# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

DEKSTOMİD 200 mcg/2 ml concentrated solution for I.V. infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active substance:**

Each 1 ml of solution contains 118 microgram dexmedetomidine hydrochloride which is the equivalent of 100 microgram dexmedetomidine (base).

**Excipients:**

Sodium chloride 9.0 mg

See 6.1 for excipients.

## 3. PHARMACEUTICAL FORM

Concentrated infusion solution

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

DEKSTOMİD is indicated for the sedation of patients who are intubated and mechanically ventilated since the beginning of their treatment at intensive care units.

DEKSTOMİD should be administered as an infusion continuously for a maximum of 24 hours.

### 4.2. Posology and method of administration

**Posology/frequency and duration of administration:**

It is for use at hospitals. DEKSTOMİD should be administered by individuals who are experienced in the treatment of patients requiring intensive care.

DEKSTOMİD dose administration should be personalized, and titrated according to the desired clinic effect.

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

Patients who are currently intubated and sedated may switch to dexmedetomidine with an initial infusion rate of 0.7 microgram/kg/hour; based on the patient's response this dose may later be adjusted gradually within the range of 0.2-1.4 microgram/kg/hour in order to achieve the desired level of sedation. A lower initial infusion rate should be considered for patients who are physically weak.

Dexmedetomidine is potent and its infusion rate is per hour. After a dose adjustment, steady sedation may not be achieved for up to an hour.

The maximum dose of 1.4 microgram/kg/hour should not be exceeded. Alternative sedative agents should be considered for patients in whom sufficient levels of sedation cannot be attained with the maximum dose of DEKSTOMİD.

The loading dose of DEKSTOMİD is not recommended as it is correlated with an increase in adverse reactions. If necessary, propofol or midazolam can be administered until the clinical effects of DEKSTOMİD have been identified.

**Method of administration:**

DEKSTOMİD should be administered as a diluted intravenous infusion using a controlled infusion device. See Section 6.6 for instructions regarding the pre-operation dilution of this medical product.

**Additional information on special population:**

**Renal failure:**

Dose adjustment is not required for patients with renal failure.

**Hepatic failure:**

As DEKSTOMİD is metabolized in the liver, it should be used with caution when patients with hepatic failure are concerned. A lower sustainment dose should be considered. (see. Sections 4.4 and 5.2).

**Pediatric population:**

There are no recommendations regarding the dosage of DEKSTOMİD for pediatric populations (see. Sections 4.8, 5.1 and 5.2).

**Geriatric population:**

A decreased dosage should be considered for patients over 65.

## 4.3. Contraindications

- Hypersensitivity against dexmedetomidine hydrochloride or any of the excipients,
- Severe heart block ($2^{nd}$ and $3^{rd}$ degree), w/o pacemaker,
- Uncontrolled hypotension,
- Acute cerebrovascular cases.

## 4.4. Special warnings and precautions for use

Administration of the drug

DEKSTOMİD should only be administered by healthcare professionals who are experienced with patients in intensive care or surgery. Due to its known pharmacological effects, patients should be monitored when taking DEKSTOMİD.

Due to risk of respiratory depression and, in some cases, apnea, respiration of non-intubated patients should be monitored (see. Section 4.8).

DEKSTOMİD should not be used as an induction agent for sedation or intubation when taking muscle relaxants.

DEKSTOMİD lowers the heart rate and the blood pressure due to its central sympatholytic effects; however, it may cause hypertension due to peripheral vasoconstriction in high concentrations (see. Section 5.1).

Caution is advised when administering dexmedetomidine to patients with bradycardia. Data regarding the effects of dexmedetomidine on patients with a heart rate lower than 60, is very limited, and these patients require special caution. Bradycardia does not typically require treatment; however, had generally responded to anti-cholinergic drugs or necessary dose decreases. Patients with high physical form, and low heart rate while at rest, may be very sensitive to the bradycardiac effects of alpha-2 receptor agonists; and cases of temporary sinus stop have been reported.

