PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

DEXMEDETOMIDINE KALCEKS CONCENTRATE FOR SOLUTION FOR INFUSION
100 MCG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 2 ml ampoule contains 200 micrograms of dexmedetomidine.

The concentration of the final solution after dilution should be 4 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 clear colourless or yellowish solution, pH 4.5 – 7.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intensive Care Unit sedation
Dexmedetomidine is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. This medicinal product should be administered by continuous infusion not to exceed 24 hours.

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

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

4.2 Posology and method of administration

Dosing guidelines

- Dosing should be individualized and titrated to desired clinical response.
- This medicinal product is not indicated for infusions lasting longer than 24 hours.
- This medicinal product should be administered using a controlled infusion device.

Posology

Table 1. Posology

Indication	**Dosage and administration**
Initiation of Intensive Care	**For adult patients:** a loading infusion of one mcg/kg over

Unit sedation:	10 minutes. **For patients over 65 years of age:** a dose reduction should be considered (see section 4.4). **For adult patients with impaired hepatic function:** a dose reduction should be considered (see sections 4.4 and 5.2).
Maintenance of Intensive Care Unit sedation:	**For adult patients:** a maintenance infusion of 0.2 to 0.7 mcg/kg/h. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation. **For patients over 65 years of age:** a dose reduction should be considered (see section 4.4). **For adult patients with impaired hepatic function:** a dose reduction should be considered (see sections 4.4 and 5.2).
Initiation of procedural sedation:	**For adult patients:** a loading infusion of one mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable. **For awake fiberoptic intubation in adult patients:** a loading infusion of one mcg/kg over 10 minutes. **For patients over 65 years of age:** a loading infusion of 0.5 mcg/kg over 10 minutes (see section 4.4). **For adult patients with impaired hepatic function:** a dose reduction should be considered (see sections 4.4 and 5.2).
Maintenance of procedural sedation:	**For adult patients:** the maintenance infusion is generally initiated at 0.6 mcg/kg/h and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/h. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. **For awake fiberoptic intubation in adult patients:** a maintenance infusion of 0.7 mcg/kg/h is recommended until the endotracheal tube is secured. **For patients over 65 years of age:** a dose reduction should be considered (see section 4.4). **For adult patients with impaired hepatic function:** a dose reduction should be considered (see sections 4.4 and 5.2).

Dosage adjustment

Due to possible pharmacodynamic interactions, a reduction in dosage of dexmedetomidine or other concomitant anaesthetics, sedatives, hypnotics or opioids may be required when co-administered (see section 4.5).

Dosage reductions may need to be considered for adult patients with hepatic impairment, and geriatric patients (see sections 4.4 and 5.2).

Method of administration

This medicine 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 6.7.

4.3 Contraindications

None

4.4 Special warnings and precautions for use

Drug administration

This medicine should be administered only by persons skilled in the management of patients in the intensive care or operating room setting. Due to the known pharmacological effects of dexmedetomidine, patients should be continuously monitored while receiving this medicine.

Hypotension, bradycardia, and sinus arrest

Clinically significant episodes of bradycardia and sinus arrest have been reported with dexmedetomidine administration in young, healthy adult volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration.

Reports of hypotension and bradycardia have been associated with dexmedetomidine infusion. Some of these cases have resulted in fatalities. If medical intervention is required, treatment may include decreasing or stopping the infusion of dexmedetomidine, increasing the rate of intravenous fluid administration, elevation of the lower extremities, and use of pressor agents. Because dexmedetomidine has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (e.g., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treatment of most episodes of dexmedetomidine-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

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

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

Transient hypertension

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

Arousability

Some patients receiving dexmedetomidine have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

Withdrawal

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

In adult subjects, tachycardia and hypertension requiring intervention in the 48 hours following study drug discontinuation occurred at frequencies of <5%. If tachycardia and/or hypertension occurs after

discontinuation of dexmedetomidine supportive therapy is indicated.

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

Tolerance and tachyphylaxis

Use of dexmedetomidine beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions (see section 4.8).

Drug abuse and dependence

Controlled substance
Dexmedetomidine (dexmedetomidine hydrochloride) is not a controlled substance.

