Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dexmedetomidine Kabi 100 microgram/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 2 ml vial contains 200 micrograms of dexmedetomidine.
Each 4 ml vial contains 400 micrograms of dexmedetomidine.
Each 10 ml vial contains 1000 micrograms of dexmedetomidine.

The concentration of the final solution after dilution should be either 4 micrograms/ml or 8 micrograms/ml.

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.

Osmolarity: approximately 290 mOsm/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to 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, i.e. procedural/awake sedation.

4.2 Posology and method of administration

For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).

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

Posology

Patients already intubated and sedated may switch to dexmedetomidine with an initial infusion rate of 0.7 micrograms/kg/h which may then be adjusted stepwise within the dose range 0.2 to 1.4 micrograms/kg/h in order to achieve the desired level of sedation, depending on the patient's response. A lower starting infusion rate should be considered for frail patients. Dexmedetomidine is very potent and the infusion rate is given per **hour**. After dose adjustment, a new steady state sedation level may not be reached for up to one hour.

Maximum dose

The maximum dose of 1.4 micrograms/kg/h should not be exceeded. Patients failing to achieve an adequate level of sedation with the maximum dose of dexmedetomidine should be switched to an alternative sedative agent.

Use of a loading dose of Dexmedetomidine Kabi in ICU sedation is not recommended and is associated with increased adverse reactions. Propofol or midazolam may be administered if needed until clinical effects of dexmedetomidine are established.

Duration

There is no experience in the use of Dexmedetomidine Kabi for more than 14 days. The use of Dexmedetomidine Kabi for longer than this period should be regularly reassessed.

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

Dexmedetomidine Kabi should be administered only by health care professionals skilled in the anaesthetic management of patients in the operating room or during diagnostic procedures. When Dexmedetomidine Kabi is administered for conscious sedation, patients should be continuously monitored by persons not involved in the conduct of the diagnostic or surgical procedure. Patients should be monitored continuously for early signs of hypotension, hypertension, bradycardia, respiratory depression, airway obstruction, apnoea, dyspnoea and/or oxygen desaturation (see section 4.8).

Supplemental oxygen should be immediately available and provided when indicated. The oxygen saturation should be monitored by pulse oximetry.

Dexmedetomidine Kabi is given as a loading infusion followed by maintenance infusion. Depending on the procedure, concomitant local anaesthesia or analgesia may be needed in order to achieve the desired clinical effect. Additional analgesia or sedatives (e.g. opioids, midazolam, or propofol) are recommended in case of painful procedures or if increased depth of sedation is necessary. The pharmacokinetic distribution half –life of Dexmedetomidine Kabi has been estimated to be around 6 min, which can be taken into consideration, together with the effects of other administered medications, when assessing the appropriate time needed for titration to desired clinical effect of Dexmedetomidine Kabi.

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.

Maintenance of Procedural Sedation

- The maintenance infusion is generally initiated at 0.6-0.7 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.

Special populations

Elderly
No dose adjustment is normally required for elderly patients (see section 5.2). Elderly patients appear to have an increased risk for hypotension (see section 4.4) but the limited data available from procedural sedation do not suggest a clear dose dependency.

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
The safety and efficacy of Dexmedetomidine Kabi in children aged 0 to 18 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Intravenous use
Dexmedetomidine Kabi must be administered only as a diluted intravenous infusion using a controlled infusion device.

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 Kabi 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 Kabi 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.

General precautions
Dexmedetomidine Kabi should not be given as a bolus dose and in the ICU a loading dose is not recommended. Users should therefore be ready to use an alternative sedative for acute control of agitation or during procedures, especially during the first few hours of treatment. During procedural sedation a small bolus of another sedative may be used if a rapid increase in sedation level is required.
Some patients receiving Dexmedetomidine Kabi 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.

Dexmedetomidine normally does not cause deep sedation and patients may be easily roused. Dexmedetomidine is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

Dexmedetomidine Kabi should not be used as a general anaesthetic induction agent for intubation or to provide sedation during muscle relaxant use.

Dexmedetomidine lacks the anticonvulsant action of some other sedatives and so will not suppress underlying seizure activity.

Care should be taken if combining dexmedetomidine with other substances with sedative or cardiovascular actions as additive effects may occur.

Dexmedetomidine Kabi is not recommended for patient controlled sedation. Adequate data is not available.