The hypotensive effects of DEKSTOMİD may be very obvious in patients with hypotension (especially in case of unresponsiveness of vasopressor), hypovolemia, chronic hypotension or low functional reserves, severe ventricular dysfunction, and in older patients. These cases require special care (see. Section 4.3). Hypotension does not require special treatment under normal circumstances; however, users should be ready to intervene with dose decreases, fluids and/or vasoconstrictors when necessary.

In patients with peripheral autonomic activity disorders (i.e. due to spinal cord damage), hemodynamic changes may be more apparent after DEKSTOMİD treatment begins, therefore these patients should be treated carefully.

Adaptive pharmacodynamic effects were not observed in clinical studies where other vasodilators and negative chronotropic drugs were used together with dexmedetomidine. Cases where these drugs are administered together with DEKSTOMİD, require caution.

Temporary hypertension

Temporary hypertension related to the initial peripheral vasoconstrictive effects of dexmedetomidine has been observed and a loading dose is not recommended. Treatment has not been necessary for the temporary hypertension; however, it may be necessary to lower the rate of sustainment infusion.

Excitability

Some patients taking dexmedetomidine were observed to be excitable and awake when they are stimulated. This should be considered to be proof of ineffectiveness in the absence of other clinical signs and symptoms.

Hepatic failure

As cases of overdosing which occur due to decreased clearance of dexmedetomidine, may cause an increase in the risks of adverse reactions, excessive sedation or increased duration of effect, severe hepatic failure require caution.

Neurological disorders

There is no impression that dexmedetomidine suppresses seizure activity, and it should not be used as a stand-alone treatment in cases of status epilepticus.

There is limited experience available regarding serious neurological disorders such as head injuries, and dexmedetomidine after neuro-surgeries; and it should be administered with caution, especially if deep sedation is necessary. DEKSTOMİD may decrease cerebral blood flow and intracranial pressure, which should be taken into consideration when choosing a treatment.

Withdrawal

Regardless of the dosage, 12 (5%) dexmedetomidine patients who took the drug for up to 7 days, experienced as least one adverse event due to withdrawal in the 24 hours after quitting the study drug, and 7 (3%) dexmedetomidine patients experienced at least one adverse event from 24 to 48 hours after quitting the study drug. Most common adverse events included nausea, vomiting and agitation.

The incidence of tachycardia and hypertension requiring an intervention in the first 48 hours after quitting the study drug was <5%. If cases of tachycardia and/or hypertension occur after stopping DEKSTOMİD, supplementary treatments are necessary.

Hyperthermia

The safety of dexmedetomidine for use with individuals sensitive to align hyperthermia is not known, and therefore it is not recommended. In case of long lasting fevers which cannot be explained, DEKSTOMİD treatment should be stopped.

Inactive ingredients

DEKSTOMİD contains less than 1 mmol (23 mg) sodium in each vial; or in other words, in principle it “does not contain sodium”.

**4.5. Interaction with other medicinal products and other forms of interaction**

Anesthetics/Sedatives/Hypnotics/Opioids

Concurrent use of dexmedetomidine may amplify the effects of anesthetics, sedatives, hypnotics and opioids. These effects were proven in specific studies involving sevoflurane, izoflurane, propofol, alfentanyl and midazolam. No pharmacokinetic interaction was observed between dexmedetomidine, and izoflurane, propofol, alfentanyl and midazolam. Additionally, due to their pharmacokinetic effects, when used concurrently, the dosage of dexmedetomidine or accompanying anesthetics, sedatives, hypnotics or opioids should be decreased.

Neuromuscular Blockers

In a study involving ten healthy individuals, administering dexmedetomidine in a 1 ng/mL plasma concentration for 45 minutes did not cause a significant increase in the size of the neuromuscular blockage that is related to the rocuronium administration.

Cytochrome P450

*In vitro* studies demonstrate that without any prominent pathways, dexmedetomidine was metabolized by several Cytochrome P450 enzymes such as CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19. Dexmedetomidine is very effective for the inhibition of CYP2D6, CYP3A4 and CYP2B6.

Inhibition of CYP enzymes including CYP2B6, by dexmedetomidine has been studied human liver microsome incubations. The *in vitro* study hints at a potential of an *in vivo* interaction between dexmedetomidine and the substrates which have dominant CYP2B6 metabolisms.