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

Hepatic impairment

Since dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function (see sections 4.2 and 5.2).

Risk of Mortality

Use of dexmedetomidine greater than 24 hours has been associated with an increased mortality in critically ill adult intensive care unit (ICU) patients 63.7 years of age and younger compared to usual care (see section 5.1).

Paediatric population

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

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

Elderly

Intensive Care Unit Sedation
A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200 patients were 75 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of dexmedetomidine. Therefore, a dose reduction may be considered in patients over 65 years of age (see sections 4.2 and 5.2).

Procedural sedation

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Neuromuscular Blockers
In one study of 10 healthy adult volunteers, administration of dexmedetomidine for 45 minutes at a plasma concentration of one ng/ml resulted in no clinically meaningful increases in the magnitude of neuromuscular blockade associated with rocuronium administration.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Pregnancy Category C: Teratogenic effects were not observed following administration of dexmedetomidine at subcutaneous doses up to 200 mcg/kg in rats from day 5 to day 16 of gestation and intravenous doses up to 96 mcg/kg in rabbits from day 6 to day 18 of gestation. The dose in rats is approximately 2 times the maximum recommended human intravenous dose on a mcg/m^2 basis. The exposure in rabbits is approximately equal to that in humans at the maximum recommended intravenous dose based on plasma area-under-the-curve values. However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live pups, was observed in rats at subcutaneous dose of 200 mcg/kg. The no-effect dose was 20 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). In another reproductive study when dexmedetomidine was administered subcutaneously to pregnant rats from gestation day 16 through nursing, it caused lower pup weights at 8 and 32 mcg/kg as well as fetal and embryocidal toxicity of second generation offspring at a dose of 32 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). Dexmedetomidine also produced delayed motor development in pups at a dose of 32 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). No such effects were observed at a dose of 2 mcg/kg (less than the maximum recommended intravenous dose on a mcg/m^2 basis).

Placental transfer of dexmedetomidine was observed when radiolabelled dexmedetomidine was administered subcutaneously to pregnant rats.

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

Labour and delivery
The safety of dexmedetomidine during labour and delivery has not been studied. Therefore,

dexmedetomidine is not recommended during labour and delivery including caesarean section deliveries.

Breast-feeding
It is not known whether dexmedetomidine is excreted in human milk. Radiolabelled dexmedetomidine administered subcutaneously to lactating female rats was excreted in milk. Because many drugs are excreted in human milk, caution should be exercised when dexmedetomidine is administered to a nursing woman.

Fertility
In the rat fertility study, dexmedetomidine had no effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery or signing legal documents, may be impaired for some time after sedation.

4.8 Undesirable effects

The following clinically significant adverse reactions are described elsewhere in the labelling:
- Hypotension, bradycardia and sinus arrest (see section 4.4)
- Transient hypertension (see section 4.4)

Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Most common treatment-emergent adverse reactions, occurring in greater than 2% of patients in both Intensive Care Unit and procedural sedation studies include hypotension, bradycardia and dry mouth.

Intensive Care Unit sedation
Adverse reaction information is derived from the continuous infusion trials of dexmedetomidine for sedation in the Intensive Care Unit setting in which 1,007 adult patients received dexmedetomidine. The mean total dose was 7.4 mcg/kg (range: 0.8 to 84.1), mean dose per hour was 0.5 mcg/kg/h (range: 0.1 to 6.0) and the mean duration of infusion of 15.9 hours (range: 0.2 to 157.2). The population was between 17 to 88 years of age, 43% ≥65 years of age, 77% male and 93% Caucasian. Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 2. The most frequent adverse reactions were hypotension, bradycardia and dry mouth (see section 4.4).