When Dexmedetomidine Kabi is used in an outpatient setting, patients should normally be discharged into the care of a suitable third party. Patients should be advised to refrain from driving or other hazardous tasks and where possible to avoid the use of other agents that may sedate (e.g, benzodiazepines, opioids, alcohol) for a suitable period of time based on observed effects of dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient.

Caution should be exercised when administering dexmedetomidine to elderly patients. Elderly patients over 65 years of age may be more prone to hypotension with the administration of dexmedetomidine, including a loading dose, for procedures. A dose reduction should be considered. Please refer to section 4.2.

Mortality in ICU patients ≤ 65 years old
In the SPICE III pragmatic randomised controlled trial of 3 904 critically ill adult ICU patients dexmedetomidine was used as primary sedative and compared with usual care. There was no overall difference in 90-day mortality between the

dexmedetomidine and usual care group (mortality 29.1% in both groups), but a heterogeneity of effect from age on mortality was observed. Dexmedetomidine was associated with an increased mortality in the age-group ≤ 65 years (odds ratio 1.26; 95% credibility interval 1.02 to 1.56) compared to alternative sedatives. While the mechanism is unclear, this heterogeneity of effect on mortality from age was most prominent in patients admitted for reasons other than post-operative care, and increased with increasing APACHE II scores and with decreasing age. These findings should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in younger patients.

Cardiovascular effects and precautions
Dexmedetomidine reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension (see section 5.1).
Dexmedetomidine is therefore not suitable in patients with severe cardiovascular instability.

Caution should be exercised when administering dexmedetomidine to patients with pre-existing bradycardia. Data on the effects of dexmedetomidine in patients with heart rate <60 are very limited and particular care should be taken with such patients. Bradycardia does not normally require treatment, but has commonly responded to anti-cholinergic medicine or dose reduction where needed. Patients with high physical fitness and slow resting heart rate may be particularly sensitive to bradycardic effects of alpha-2 receptor agonists and cases of transient sinus arrest have been reported. Also, cases of cardiac arrest, often preceded by bradycardia or atrioventricular block, have been reported (see section 4.8).

The hypotensive effects of dexmedetomidine may be of greater significance in those patients with preexisting hypotension (especially if not responsive to vasopressors), hypovolaemia, chronic hypotension or reduced functional reserve such as patients with severe ventricular dysfunction and the elderly and special care is warranted in these cases (see section 4.3). Hypotension does not normally require specific treatment but, where needed, users should be ready to intervene with dose reduction, fluids and/or vasoconstrictors.

Patients with impaired peripheral autonomic activity (e.g. due to spinal cord injury) may have more pronounced haemodynamic changes after starting dexmedetomidine and so should be treated with care.

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.

Local vasoconstriction at higher concentration may be of greater significance in patients with ischaemic heart disease or severe cerebrovascular disease who should be monitored closely. Dose reduction or discontinuation should be considered in a patient developing signs of myocardial or cerebral ischaemia.

Caution is advised when administering dexmedetomidine together with spinal or epidural anaesthesia due to possible increased risk of hypotension or bradycardia.

Patients with hepatic impairment
Care should be taken in severe hepatic impairment as excessive dosing may increase the risk of adverse reactions, over-sedation or prolonged effect as a result of reduced dexmedetomidine clearance.

Patients with neurological disorders
Experience of dexmedetomidine in severe neurological disorders such as head injury and after neurosurgery is limited and it should be used with caution here, especially if deep sedation is required. Dexmedetomidine may reduce cerebral blood flow and intracranial pressure and this should be considered when selecting therapy.

Other
Alpha-2 agonists have rarely been associated with withdrawal reactions when stopped abruptly after prolonged use. This possibility should be considered if the patient develops agitation and hypertension shortly after stopping dexmedetomidine.

Dexmedetomidine may induce hyperthermia that may be resistant to traditional cooling methods.
Dexmedetomidine treatment should be discontinued in the event of a sustained unexplained fever and is not recommended for use in malignant hyperthermia-sensitive patients.

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.

Dexmedetomidine Kabi contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

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 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.

Inhibition of CYP enzymes including CYP2B6 by dexmedetomidine has been studied in human liver microsome incubations. In vitro study suggests that interaction potential in vivo exists between dexmedetomidine and substrates with dominant CYP2B6 metabolism.

Induction of dexmedetomidine *in vitro* was observed on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4, and induction *in vivo* cannot be excluded. The clinical significance is unknown.

The possibility of enhanced hypotensive and bradycardic effects should be considered in patients receiving other medicinal products causing these effects, for example beta blockers, although additional effects in an interaction study with esmolol were modest.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of dexmedetomidine in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). Dexmedetomidine Kabi should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexmedetomidine.