In an *in vitro* environment, dexmedetomidine was observed to have an induction over CYP1A2, CYP2B6, CYP2C8, Cyp2C9 and CYP3A4, and the possibility of *in vivo* induction cannot be ruled out. The clinical significance of this phenomenon is unknown. Furthermore, administration of DEKSTOMİD together with drugs that are metabolized with CYP2D6, CYP3A4 and CYP2B6 require special caution.

In an interaction study, while interaction with esmolol is at a reasonable level, the possibility of hypotensive and bradycardiac effects should be taken into consideration for patients taking other medical products such as beta blockers which cause these effects.

**Pediatric population:**

As interaction studies have only been performed for adults, there is no information regarding pediatric populations.

**4.6. Pregnancy and Lactation**

**General recommendations**

Pregnancy category: C

**Women with childbearing potential/Contraception**

Animal studies demonstrated a fertility toxicity (see. Section 5.3). Potential risk towards humans is unknown.

A proper method of birth control should be administered to women with the potential to bear children.

**Pregnancy**

There aren't enough and controlled studies regarding the use of dexmedetomidine in pregnant women. In an *in vitro* human placenta study, dexmedetomidine crossed over through the placenta. A study involving pregnant rats demonstrated a transfer dexmedetomidine through the placenta when radioactively marked dexmedetomidine was administered subcutaneously.

There fore, fetal exposure should be expected in humans; and DEKSTOMİD should be used during pregnancy only if its potential benefits outweigh the potential risks on the fetus.

**Lactation**
It is unknown whether dexmedetomidine chloride is discharged through human milk.

As radioactively marked dexmedetomidine was discharged in lactating female rats through the milk, administering DEKSTOMİD to breastfeeding women requires special caution. Quitting breastfeeding or the treatment should be determined based on the benefits for the child and the mother.

**Fertility**
For fertility, please see. Section 5.3.

**4.7. Effects on ability to drive and use machines**
Patients should be informed about the possibility of the incapability to perform activities that require cunningness such as driving motor vehicles or operating dangerous machinery or signing legal documents for a while after being sedated.

**4.8. Undesirable effects**
Adverse reactions caused with DEKSTOMİD have been listed according to their MedDRA System Organ Class (SOC). Adverse reactions have been listed in each SOC according to their incidence categories, and are listed in a decreasing order of severity. Incidence is 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), unknown (unpredictable with the available data).

**Metabolism and nutrition disorders**
Common: Hypovolemia, hyperglycemia, hypocalcaemia
Uncommon: Metabolic acidosis. hypoalbuminemia

**Psychiatric disorders**
Common: Agitation
Uncommon: Hallucination

**Cardiac disorders**
Very common: Bradycardia
Common: Arterial fibrillation, myocardium ischemia or infarction, tachycardia, sinus tachycardia
Uncommon: 1$^{st}$ degree atrioventricular block, decreased cardiac output, ventricular tachycardia

**Vascular disorders**
Very common: Hypotension, hypertension

**Respiratory, chest and mediastinal disorders**
Common: Respiratory depression, atelectasis, pleural effusion, hypoxia, pulmonary edema
Uncommon: Dyspnea, apnea

**Gastrointestinal disorders**
Common: Nausea, vomiting, dry mouth
Uncommon: Flatulence

**General disorders and diseases specific to the administration site**
Common: Withdrawal syndrome, hyperthermia, cold-shivering, peripheral edema
Uncommon: Ineffectiveness, thirst

**Researches**
Common: Decreased urination

**Surgical and medical procedures**
Common: Post-procedural bleeding

After-marketing reports
In addition to the events reported during clinical studies, the following adverse reactions have been defined to be related to the post-approval administration of dexmedetomidine. As these reactions are voluntarily reported in a population of unknown numbers, it is not always possible to determine their incidence or their relation to the drug exposure.