Table 2. Adverse reactions with an incidence >2% - Intensive Care Unit sedation population

Body system/ Adverse event	**All dexmedetomidine N = 1007**	**Randomized dexmedetomidine N = 798**	**Placebo N = 400**	**Propofol N = 188**
	n (%)	n (%)	n (%)	n (%)
Vascular disorders				
Hypotension	248 (25%)	191 (24%)	48 (12%)	25 (13%)
Hypertension	123 (12%)	101 (13%)	76 (19%)	7 (4%)
Gastrointestinal disorders				
Nausea	90 (9%)	73 (9%)	36 (9%)	20 (11%)
Dry mouth	35 (4%)	22 (3%)	4 (1%)	1 (1%)
Vomiting	34 (3%)	26 (3%)	21 (5%)	6 (3%)

Cardiac disorders				
Bradycardia	52 (5%)	36 (5%)	10 (3%)	0
Atrial fibrillation	44 (4%)	37 (5%)	13 (3%)	14 (7%)
Tachycardia	20 (2%)	15 (2%)	17 (4%)	2 (1%)
Sinus tachycardia	6 (1%)	6 (1%)	2 (1%)	4 (2%)
Ventricular tachycardia	4 (0%)	4 (1%)	3 (1%)	9 (5%)
General disorders and administration site conditions				
Pyrexia	35 (4%)	31 (4%)	15 (4%)	8 (4%)
Hyperthermia	19 (2%)	16 (2%)	12 (3%)	0
Chills	17 (2%)	14 (2%)	13 (3%)	4 (2%)
Oedema peripheral	4 (0%)	2 (0%)	2 (1%)	4 (2%)
Metabolism and nutrition disorders				
Hypovolemia	31 (3%)	22 (3%)	9 (2%)	9 (5%)
Hyperglycaemia	17 (2%)	15 (2%)	7 (2%)	5 (3%)
Hypocalcaemia	7 (1%)	7 (1%)	0	4 (2%)
Acidosis	6 (1%)	5 (1%)	4 (1%)	4 (2%)
Respiratory, thoracic and mediastinal disorders				
Atelectasis	29 (3%)	23 (3%)	13 (3%)	12 (6%)
Pleural effusion	23 (2%)	16 (2%)	4 (1%)	12 (6%)
Hypoxia	16 (2%)	13 (2%)	8 (2%)	5 (3%)
Pulmonary oedema	9 (1%)	9 (1%)	3 (1%)	5 (3%)
Wheezing	4 (0%)	4 (1%)	1 (0%)	4 (2%)
Psychiatric disorders				
Agitation	20 (2%)	16 (2%)	11 (3%)	1 (1%)
Blood and lymphatic system disorders				
Anaemia	19 (2%)	18 (2%)	7 (2%)	4 (2%)
Injury, poisoning and procedural complications				
Post-procedural haemorrhage	15 (2%)	13 (2%)	10 (3%)	7 (4%)
Investigations				
Urine output decreased	6 (1%)	6 (1%)	0	4 (2%)

Adverse reaction information was also derived from the placebo-controlled, continuous infusion trials of dexmedetomidine for sedation in the surgical intensive care unit setting in which 387 adult patients received dexmedetomidine for less than 24 hours. The most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anaemia (see Table 3).

Table 3. Treatment-emergent adverse events occurring in >1% of all dexmedetomidine-treated adult patients in the randomized placebo-controlled continuous infusion <24 hours ICU sedation studies

Adverse event	**Randomized dexmedetomidine (N = 387)**	**Placebo (N = 379)**
Hypotension	28%	13%
Hypertension	16%	18%

Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Haemorrhage	3%	4%
Anaemia	3%	2%
Dry Mouth	3%	1%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycaemia	2%	2%
Acidosis	2%	2%
Pleural Effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

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

Table 4. Key treatment-emergent adverse events occurring in dexmedetomidine- or midazolam-treated adult patients in the randomized active comparator continuous infusion long-term intensive care unit sedation study

Adverse event	**Dexmedetomidine (N = 244)**	**Midazolam (N = 122)**
Hypotension[1]	56%	56%
Hypotension requiring intervention	28%	27%
Bradycardia[2]	42%	19%
Bradycardia requiring intervention	5%	1%
Systolic hypertension[3]	28%	42%
Tachycardia[4]	25%	44%
Tachycardia requiring intervention	10%	10%
Diastolic hypertension[3]	12%	15%
Hypertension[3]	11%	15%
Hypertension requiring intervention[†]	19%	30%
Hypokalaemia	9%	13%
Pyrexia	7%	2%
Agitation	7%	6%
Hyperglycaemia	7%	2%
Constipation	6%	6%

Hypoglycaemia	5%	6%
Respiratory failure	5%	3%
Renal failure acute	2%	1%
Acute respiratory distress syndrome	2%	1%
Generalized oedema	2%	6%
Hypomagnesemia	1%	7%

† Includes any type of hypertension.