Breastfeeding
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 the rat fertility study, dexmedetomidine had no effect on male or female fertility. No human data on fertility are available.

4.7 Effects on 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 Kabi for procedural sedation.

4.8 Undesirable effects

Summary of the safety profile

Sedation of adult ICU patients
The most frequently reported adverse reactions with dexmedetomidine in ICU setting are hypotension, hypertension and bradycardia, occurring in approximately 25%, 15% and 13% of patients, respectively. Hypotension and bradycardia were also the most frequent dexmedetomidine-related serious adverse reactions occurring in 1.7% and 0.9% of randomised ICU patients, respectively.

Procedural/awake sedation

The most frequently reported adverse reactions with dexmedetomidine in procedural sedation are listed below (the protocols of phase III studies contained pre-defined thresholds for reporting changes in blood pressure, respiratory rate and heart rate as adverse events).
- Hypotension (55% in dexmedetomidine-group vs. 30% in placebo-group receiving rescue midazolam and fentanyl)
- Respiratory depression (38% in dexmedetomidine-group vs. 35% in placebo-group receiving rescue midazolam and fentanyl)
- Bradycardia (14% in dexmedetomidine-group vs. 4% in placebo-group receiving rescue midazolam and fentanyl)

Tabulated list of adverse reactions
The adverse reactions listed in Table 1 have been accumulated from pooled data of clinical trials in intensive care.
Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: 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).

System Organ Class	**Frequency**	**Undesirable Effects**
Endocrine disorders	Unknown	Diabetes insipidus
Metabolism and Nutrition disorders	Common	Hyperglycaemia, hypoglycaemia
	Uncommon	Metabolic acidosis, hypoalbuminaemia
Psychiatric disorders	Common	Agitation
	Uncommon	Hallucination
Cardiac disorders	Very common	Bradycardia [1,2]
	Common	Myocardial ischaemia or infarction, tachycardia
	Uncommon	Atrioventricular block[1], cardiac output decreased, 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	Dyspnoea, apnoea
Gastrointestinal disorders	Common	Nausea[2], vomiting, dry mouth[2]
	Uncommon	Abdominal distension
General disorders and administration site conditions:	Common	Withdrawal syndrome, hyperthermia
	Uncommon	Drug ineffective, thirst

[1] See section on Description of selected adverse reactions
[2] Adverse reaction observed also in procedural sedation studies
[3] Incidence 'common' in ICU sedation studies

Description of selected adverse reactions
Clinically significant hypotension or bradycardia should be treated as described in section 4.4.

In relatively healthy non-ICU subjects treated with dexmedetomidine, bradycardia has occasionally led to sinus arrest or pause. The symptoms responded to leg raising and anticholinergics such as atropine or glycopyrrolate. In isolated cases bradycardia has 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 reducing the infusion rate or size of the loading dose.

Paediatric population
Children > 1 month post-natal, predominantly post-operative, have been evaluated for treatment up to 24 hours in the ICU and demonstrated a similar safety profile as in adults. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to maintenance doses ≤ 0.2 mcg/kg/h. A single case of hypothermic bradycardia in a neonate has been reported in the literature.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 HPRA Pharmacovigilance Webiste: www.hpra.ie

4.9 Overdose

Symptoms

Several cases of dexmedetomidine overdose have been reported both in the clinical trial and the postmarketing data. The reported highest infusion rates of dexmedetomidine in these cases have reached up to 60 µg/kg/h for 36 minutes and 30 µg/kg/h for 15 minutes in a 20-month-old child and in an adult, respectively. The most common adverse reactions reported in conjunction with overdose include bradycardia, hypotension, hypertension, oversedation, respiratory depression and cardiac arrest.

Management
In cases of overdose with clinical symptoms, dexmedetomidine infusion should be reduced or stopped. Expected effects are primarily cardiovascular and should be treated as clinically indicated (see section 4.4). At high concentration hypertension may be more prominent than hypotension. In clinical studies, cases of sinus arrest reversed spontaneously or responded to treatment with atropine and glycopyrrolate. Resuscitation was required in isolated cases of severe overdose resulting in cardiac arrest.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 of adult ICU (Intensive Care Unit) patients
In placebo controlled trials in a post-operative ICU population previously intubated and sedated with midazolam or propofol, dexmedetomidine significantly reduced the requirement for both rescue sedative (midazolam or propofol) and opioids during sedation for up to 24 hours. Most dexmedetomidine patients required no additional sedative treatment. Patients could be successfully extubated without stopping the dexmedetomidine infusion. Studies from outside the ICU have confirmed that dexmedetomidine can be administered safely to patients without endotracheal intubation provided adequate monitoring is in place.

