PRECEDEX should not be used outside an Intensive Care Unit setting or surgical operating theatres. There should be continuous monitoring of vital parameters.

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

PRECEDEX® concentrated solution for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of concentrated solution contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine. Vials of PRECEDEX are intended for single patient use only.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrated solution for intravenous infusion.

A clear, colourless concentrated solution for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRECEDEX is an alpha$_2$ adrenoreceptor agonist sedative with analgesic properties indicated for:

Intensive care unit sedation

- Sedation of intubated and mechanically ventilated adult post-surgical patients during treatment in an intensive care setting.

Monitored anaesthesia care (MAC)/Conscious sedation in a theatre or intensive care setting for:

- Minor surgical procedures under local anaesthesia
- Fibreoptic intubation

PRECEDEX is indicated for sedation of non-intubated paediatric patients from 1 month to less than 18 years of age prior to and during non-invasive procedures.

4.2 Posology and method of administration

NOTE: PRECEDEX should be administered only by healthcare providers skilled in the management of patients in the intensive care setting. Continuous monitoring of vital signs, in particular blood pressure, heart rate and oxygen saturation is mandatory during infusion of PRECEDEX.

In order to minimise undesirable pharmacologic side effects, bolus injections of PRECEDEX should not be used. Clinically significant events of bradycardia and sinus arrest have been associated with PRECEDEX administration in young healthy adult volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of PRECEDEX.

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

Fluid supplementation should be administered prior to and during administration of PRECEDEX to ensure normovolaemia.

PRECEDEX has been administered to patients requiring mechanical ventilation as well as to patients breathing spontaneously after extubation. There is no respiratory depression associated with the administration of PRECEDEX. Patients receiving PRECEDEX have been observed to be arousable and alert when stimulated. This is an expected component of PRECEDEX sedation and should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms. PRECEDEX has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post extubation. It is not necessary to discontinue PRECEDEX prior to extubation.

Posology

Adults

ICU sedation

PRECEDEX dosage should be individualised and titrated to the desired clinical effect.

Initiation

For adult patients, it is recommended to initiate PRECEDEX with a loading dose of 1,0 microgram/kg over ten minutes.

Maintenance of ICU sedation

Adult patients will generally require a maintenance infusion in the range of 0,2 to 0,7 microgram/kg/hr. The rate of the maintenance infusion can be adjusted in order to achieve the desired clinical effect. Dosages as low as 0,05 micrograms/kg/hr have been used in clinical studies.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic or renal function and in patients over 65 years of age (see sections 4.3, 4.4 and 5.2).

Conscious sedation

Monitored anaesthesia care (MAC) with an adequate nerve block and awake fibreoptic intubation (AFI)

PRECEDEX dosing should be individualised and titrated to the desired clinical effect.

Initiation

For adult patients, PRECEDEX is generally initiated with a loading infusion of 1 (one) microgram/kg over 10 minutes.

For patients over 65 years of age or those undergoing less invasive procedures such as ophthalmic surgery, a loading infusion of 0,5 microgram/kg over 10 minutes may be suitable.

Maintenance of conscious sedation

MAC

Following the load, maintenance dosing of PRECEDEX should generally be initiated at 0,6 microgram/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0,2 to 1 microgram/kg/hr for all procedures. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

AFI

Following the load in awake fibreoptic intubation, a fixed maintenance dose of 0,7 microgram/kg/hr should be used.

Dosage adjustment

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

Special populations

Impaired hepatic function

Dosage reductions may need to be considered for patients with hepatic impairment, as PRECEDEX is metabolised primarily in the liver.

Impaired renal function

Since the majority of metabolites are excreted in the urine, dosage reductions may need to be considered for patients with renal impairment.

Elderly population

Since the elderly are more sensitive to the effects of PRECEDEX, dosage reductions may need to be considered.

Paediatric population

The efficacy and safety of PRECEDEX have not been established in paediatric patients less than 1 month of age.

Initiation of sedation during non-invasive procedures

- 1 month to less than 2 years of age: a loading infusion of 1,5 mcg/kg over 10 minutes.
- 2 to less than 18 years of age: a loading infusion of 2 mcg/kg over 10 minutes.

Consider a reduction in dosage if clinically indicated.

Maintenance of sedation during non-invasive procedures

- 1 month to less than 18 years of age: the maintenance infusion is generally initiated at 1,5 mcg/kg/hour and titrated to achieve desired clinical effect with dosage ranging from 0,5 to 1,5 mcg/kg/hour.

As clinically warranted, titrate the maintenance dose to individual patient clinical response.