1 Hypotension was defined in absolute terms as systolic blood pressure of <80 mmHg or diastolic blood pressure of <50 mmHg or in relative terms as ≤30% lower than pre-study drug infusion value.

2 Bradycardia was defined in absolute terms as <40 bpm or in relative terms as ≤30% lower than pre-study drug infusion value.

3 Hypertension was defined in absolute terms as systolic blood pressure >180 mmHg or diastolic blood pressure of >100 mmHg or in relative terms as ≥30% higher than pre-study drug infusion value.

4 Tachycardia was defined in absolute terms as >120 bpm or in relative terms as ≥30% greater than pre-study drug infusion value.

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

Table 5. Number (%) of adult subjects who had a dose-related increase in treatment emergent adverse events by maintenance adjusted dose rate range in the dexmedetomidine group

	Dexmedetomidine (mcg/kg/h)		
Adverse event	**≤0.7* (N = 95)**	**>0.7 to ≤1.1* (N = 78)**	**>1.1* (N = 71)**
Constipation	6%	5%	14%
Agitation	5%	8%	14%
Anxiety	5%	5%	9%
Oedema peripheral	3%	5%	7%
Atrial fibrillation	2%	4%	9%
Respiratory failure	2%	6%	10%
Acute respiratory distress syndrome	1%	3%	9%

* Average maintenance dose over the entire study drug administration.

Procedural sedation

Adverse reaction information is derived from the two trials for procedural sedation (see section 5.2) in which 318 adult patients received dexmedetomidine. The mean total dose was 1.6 mcg/kg (range: 0.5 to 6.7), mean dose per hour was 1.3 mcg/kg/h (range: 0.3 to 6.1) and the mean duration of infusion of 1.5 hours (range: 0.1 to 6.2). The population was between 18 to 93 years of age, ASA I-IV, 30% ≥65 years of age, 52% male and 61% Caucasian.

Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 6. The most frequent adverse reactions were hypotension, bradycardia, and dry mouth (see section 4.4). Pre-specified criteria for the vital signs to be reported as adverse reactions are footnoted below the table. The decrease in respiratory rate and hypoxia was similar between dexmedetomidine and comparator groups in both studies.

Table 6. Adverse reactions with an incidence >2% - procedural sedation population

	Dexmedetomidine N = 318	**Placebo N = 113**

Body System/ Adverse Event	n (%)	n (%)
Vascular disorders		
Hypotension[1]	173 (54%)	34 (30%)
Hypertension[2]	41 (13%)	27 (24%)
Respiratory, thoracic and mediastinal disorders		
Respiratory depression[5]	117 (37%)	36 (32%)
Hypoxia[6]	7 (2%)	3 (3%)
Bradypnea	5 (2%)	5 (4%)
Cardiac disorders		
Bradycardia[3]	45 (14%)	4 (4%)
Tachycardia[4]	17 (5%)	19 (17%)
Gastrointestinal disorders		
Nausea	10 (3%)	2 (2%)
Dry mouth	8 (3%)	1 (1%)

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

Post-marketing experience

The following adverse reactions have been identified during post-approval use of dexmedetomidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypotension and bradycardia were the most common adverse reactions associated with the use of dexmedetomidine during post-approval use of the drug.

Table 7. Adverse reactions experienced during post-approval use of dexmedetomidine

Body system	**Preferred term**
Body as a whole	Fever, hyperpyrexia, hypovolemia, light anaesthesia, pain, rigors
Cardiovascular disorders, general	Blood pressure fluctuation, heart disorder, hypertension, hypotension, myocardial infarction
Central and peripheral nervous system disorders	Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion
Gastrointestinal system disorders	Abdominal pain, diarrhoea, vomiting, nausea
Heart rate and rhythm disorders	Arrhythmia, ventricular arrhythmia, bradycardia, hypoxia, Atrioventricular block, cardiac arrest, extrasystoles, atrial fibrillation, heart block, t wave inversion, tachycardia, supraventricular tachycardia, ventricular tachycardia
Liver and biliary system disorders	Increased gamma-glutamyl transpeptidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase
Metabolic and nutritional disorders	Acidosis, respiratory acidosis, hyperkalaemia, increased alkaline phosphatase, thirst, hypoglycaemia