Dexmedetomidine was similar to midazolam (Ratio 1.07; 95% CI 0.971, 1.176) and propofol (Ratio 1.00; 95% CI 0.922, 1.075) on the time in target sedation range in a predominently medical population requiring prolonged light to moderate sedation (RASS 0 to -3) in the ICU for up to 14 days, reduced the duration of mechanical ventilation compared to midazolam and reduced the time to extubation compared to midazolam and propofol. Compared to both propofol and midazolam, patients were more easily roused, more cooperative and better able to communicate whether or not they had pain.
Dexmedetomidine treated patients had more frequent hypotension and bradycardia but less tachycardia than those receiving midazolam and more frequent tachycardia but similar hypotension to propofol treated patients. Delirium measured by the CAM-ICU scale was reduced in a study compared to midazolam and delirium-related adverse events were lower on dexmedetomidine compared to propofol. Those patients who withdrew due to insufficient sedation were switched to either propofol or midazolam. The risk of insufficient sedation was increased in patients who were difficult to sedate with standard care immediately prior to switching.

Evidence of paediatric efficacy was seen in a dose-controlled ICU study in a largely post-operative population aged 1 month to ≤ 17 years. Approximately 50% of patients treated with dexmedetomidine did not require rescue addition of midazolam during a median treatment period of 20.3 hours, not exceeding 24 hours. Data on treatment for > 24 hours is not available. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to low doses (≤ 0.2 mcg/kg/h) (see sections 5.2 and 4.4). New-born infants may be particularly sensitive to the bradycardic effects of dexmedetomidine in the presence of hypothermia and in conditions of heart rate-dependent cardiac output.

In double blind comparator controlled ICU studies, the incidence of cortisol suppression in patients treated with dexmedetomidine (n=778) was 0.5% compared with 0% in patients treated with either midazolam (n=338) or propofol (n=275). The event was reported as mild in 1 and moderate in 3 cases.

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 to 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 midazoloam 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 to 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.

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.

Distribution

Dexmedetomidine exhibits a two-compartment disposition model. In healthy volunteers it exhibits a rapid distribution phase with a central estimate of the distribution half-life (t1/2α) of about 6 minutes. The mean estimate of the terminal elimination half-life (t1/2) is approximately 1.9 to 2.5 h (min 1.35, max 3.68 h) and the mean estimate of the steady-state volume of distribution (Vss) is approximately 1.16 to 2.16 l/kg (90 to 151 litres). Plasma clearance (Cl) has a mean estimated value of 0.46 to 0.73 l/h/kg (35.7 to 51.1 l/h). The mean body weight associated with these Vss and Cl estimates was 69 kg. Plasma pharmacokinetics of dexmedetomidine is similar in the ICU population following infusion >24 h. The estimated pharmacokinetic parameters are: t1/2 approximately 1.5 hours, Vss approximately 93 litres and Cl approximately 43 l/h. The pharmacokinetics of dexmedetomidine is linear in the dosing range from 0.2 to 1.4 µg/kg/h and it does not accumulate in treatments lasting up to 14 days. Dexmedetomidine is 94% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.85 to 85 ng/ml. Dexmedetomidine binds to both human serum albumin and Alpha-1-acid glycoprotein with serum albumin as the major binding protein of dexmedetomidine in plasma.

Biotransformation and Elimination

Dexmedetomidine is eliminated by extensive metabolism in the liver. There are three types of initial metabolic reactions; direct N-glucuronidation, direct N-methylation and cytochrome P450 catalysed oxidation. The most abundant circulating dexmedetomidine metabolites are two isomeric N-glucuronides.

Metabolite H-1, N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide is also a major circulating product of dexmedetomidine biotransformation. Cytochrome P-450 catalyses the formation of two minor circulating metabolites, 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 the formation of the oxidised metabolites is mediated by several CYP forms (CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19). These metabolites have negligible pharmacological activity.