Method of administration

For intravenous infusion.

For instructions on preparation and dilution of the product before administration, see section 6.6.

4.3 Contraindications

PRECEDEX is contraindicated in

- patients with a known hypersensitivity to dexmedetomidine or to any of the excipients of PRECEDEX listed in section 6.1
- patients with sepsis
- unstable trauma patients
- hypovolaemic patients
- heart block
- uncontrolled cardiac failure
- imminent hepatic failure

4.4 Special warnings and precautions for use

PRECEDEX should be administered only by health care providers skilled in the management of patients in the intensive care setting and who have received complete training in the use of PRECEDEX in the ICU setting.

Safety and efficacy of PRECEDEX in non-surgical intensive care patients have not been established.

Clinical events of bradycardia and sinus arrest have been associated with PRECEDEX administration in some young, healthy adult volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of PRECEDEX. Bolus injections of PRECEDEX should not be used, in order to minimise undesirable pharmacological side effects.

Elderly population

The elderly are more prone to cardiovascular adverse events e.g. hypotension and bradycardia and the dose must be carefully titrated to obtain the desired effect. Close CVS monitoring is required. Elderly patients (over 65 years) often require lower doses of PRECEDEX.

Special precautions

NOTE: PRECEDEX should be administered only by health care providers skilled in the management of patients in the intensive care setting. Continuous electrocardiogram (ECG), blood pressure and oxygen saturation monitoring are mandatory during infusion of PRECEDEX.

Caution should be exercised in patients with pre-existing severe bradycardia disorders (i.e. advanced heart block), or patients with pre-existing severe ventricular dysfunction (e.g., ejection fraction < 30 %) including congestive heart failure and cardiac failure in whom sympathetic tone is critical for maintaining haemodynamic balance (see section 4.3).

Hypotension, bradycardia and sinus arrest

Clinical events of bradycardia and sinus arrest have been associated with PRECEDEX administration in young, healthy adult volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of PRECEDEX (see boxed warning above).

Decreased blood pressure and/or heart rate may occur with the administration of PRECEDEX. Based on clinical experience with PRECEDEX, if medical intervention is required, treatment may include decreasing or stopping the infusion of PRECEDEX, increasing the rate of intravenous fluid administration, elevation of the lower extremities and use of pressor medicines. Because PRECEDEX has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic medicines should be considered to modify vagal tone. In clinical trials, atropine and glycopyrrolate were effective in the treatment of most episodes of PRECEDEX-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

PRECEDEX decreases sympathetic nervous activity and therefore, these effects may be expected to be most pronounced in patients with desensitised autonomic nervous system control (i.e. elderly, diabetes, chronic hypertension, severe cardiac disease).

Prevention of hypotension and bradycardia should take into consideration the haemodynamic stability of the patient and normovolaemia must be ensured prior to the administration of PRECEDEX. Patients who are hypovolaemic may become hypotensive under PRECEDEX therapy. Therefore, fluid supplementation should be administered prior to and during the administration of PRECEDEX.

Additionally, in situations where other vasodilators or negative chronotropic medicines are administered, co-administration of PRECEDEX could have an additive pharmacodynamic effect and should be administered with caution and careful titration (see section 4.5).

Clinical events of bradycardia or hypotension may be potentiated when PRECEDEX is used concurrently with propofol or midazolam. Therefore, consider a dose reduction of propofol or midazolam (see section 4.5).

Transient hypertension

Transient hypertension has been observed primarily during the loading infusion, associated with initial peripheral vasoconstrictive effects of PRECEDEX and relatively higher plasma concentrations achieved during the loading infusion. If intervention is necessary, reduction of the loading infusion rate may be

considered. Following the loading infusion, the central effects of PRECEDEX dominate and the blood pressure usually decreases.

Hyperthermia or pyrexia

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

PRECEDEX may cause reduced lacrimation. Lubrication of the patient's eyes may be considered when administering PRECEDEX to avoid corneal dryness.

Paediatric population

Sedation for non-invasive procedures

The safety and efficacy of PRECEDEX have been established in paediatric patients 1 month to less than 18 years of age for sedation during non-invasive procedures. Use in this age group is based on one randomized double-blind, dose-ranging safety and efficacy trial in non-intubated paediatric patients 1 month to less than 17 years of age who required sedation prior to undergoing magnetic resonance imaging (MRI) scans. An increase in frequency of bradypnea, bradycardia, hypertension and hypotension was observed in paediatric patients treated with PRECEDEX (see section 4.8). The overall safety profile of PRECEDEX in paediatric patients was consistent with the known safety profile in adults (see section 4.8).