Psychiatric disorders	Agitation, confusion, delirium, hallucination, illusion
Red blood cell disorders	Anaemia
Renal disorders	Blood urea nitrogen increased, oliguria
Respiratory system disorders	Apnoea, bronchospasm, dyspnoea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Skin and appendages disorders	Increased sweating
Vascular disorders	Haemorrhage
Vision disorders	Photopsia, abnormal vision

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 the national reporting system.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Dexmedetomidine is a relatively selective alpha$_2$-adrenergic agonist with sedative properties. Alpha$_2$ selectivity is observed in animals following slow intravenous infusion of low and medium doses (10-300 mcg/kg). Both alpha$_1$ and alpha$_2$ activity is observed following slow intravenous infusion of high doses (≥1,000 mcg/kg) or with rapid intravenous administration.

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

Clinical studies
The safety and efficacy of dexmedetomidine has been evaluated in four randomized, double-blind, placebo-controlled multicenter clinical trials in 1,185 adult patients.

Intensive Care Unit sedation

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

Table 9. Ramsay Level of Sedation Scale

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

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

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

Table 10. Midazolam use as rescue medication during intubation (ITT)
Study one

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

ITT (intent-to-treat) population includes all randomized patients.
* ANOVA model with treatment center.
** Chi-square.

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

175 patients) in the placebo group.

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

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

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

Table 11. Propofol use as rescue medication during intubation (ITT)
Study two

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

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

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

In a controlled clinical trial, dexmedetomidine was compared to midazolam for ICU sedation exceeding 24 hours duration. Dexmedetomidine was not shown to be superior to midazolam for the primary efficacy endpoint, the percent of time patients were adequately sedated (81% versus 81%). In addition, administration of dexmedetomidine for longer than 24 hours was associated with tolerance, tachyphylaxis, and a dose-related increase in adverse events (see section 4.8).

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

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

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

3005012
The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 64.6 (60.0 to 69.1)% for subjects on dexmedetomidine and 64.7 (59.9 to 69.4)% for subjects on propofol. As the lower limit of the 2-sided 95% CI for the estimated ratio of

dexmedetomidine vs. propofol (0.92) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to propofol in maintaining a target depth of sedation. The median duration of mechanical ventilation was 21 hours shorter in the dexmedetomidine group (96.5 hours) than in the propofol group (117.5 hours).

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

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

3005013
The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 60.7 (55.4 to 66.1)% for subjects on dexmedetomidine and 56.6 (51.2 to 61.9)% for subjects on midazolam. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. midazolam (0.97) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to midazolam in maintaining a target depth of sedation. The median duration of mechanical ventilation was 41 hours shorter in the dexmedetomidine group (123.0 hours) than in the midazolam group (164.0 hours).

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

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

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

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

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

administration should not exceed 24 hours (see section 4.2).

Procedural sedation
The safety and efficacy of dexmedetomidine for sedation of non-intubated patients prior to and/or during surgical and other procedures was evaluated in two randomized, double-blind, placebo-controlled multicenter clinical trials. Study 1 evaluated the sedative properties of dexmedetomidine in patients having a variety of elective surgeries/procedures performed under monitored anaesthesia care. Study 2 evaluated dexmedetomidine in patients undergoing awake fiberoptic intubation prior to a surgical or diagnostic procedure.

In Study 1, the sedative properties of dexmedetomidine were evaluated by comparing the percent of patients not requiring rescue midazolam to achieve a specified level of sedation using the standardized Observer's Assessment of Alertness/Sedation Scale (see Table 12).