**Blood and lymphatic system disorders**
Unknown: Anemia

**Metabolism and nutrition disorders**
Unknown: Acidosis, respiratory acidosis, hyperkalemia, alkaline phosphatase increase, thirst, hypoglycemia

**Psychiatric disorders**
Unknown: Agitation, confusion, delirium, illusion

**Nervous system disorders**
Unknown: Vertigo, headache, neuralgia, neuritis, speech disorder, convulsions.

**Ophthalmic disorders**
Unknown: Photopsy, abnormal vision

**Cardiac disorders**
Unknown: Arrhythmia, ventricular arrhythmia, atrioventricular block, cardiac arrest, extrasystole, heart block, t wave inversion, supraventricular tachycardia, heart disease

**Vascular disorders**
Unknown: Bleeding, blood pressure fluctuations

**Respiratory, chest and mediastinal disorders**
Unknown: Bronchospasm, hypercapnia, hypoventilation, pulmonary congestion

**Gastrointestinal disorders**
Unknown: Abdominal pain, diarrhea

**Hepatobiliary disorders**
Unknown: Gamma-glutamile transpeptidasis increase, abnormal hepatic functions, hyperbilirubinemia, alanine transaminase increase, aspartate aminotransferase increase

**Cutaneous and subcutaneous tissue disorders**
Unknown: Increased sweating

**Renal and urinary disorders**
Unknown: Increase in blood urea, oliguria, polyuria

**General disorders and diseases specific to the administration site**
Unknown: Fever, hyperpyrexia, hypovolemia, mild anesthesia, pain, rigor

**Pediatric population:**
Mostly post-operative, after birth, babies > 1 month were assessed in terms of the treatment for 24 hours in the intensive care unit, and demonstrated a safety profile similar to adults. Data regarding new-borns (28-44 week gestation) is very limited and limited to <0.2 microgram/kg/hour sustainment doses. A single case of bradycardia in a newborn reported in the literature.

**4.9. Overdose and therapy**
Several cases of overdosing with dexmedetomidine have been reported both in clinical studies and in after-marketing data. The highest infusion rate reported in these cases was 60 microgram/kg/hour for 36 minutes for a 20 month-old, and 30 microgram/kg/hour for 15 minutes for an adult. The most common adverse reactions reported in connection with overdosing are bradycardia, hypotension, over sedation, numbness and cardiac arrest.

Tolerability of dexmedetomidine was investigated in a study where the recommended doses or 0.2 to 0.7 microgram/kg/hour, and higher doses were administered to healthy volunteers. The highest blood concentration attained in this study was approximately 13 times the maximum threshold of the therapeutic range. The most significant effects observed in two volunteers using the highest dose were first degree atrioventricular block and second degree heart block. A hemodynamic disorder was not observed in atrioventricular block, and the heart block was recovered in a minute, on its own.

In the intensive care sedation studies, five patients received excessive doses of dexmedetomidine. No symptoms were reported in either of these patients; one patient received 2 microgram/kg loading dose for 10 minutes (twice the recommended loading dose) while another patient received 0.8 microgram/kg/hour sustainment infusion. Another two patients receiving 2 microgram/kg loading dose for 10 minutes developed bradycardia and/or hypotension. Cardiac arrest occurred in a patient receiving an undiluted dexmedetomidine loading bolus dose (19.4 microgram/kg); however, resuscitation was successful.

In cases of overdosing accompanied by clinical symptoms, dexmedetomidine infusion should be decreased or stopped. The desired effect is, in principle, cardiovascular and should be treated as required by the clinical condition (see. Section 4.4). Hypertension and hypotension may be more obvious in high concentrations. In clinical studies, cases of sinus arrest reverted back to normal on their own or responded to atropine or glycopyrrolate treatments. Isolated cases of severe overdosing resulting in cardiac arrest required resuscitation.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

