dilution, the chemical and physical stability of the product has been shown for 24 hours at room temperature below 25°C. From a microbiological perspective, the product should be used immediately. If not used immediately, the storage time and conditions prior to the use are the responsibility of the user (professional healthcare personnel).

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)

2017/507

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 14.07.2017
Date of latest renewal :

10. DATE OF REVISION OF THE SPC