Table 12. Observer's Assessment of Alertness/Sedation

Assessment categories				
Responsiveness	**Speech**	**Facial expression**	**Eyes**	**Composite score**
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	--	--	2
Does not respond to mild prodding or shaking	--	--	--	1 (deep sleep)

Patients were randomized to receive a loading infusion of either dexmedetomidine 1 mcg/kg, dexmedetomidine 0.5 mcg/kg, or placebo (normal saline) given over 10 minutes and followed by a maintenance infusion started at 0.6 mcg/kg/h. The maintenance infusion of study drug could be titrated from 0.2 mcg/kg/h to 1 mcg/kg/h to achieve the targeted sedation score (Observer's Assessment of Alertness/Sedation Scale ≤4). Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an Observer's Assessment of Alertness/Sedation Scale ≤4. After achieving the desired level of sedation, a local or regional anaesthetic block was performed. Demographic characteristics were similar between the dexmedetomidine and comparator groups. Efficacy results showed that dexmedetomidine was more effective than the comparator group when used to sedate non-intubated patients requiring monitored anaesthesia care during surgical and other procedures (see Table 13).

In Study 2, the sedative properties of dexmedetomidine were evaluated by comparing the percent of patients requiring rescue midazolam to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale score ≥2 (Table 9). Patients were randomized to receive a loading infusion of dexmedetomidine 1 mcg/kg or placebo (normal saline) given over 10 minutes and followed by a fixed maintenance infusion of 0.7 mcg/kg/h. After achieving the desired level of sedation, topicalization of the airway occurred. Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain a Ramsay Sedation Scale ≥2. Demographic characteristics were similar between the dexmedetomidine and comparator groups. For efficacy results see Table 13.

Table 13. Key efficacy results of procedural sedation studies

Study	Loading infusion treatment arm	Number of patients enrolled[a]	% Not requiring midazolam rescue	Confidence[b] interval on the difference vs. placebo	Mean (SD) total dose (mg) of rescue midazolam required	Confidence[b] intervals of the mean rescue dose
Study 1	Dexmedetomidine 0.5 mcg/kg	134	40	37 (27, 48)	1.4 (1.7)	-2.7 (-3.4, -2.0)
	Dexmedetomidine 1 mcg/kg	129	54	51 (40, 62)	0.9 (1.5)	-3.1 (-3.8, -2.5)
	Placebo	63	3	–	4.1 (3.0)	–
Study 2	Dexmedetomidine 1 mcg/kg	55	53	39 (20, 57)	1.1 (1.5)	-1.8 (-2.7, -0.9)
	Placebo	50	14	–	2.9 (3.0)	–

[a] Based on ITT population defined as all randomized and treated patients.
[b] Normal approximation to the binomial with continuity correction.

5.2 Pharmacokinetic properties

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

Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/h when administered by intravenous infusion for up to 24 hours. Table 8 shows the main pharmacokinetic parameters when dexmedetomidine was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 mcg/kg/h (target plasma concentration of 0.3 ng/ml) for 12 and 24 hours, 0.33 mcg/kg/h (target plasma concentration of 0.6 ng/ml) for 24 hours, and 0.70 mcg/kg/h (target plasma concentration of 1.25 ng/ml) for 24 hours.

Table 8. Mean ± SD pharmacokinetic parameters

Parameter	Loading infusion (min)/total infusion duration (h)			
	10 min/12 h	10 min/24 h	10 min/24 h	35 min/24 h
	Dexmedetomidine target plasma concentration (ng/ml) and dose (mcg/kg/h)			
	0.3/0.17	0.3/0.17	0.6/0.33	1.25/0.70
$t_{1/2}$*, hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
CL, litre/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}, litre	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg C_{ss}#, ng/ml	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

Abbreviations: $t_{1/2}$ = half-life, CL = clearance, V_{ss} = steady-state volume of distribution.
* Presented as harmonic mean and pseudo standard deviation.
\# Mean C_{ss} = Average steady-state concentration of dexmedetomidine. The mean C_{ss} was calculated based on post-dose sampling from 2.5 – 9 hours samples for 12 hour infusion and post-dose sampling from 2.5 – 18 hours for 24 hour infusions.

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

respectively.

Dexmedetomidine pharmacokinetic parameters after dexmedetomidine maintenance doses of 0.2 to 1.4 mcg/kg/h for >24 hours were similar to the pharmacokinetic (PK) parameters after dexmedetomidine maintenance dosing for <24 hours in other studies. The values for clearance (CL), volume of distribution (V), and $t_{1/2}$ were 39.4 l/h, 152 l, and 2.67 hours, respectively.