**Pharmacotherapeutic group:** Other hypnotics and sedatives
**ATC code:** N05CM18

Mechanism of Action:
Dexmedetomidine is a selective alpha-2 receptor agonist with a wide range of pharmacological characteristics. It decreases the secretion of noradrenalin through sympathetic nerve endings and has sympathetic effects. Alpha2 selectivity was observed in animals after the slow intravenous infusion of low and medium doses (10-300 microgram/kg). Both alpha1 and alpha2 selectivity was observed in animals after the slow intravenous infusion of high doses (≥1000 microgram/kg). Decreased inflammation of locus coeruleus which is the dominant noradrenergic core built in the brain stem mediate the sedative effects. Dexmedetomidine has analgesic and anesthetic/analgesic preservative effects. Cardiovascular effects are dose-dependant; in lower infusion rates central effects are more dominant and cause a decrease in the heart rate and the blood pressure. In higher doses, peripheral vasoconstrictive effects become apparent and cause an increase in systemic vascular resistance and blood pressure, while bradycardiac effect also becomes more apparent. When dexmedetomidine is administered to the healthy volunteers, respiratory depression is not caused.

In a study involving healthy volunteers (N=10), when dexmedetomidine was administered as an intravenous infusion at the recommended dose range (0.2-0.7 microgram/kg /kg/hour), respiration rate and oxygen saturation remained within the regular thresholds, there weren't any cases indicating respiratory depression.

In placebo controlled studies involving post-operative intensive care populations who were previously intubated and sedated with midazolam or propofol, the need for rescue sedatives (midazolam or propofol) and opioids significantly decreased. Additional sedative treatment was not necessary for the majority of the patients in the dexmedetomidine branch. Patients are successfully intubated without interrupting dexmedetomidine infusion. Studies not involving intensive care demonstrated that dexmedetomidine could be safely administered to patients without endotracheal intubation provided that sufficient supervision is ensured.

In a population requiring mild to medium degree of sedation (RASS 0 to -3) for 14 days at a medical heavy and intensive care unit, in terms of period of time at desired sedation range dexmedetomidine was similar to midazolam (Ratio 1.07; 95% GA 0.971, 1.176) and propofol (Ratio 1.00; 95% GA 0.922, 1.057); decreased the duration of mechanical ventilation when compared with midazolam and decreased the duration of extubation when compared with propofol. Compared with midazolam and propofol, patients were easier to wake up, more cooperative, and were able to communicate better regardless of pain. In patients treated with dexmedetomidine, cases of hypotension and bradycardia were more frequent, and cases of tachycardia were rarer compared with those treated with midazolam, and the cases of tachycardia were more frequent and the cases of hypotension were similar when compared with those treated with propofol. In a study, delirium measured according to CAM-ICU scale decreased compared with midazolam and the delirium related adverse reactions occurred in dexmedetomidine treatment were more rare when compared with midazolam. Patients who withdrew from the treatment due to insufficient sedation switched to propofol or midazolam. The risk of insufficient sedation increased in patients for whom it was difficult to achieve sedation with the standard treatment before the switch.

Pediatric efficacy was observed in the dosage controlled intensive care unit studies of a population which in majority consists of post-operative patients and has an age group of 1 month to < 17 years. Approximately 50% of the patients treated with dexmedetomidine did not require a rescue midazolam additive during the treatment process of 24 hours in maximum and 20.3 hours in median. There is no data available for treatments lasting longer than 24 hours. Data regarding new-borns (28-44 week gestation) is very limited and limited to low doses (<0.2 microgram/kg/hour) (see. Sections 4.4 and 5.2). In cases of hypothermia and in cases with heart rate dependant cardiac output, new borns may be explicitly sensitive to the bradycardiac effects of DEKSTOMİD.

In double-blind, comparative product controlled, intensive care unit studies, incidence of cortisol suppression of patients treated with dexmedetomidine (n=778) was 0.5%, whereas this value was 0% for patients treated with midazolam (n=338) and propofol (n=275). This case was reported to be of mild severity in 1 patient and medium severity in 3 patients.

## 5.2.Pharmacokinetic properties

**General Properties**

Dexmedetomidine exhibits the following pharmacokinetic parameters after intravenous administration: a quick distribution phase where distribution half-life ($t_{1/2}$) is approximately 6 minutes; a terminal elimination half-life of approximately 2 hours; a steady state distribution volume of approximately 118 liters (Vss). Clearance is expected to be approximately 39 L/s. The related body weight related to this estimated clearance is 72 kg.