Following IV administration of radiolabeled dexmedetomidine an average 95% of radioactivity was recovered in the urine and 4% in the faeces after nine days. The major urinary metabolites are the two isomeric N-glucuronides, which together accounted for approximately 34% of the dose and N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide that accounted for 14.51% of the dose. The minor metabolites dexmedetomidine carboxylic acid, 3-hydroxymethyl dexmedetomidine and its O-glucuronide individually comprised 1.11 to 7.66% of the dose. Less than 1% of unchanged parent drug was recovered in the urine. Approximately 28% of the urinary metabolites are unidentified minor metabolites.

Special Populations
No major pharmacokinetic differences have been observed based on gender or age.

Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment compared with healthy subjects. The mean percentage of unbound dexmedetomidine in plasma ranged from 8.5% in healthy subjects to 17.9% in subjects with severe hepatic impairment. Subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C) had decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. 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. The mean $t_{1/2}$ for the subjects with mild, moderate or severe hepatic impairment was prolonged to 3.9, 5.4, and 7.4 hours, 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.

The pharmacokinetics of dexmedetomidine in subjects with severe renal impairment (creatinine clearance <30 ml/min) is not altered relative to healthy subjects.

Data in new-born infants (28 - 44 weeks gestation) to children 17 years of age are limited.
Dexmedetomidine half life in children (1 month to 17 years) appears similar to that seen in adults, but in new-born infants (under 1 month) it appears higher. In the age groups 1 month to 6 years, body weight-adjusted plasma clearance appeared higher but decreased in older children. Body weight-adjusted plasma clearance in new-born infants (under 1 month) appeared lower (0.9 l/h/kg) than in the older groups due to immaturity. The available data is summarised in the following table.

Age	**N**	**Mean (95% CI)**	
		Cl (l/h/kg)	**$t_{1/2}$ (h)**
Under 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 (1.00, 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)

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 the reproductive toxicity studies, dexmedetomidine had no effect on male or female fertility in the rat, and no teratogenic effects were observed in the rat or rabbit. In the rabbit study intravenous administration of the maximum dose, 96 µg/kg/day, produced exposures that are similar to those observed clinically. In the rat, subcutaneous administration at the maximum dose, 200 µg/kg/day, caused an increase in embryofoetal death and reduced the foetal body weight. These effects were associated with clear maternal toxicity. Reduced foetal body weight was noted also in the rat fertility study at dose 18 µg/kg/day and was accompanied with delayed ossification at dose 54 µg/kg/day. The observed exposure levels in the rat are below the clinical exposure range.

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

2 years

Shelf life after first opening:
The medicinal product must be used immediately after first opening.

Shelf life after dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C and for 24 hours at 2 °C to 8 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ° to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Clear glass vials (Type I), with filling volumes of 2, 4 and 10 ml, closed with an elastomeric fluoropolymer coated bromobutyl stopper with flip-off cap.

Pack sizes
10 x 2 ml vials
25 x 2 ml vials
1 x 4 ml vial
4 x 4 ml vials
10 x 4 ml vials
4 x 10 ml vials
10 x 10 ml vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vials are intended for single patient use only.

Dexmedetomidine Kabi can be diluted in the following infusion fluids to achieve the required concentration of either 4 micrograms/ml or 8 micrograms/ml prior to administration:

- Sodium chloride 9 mg/mL (0.9%)
- Glucose 50 mg/mL (5%)

- Ringer's solution
- Lactated Ringers
- Mannitol 200 mg/mL (20%)

In case the required concentration is 4 micrograms/ml:

Volume of Dexmedetomidine Kabi 100 micrograms/ml 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

In case the required concentration is 8 micrograms/ml:

Volume of Dexmedetomidine Kabi 100 micrograms/ml concentrate for solution for infusion	**Volume of diluent**	**Total volume of infusion**
4 ml	46 ml	50 ml
8 ml	92 ml	100 ml
20 ml	230 ml	250 ml
40 ml	460 ml	500 ml

The solution should be shaken gently to mix well.
Dexmedetomidine Kabi should be inspected visually for particulate matter and discoloration prior to administration.

Dexmedetomidine has been shown to be compatible when administered with the following intravenous fluids and medicinal products:
Lactated Ringers, 5% glucose solution, sodium chloride 9 mg/ml (0.9%) solution for injection, mannitol 200 mg/ml (20%), thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, rocuronium bromide, glycopyrrolate bromide, phenylephrine HCl, atropine sulfate, dopamine, noradrenaline, dobutamine, midazolam, morphine sulfate, fentanyl citrate, and a plasma-substitute.

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

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

PA2059/076/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd October 2021
Date of last renewal: 22nd July 2026

10 DATE OF REVISION OF THE TEXT

March 2026