Distribution

The steady-state volume of distribution (V_{ss}) of dexmedetomidine is approximately 118 litres. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female subjects. The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects.

The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored *in vitro*, and negligible changes in the plasma protein binding of dexmedetomidine were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by dexmedetomidine was explored *in vitro* and none of these compounds appeared to be significantly displaced by dexmedetomidine.

Elimination

Metabolism

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and faeces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. The major metabolic pathways of dexmedetomidine are: direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6 with a minor role of CYP1A2, CYP2E1, CYP2D6 and CYP2C19) of dexmedetomidine to generate 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxy-dexmedetomidine; and N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronide.

Excretion

The terminal elimination half-life ($t_{1/2}$) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39 l/h. A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following intravenous administration of radiolabelled dexmedetomidine, was recovered in the urine and 4% in the faeces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated that products of N-glucuronidation accounted for approximately 34% of the cumulative urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxylic acid-dexmedetomidine together represented approximately 14% of the dose in urine. N-methylation of dexmedetomidine to form 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for approximately 18% of the dose in urine. The N-Methyl metabolite itself was a minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have not been identified.

Specific populations

Male and female patients

There was no observed difference in dexmedetomidine pharmacokinetics due to gender.

Geriatric patients

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

elderly (>65 years) subjects.

Patients with hepatic impairment
In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine were lower than in healthy subjects. The mean clearance values for patients with mild, moderate, and severe hepatic impairment were 74%, 64% and 53% of those observed in the normal healthy subjects, respectively. Mean clearances for free drug were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively.
Although dexmedetomidine is dosed to effect, it may be necessary to consider dose reduction in subjects with hepatic impairment (see sections 4.2 and 4.4).

Patients with renal impairment
Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL, and V_{ss}) were not significantly different in patients with severe renal impairment (creatinine clearance: <30 ml/min) compared to healthy subjects.

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

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility
Carcinogenesis
Animal carcinogenicity studies have not been performed with dexmedetomidine.

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

Impairment of fertility
Fertility in male or female rats was not affected after daily subcutaneous injections at doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). Dexmedetomidine was dosed from 10 weeks prior to mating in males and 3 weeks prior to mating and during mating in females.

Animal toxicology and/or pharmacology
There were no differences in the adrenocorticotropic hormone (ACTH)-stimulated cortisol response in dogs following a single dose of dexmedetomidine compared to saline control. However, after continuous subcutaneous infusions of dexmedetomidine at 3 mcg/kg/h and 10 mcg/kg/h for one week in dogs (exposures estimated to be within the clinical range), the ACTH-stimulated cortisol response was diminished by approximately 27% and 40%, respectively, compared to saline-treated control animals indicating a dose-dependent adrenal suppression.

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 6.7.

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

There is a 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.

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

6.3 Shelf life

5 years.

6.4 Shelf life after dilution

Chemical and physical in-use stability of the diluted infusions has been demonstrated for 36 hours at 30°C and at refrigerated conditions (2°C – 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 the use are the responsibility of the user and would not normally be longer than 24 hours at 2° to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Special precautions for storage

Do not store above 30°C.
For storage conditions after dilution of the medicinal product, see section 6.4.

6.6 Nature and contents of containers

Type I colourless glass ampoules of 2 ml with one point cut.

Pack size: 5 ampoules

6.7 Special precautions for disposal and other handling

Ampoules are intended for single patient use only.

Strict aseptic technique must always be maintained during handling of this medicinal product.

Preparation of solution
This medicine can be diluted in glucose 50 mg/ml (5%), Ringers, Lactated Ringer, mannitol or sodium chloride 9 mg/ml (0.9%) solution for injection to achieve the required concentration of 4 micrograms/ml prior to administration. Please see below in tabulated form the volumes needed to prepare the infusion. Preparation of solutions is the same, whether for the loading dose or maintenance infusion.