When administered as an intravenous infusion for up to 24 hours, dexmedetomidine exhibits linear pharmacokinetics between the dosage range of 0.2 to 0.7 microgram/kg/hour. Table 1 shows the major pharmacokinetic parameters observed when dexmedetomidine is administered with a sustainment infusion ratio of 0.17 microgram/kg/hour (0.3 ng/mL target plasma concentration) for 12 and 24 hours, 0.33 microgram/kg/hour (0.6 ng/mL target plasma concentration) for 24 hours, and 0.70 microgram/kg/hour (1.25 ng/mL target plasma concentration) for 24 hours.

**Table 1: Average ± SS Pharmacokinetic Parameters**

| | **Loading infusion (min)/ Total Infusion Duration (hour)** | | | |
|---|---|---|---|---|
| | **10 min/12hour** | **10 min/24 hour** | **10 min/24hour** | **35 min/24hour** |
| | **Dexmedetomidine Target Plasma Concentration (ng/mL) and Dosage (microgram/kg/hour)** | | | |
| **Parameter** | **0.3/0.17** | **0.3/0.17** | **0.6/0.33** | **1.25/0.70** |
| **$t_{1/2}$*, hour** | 1.78 ± 0.30 | 2.22 ± 0.59 | 2.23 ± 0.21 | 2.50 ± 0.61 |
| **KL, 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 |

* Shown as harmonic average and pseudo standard deviation.

# Average Css = Average steady state concentration of dexmedetomidine. Average Css has been calculated based on the samples taken after 2.5 to 9 hours of dosing in 12 hour infusions and samples taken after 2.5 to 18 hours of dosing in 24 hour infusions.

The loading doses for each of the aforementioned groups were 0.5, 0.5, 1 and 2.2 microgram/kg respectively.

After DEKSTOMİD sustainment doses of 0.2 to 1.4 microgram/kg/hour for > 24 hours, pharmacokinetic parameters of dexmedetomidine were similar to the pharmacokinetic parameters observed after sustainment infusion administrations for < 24 hours. Clearance (KL), distribution volume (V) and $t_{1/2}$ values were 39.4 L/hour, 152 L and 2.67 hours respectively.

Distribution:
Steady state distribution volume of dexmedetomidine (Vss) was approximately 118 liters. Dexmedetomidine was assessed in the plasma of healthy male and female volunteers with normal protein binding. The average protein binding rate was 94% and the tested plasma concentrations were noted as steady. Protein binding was similar in men and women. The part of dexmedetomidine binding to plasma proteins was significantly lower in volunteers with hepatic failure when compared with healthy volunteers.

The possibility of fentanyl, ketorolac, theophylline, digoxin and lidocaine passing over instead of the binding of dexmedetomidine hydrochloride was investigated in an *in vitro* environment, which revealed a negligible change in the protein binding of dexmedetomidine hydrochloride in the plasma. Dexmedetomidine hydrochloride passing over instead of the binding of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin was also assessed in an *in vitro* environment, dexmedetomidine hydrochloride replacing any of these compounds was regarded to be insignificant.

Biotransformation:
Dexmedetomidine is almost completely biotransformed and is eliminated as small amounts of untransformed dexmedetomidine in urine and feces. Biotransformation contains cytochrome P450 mediated metabolism in addition to direct glucuronidation. The major metabolic pathways of dexmedetomidine are as follows: direct N-glucuronidation to inactive metabolites; 3- hydroxy-dexmedetomidine, 3-hydroxy-dexmedetomidine glucuronide, and 3-carboxy- dexmedetomidine producing aliphatic hydroxylation of dexmedetomidine (in principle, mediated by CYP2A6) and 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyldexmedetomidine and dexmedetomidine-N-methyl O-glucuronide producing dexmedetomidine N-methylation.

Elimination:
The terminal half-life of dexmedetomidine ($t_{1/2}$) is approximately 2 hours and clearance is expected to be 39 L/hour approximately. A mass balance study showed that nine days after the intravenous administration of radioactively marked dexmedetomidine, approximately 95% of the radioactivity was identified in the urine and 4% was identified in the feces.