For required concentration of 4 micrograms/ml:

Volume of DEXMEDETOMIDINE KALCEKS CONCENTRATE FOR SOLUTION FOR INFUSION 100 MCG/ML	Volume of diluent	Total volume of infusion
2 ml	48 ml	50 ml
4 ml	96 ml	100 ml
10 ml	240 ml	250 ml
20 ml	480 ml	500 ml

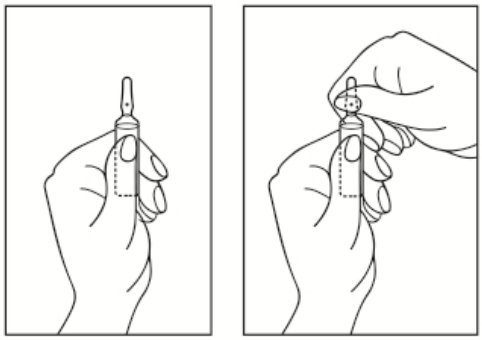
The solution should be shaken gently to mix well.

This medicine should be inspected visually for particulate matter and discoloration prior to administration.

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

Sodium chloride 9 mg/ml (0.9%) solution for injection, 5% glucose solution, mannitol 200 mg/ml (20%), Ringers, lactated Ringer's solution, alfentanil hydrochloride, amikacin sulfate, aminophylline, amiodarone hydrochloride, ampicillin sodium, ampicillin sodium-sulbactam sodium, atracurium besylate, atropine sulfate, azithromycin, aztreonam, bretylium tosylate, bumetanide, butorphanol tartrate, calcium gluconate, cefazolin sodium, cefepime hydrochloride, cefoperazone sodium, cefotaxime sodium, cefotetan sodium, cefoxitin sodium, ceftazidime, ceftizoxime sodium, ceftriaxone sodium, cefuroxime sodium, chlorpromazine hydrochloride, cimetidine hydrochloride, ciprofloxacin, cisatracurium besylate, clindamycin phosphate, dexamethasone sodium phosphate, digoxin, diltiazem hydrochloride, diphenhydramine hydrochloride, dobutamine hydrochloride, dolasetron mesylate, dopamine hydrochloride, doxycycline hyclate, droperidol, enalaprilat, ephedrine hydrochloride, epinephrine hydrochloride, erythromycin lactobionate, esmolol, etomidate, famotidine, fenoldopam mesylate, fentanyl citrate, fluconazole, furosemide, gatifloxacin, gentamicin sulfate, glycopyrrolate bromide, granisetron hydrochloride, haloperidol lactate, heparin sodium, hydrocortisone sodium succinate, hydromorphone hydrochloride, hydroxyzine hydrochloride, inamrinone lactate, isoproterenol hydrochloride, ketorolac tromethamine, labetalol, levofloxacin, lidocaine hydrochloride, linezolid, lorazepam, magnesium sulfate, meperidine hydrochloride, methylprednisolone sodium succinate, metoclopramide hydrochloride, metronidazole, midazolam, milrinone lactate, mivacurium chloride, morphine sulfate, nalbuphine hydrochloride, nitroglycerin, norepinephrine bitartrate, ofloxacin, ondansetron hydrochloride, pancuronium bromide, phenylephrine hydrochloride, piperacillin sodium, piperacillin sodium-tazobactam sodium, potassium chloride, procainamide hydrochloride, prochlorperazine edisylate, promethazine hydrochloride, propofol, ranitidine hydrochloride, rapacuronium bromide, remifentanil hydrochloride, rocuronium bromide, sodium bicarbonate, sodium nitroprusside, succinylcholine, sufentanil citrate, sulfamethoxazole-trimethoprim, theophylline, thiopental sodium, ticarcillin disodium, ticarcillin disodium-clavulanate potassium, tobramycin sulfate, vancomycin hydrochloride, vecuronium bromide, verapamil hydrochloride, and a plasma-substitute.

Instruction of ampoule opening:
1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



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

7. PRODUCT OWNER AND MANUFACTURER

Product Owner:
AS KALCEKS
Krustpils iela 71E, Rīga, LV-1057, Latvia

Manufacturer:
HBM Pharma s.r.o.
Sklabinska 30, 036 80 Martin, Slovakia

8. MARKETING AUTHORISATION NUMBER(S)

SIN16554P

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19.07.2022

10. DATE OF REVISION OF THE TEXT

02/2023