Approximately 85% of the radioactivity identified in the urine was discharged in 24 hours after the infusion. The fraction of radioactivity discharged through urine shows that N-glucuronidation products make up approximately 4% of the cumulative urinary discharge.

Additionally, 3-hydroxy-dexmedetomidine glucuronide and 3-carboxy-dexmedetomidine producing aliphatic hydroxylation of the main drug make up approximately 14% of the dose in the urine. 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyldexmedetomidine and N-methyl O-glucuronide dexmedetomidine producing dexmedetomidine N-methylation make up approximately 18% of the dose in the urine. N-Methyl is a minor compound in the circulation and was not identified in the urine. Approximately 28% of the urinary metabolites were not identified.

**Patient characteristics**

Geriatric patients:

Pharmacokinetic profile of DEKSTOMİD does not depend on age. Pharmacokinetics of dexmedetomidine showed no difference among young (ages 18-40), middle-aged (ages 41-65) and old (ages >65) patients showed no difference.

Renal failure:

When compared with health volunteers, dexmedetomidine pharmacokinetics ($C_{max}$, $T_{max}$, EAA,$t_{1/2}$, KL and Vss) showed no significant difference from patients with severe renal failure (creatinine clearance: <30 mL/min).

Hepatic failure:

Plasma protein bonding ratio of dexmedetomidine was lower in patients with hepatic failure than in healthy volunteers. The average percentage of plasma unbounded dexmedetomidine was 8.5% in healthy volunteers and 17.9% in patients with severe hepatic failure. In patients with different degrees of hepatic failure (Child-Pugh, class A, B, C), hepatic dexmedetomidine clearance was lower and plasma elimination ($t_{1/2}$) took longer. The average plasma clearance values of unbinded dexmedetomidine in patients with mild, medium and severe hepatic failure were respectively 59%, 51% and 32% of the values observed in healthy volunteers. The average $t_{1/2}$ values of patients with mild, medium and severe hepatic failure increased to 3.9, 5.4, and 7.4 hours respectively. While dexmedetomidine is not used for an effect, depending on the degree of failure and response in patients with hepatic failure, it may be necessary to consider decreasing the initial dose/sustainment dose.

While DEKSTOMİD dose is adjusted based on the effect, it may be necessary to consider decreasing the dose for patients with hepatic failure (See Section 4.2).

Gender:

A gender specific difference was not observed in the pharmacokinetics of dexmedetomidine.

Pediatric population:

Data regarding newborn babies (28-44 week gestation) to children aged 17 is limited. The half-life of dexmedetomidine observed in children (month 1 to age 17) was observed to be similar to that of adults, but higher than that of newborns (<1 month). It was observed that plasma clearance which was adjusted according to the body weight, was higher in the age group of 1 month-age 6, but lower in older children. Plasma clearance adjusted according to the body weight, was found to be lower in newborn babies (<1 month) than older age groups due to immaturity (0.9 l/hour/kg). The available data has been summarized as followed:

| | | Average (95% GA) | |
|---|---|---|---|
| Age | N | KL (l/hour/kg) | $t_{1/2}$ (hour) |
| <1 | 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 (1.00, 1.23) | 1.75 (1.57, 1.96) |
| 6 to < 17 years | 28 | 0.80 (0.69, 0.92) | 2.03 (1.78, 2.31) |

Linearity/Non-linearity:
When administered as an intravenous infusion for up to 24 hours, dexmedetomidine exhibits linear pharmacokinetics between the dosage range of 0.2 to 0.7 microgram/kg/hour.

**5.3. Preclinical safety data**
Dexmedetomidine is not mutagenic in the *in vitro* bacterial reverse mutation measurements (*E. coli and Salmonella typhimurium*) or mammal advanced mutation measurements (mouse lymphoma). In the presence of rat S9 metabolic activation, dexmedetomidine is clastogenic in the aberration test of *in vitro* lymphocyte chromosome. Despite this, dexmedetomidine is not clastogenic in *in vitro* human lymphocyte chromosome aberration test in the presence or absence of human S9 metabolic activation. While dexmedetomidine is clastogenic in *in vivo* mouse micronucleus tests performed in NMRI mouse, there is no proof of clastogenicity in CD-1 mice.

In male and female rats after daily, subcutaneous injections of 54 microgram/kg (less than the recommended maximum human dose based on microgram/$m^2$) administered to male rats 10 weeks before mating, and to females 3 weeks before mating and during mating, fertility was not affected.

Following the administration of dexmedetomidine to rats during fetal organogenesis (between gestation days 5 and 16) in doses up to 200 µg/kg/day (a dose that is approximately equal to the recommended maximum human intravenous dose based on the body surface area), subcutaneously to rabbits during fetal organogenesis (between gestations days 6 and 18) in intravenous doses up to 96 µg/kg/day (approximately half the recommended maximum dose of human exposure based on the surface comparison remaining under the plasma curve), no teratogenic effects were observed. On the other hand, after implantation in rats with 200 microgram/kg subcutaneous dose, an increase in fatality, decrease in live offspring, and fetal toxicity were observed. The dose with which effects were observed with the rats is 20 microgram/kg (a dose that is lower than the maximum recommended human intravenous dose based on body surface area comparison). In another reproduction study, when dexmedetomidine was subcutaneously administered to pregnant rats in doses of 8 microgram/kg and 32 microgram/kg (a dose that is lower than the maximum recommended human intravenous dose based on body surface area comparison) from gestation day 16 to ablactating period, offspring weight was observed to be lower.

Furthermore, when the offspring in the 32 microgram/kg group were allowed to mate, the second generation demonstrate a higher fetal and embriocidal toxicity and delayed motor development.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Sodium chloride
Water for injection

### 6.2. Incompatibilities

As physical compatibility has not been identified, DEKSTOMİD infusion should not be administered together with blood and plasma through one intravenous catheter.
DEKSTOMİD proved to be incompatible with the following drugs: Amphotericin B, diazepam.
DEKSTOMİD proved to be compatible with the following intravenous solutions
- 0.9% sodium chloride in water
- 5% dextrose in water
- 20% mannitol
- Ringer Lactate solution
- 100 mg/mL magnesium sulfate solution
- 0.3% potassium chloride solution

Compatibility studies revealed the potential of dexmedetomidine to be absorbed into some, natural types of rubber. While DEKSTOMİD is used in doses that will provide an effect, the use of administration compounds made from synthetic or coated natural rubber is recommended.

### 6.3. Shelf life

36 months

### 6.4. Special precautions for storage

It should be stored at room temperature under 25°C, in its original box.

### 6.5. Nature and contents of container

Colorless Type 1 vial with aluminum-polypropylene flip-off cap and rubber stopper as
5 pieces in each box

### 6.6. Special precautions for disposal and other handling

Used products or waste material must be disposed of in line with “Regulation on Medical Waste Control” and “Regulation on Packaging and Packaging Waste Control”.

Aseptic techniques must be followed at all times while preparing DEKSTOMİD.

DEKSTOMİD must be visually checked for particle matter and discoloring when the solution and its container allows.

*Preparation instructions:*
DEKSTOMİD Injection, 200 microgram/2 mL (100 µg/mL)
DEKSTOMİD should be diluted with 0.9% sodium chloride injection to obtain the desired concentration (4 microgram/ml) before the procedure. The preparation of the solution is the same for both loading dose and sustainment infusion.

Draw 2 mL of DEKSTOMİD infusion solution to prepare the infusion. Add
48 mL of 0,9% sodium chloride to obtain 50 mL in total.
Gently shake it to mix the solution thoroughly.
After diluting, chemical and physical stability in use is demonstrated for 24 hours at 25 °C.

In terms of microbiology, the product must be used immediately. If it cannot be used immediately, the duration and conditions of storage before starting to use is the responsibility of the user. If dilution is not performed under controlled and validated aseptic conditions, storage duration and conditions should be between 2°C and 8°C, and not longer than 24 hours.

## 7. MARKETING AUTHORISATION HOLDER

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## 10. DATE OF REVISION OF THE TEXT