The safety and effectiveness of PRECEDEX have not been established in paediatric patients less than 1 month of age (see Section 4.2).

ICU sedation

The safety and efficacy of PRECEDEX have not been established in paediatric patients for ICU sedation. One assessor-blinded trial in paediatric 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 PRECEDEX for these patient populations.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P-450

In vitro studies indicate that clinically relevant cytochrome P450 mediated medicine interactions are unlikely.

Anaesthetics/sedatives/hypnotics/opioids

Co-administration of PRECEDEX is likely to lead to an enhancement of effects with anaesthetics, sedatives, hypnotics and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between PRECEDEX and isoflurane, propofol, alfentanil, and midazolam were demonstrated. However, due to pharmacodynamic effects, when co-administered with PRECEDEX a reduction in dosage of these medicines may be required.

Neuromuscular blockers

No clinically meaningful increases in the magnitude of neuromuscular blockade and no pharmacokinetic interactions were observed with PRECEDEX and rocuronium administration.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Labour and delivery

The safety of PRECEDEX in labour and delivery has not been studied and it is therefore not recommended for obstetrics, including caesarean section deliveries.

Breastfeeding

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

In two published clinical studies, a total of 14 women were given intravenous dexmedetomidine 6 micrograms/kg/hour for 10 minutes after delivery followed by continuous infusion of 0,2 – 0,7 microgram/kg/hour. Breast milk and maternal blood samples were collected at 0, 6, 12, and 24 hours after discontinuation of dexmedetomidine. Plasma and milk dexmedetomidine concentrations were detectable up to 6 hours in most individuals, up to 12 hours in one individual and undetectable in all at 24 hours. The milk-to-plasma ratio from single paired maternal milk and plasma concentrations at each time point ranged from 0,53 to 0,95. The relative infant dose was estimated to range from 0,02 to 0,098 %.

4.7 Effects on ability to drive and use machines

The patient should not drive or operate machinery or make legal decisions until 24 hours after recovery from a surgical procedure in which PRECEDEX was used.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Adult ICU sedation

Adverse event information is derived from the continuous infusion trials of PRECEDEX when dosed at a maintenance dose range of 0,2 to 0,7 microgram/kg/hr to achieve the desired clinical effect for sedation in the ICU setting. 1 007 adult patients received PRECEDEX. Treatment-emergent adverse events occurring at an incidence of > 2 % are provided in Table 1. The adverse reactions are displayed by system organ class.

The most frequently observed treatment-emergent adverse events include hypotension, hypertension, bradycardia, nausea, dry mouth and hypoxia (see section 4.4).

Table 1: Adverse events with an incidence > 2 % - Adult ICU sedation population

Body System (MedDRA)/ Adverse Event	**All PRECEDEX N = 1007**	**Randomised PRECEDEX N = 798**	**Placebo N = 400**
	n (%)	n (%)	n (%)
Blood and lymphatic system disorders			
Anaemia	19 (1,9 %)	18 (2,3 %)	7 (1,8 %)
Metabolism and nutrition disorders			
Hypovolaemia	31 (3,1 %)	22 (2,8 %)	9 (2,3 %)
Hyperglycaemia	17 (1,7 %)	15 (1,9 %)	7 (1,8 %)
Hypocalcaemia	7 (0,7 %)	7 (0,9 %)	0
Acidosis	6 (0,6 %)	5 (0,6 %)	4 (1,0 %)
Psychiatric disorders			
Agitation	20 (2,0 %)	16 (2,0 %)	11 (2,8 %)
Cardiac disorders			
Bradycardia	52 (5,2 %)	36 (4,5 %)	10 (2,5 %)
Atrial fibrillation	44 (4,4 %)	37 (4,6 %)	13 (3,3 %)
Tachycardia	20 (2,0 %)	15 (1,9 %)	17 (4,3 %)
Sinus tachycardia	6 (0,6 %)	6 (0,8 %)	2 (0,5 %)
Ventricular tachycardia	4 (0.4 %)	4 (0,5 %)	3 (0,8 %)

Vascular disorders			
Hypotension	248 (24,6 %)	191 (23,9 %)	48 (12,0 %)
Hypertension	123 (12,2 %)	101 (12,7 %)	76 (19,0 %)
Respiratory, thoracic and mediastinal disorders			
Atelectasis	29 (2,9 %)	23 (2,9 %)	13 (3.3 %)
Pleural effusion	23 (2,3 %)	16 (2,0 %)	4 (1,0 %)
Hypoxia	16 (1,6 %)	13 (1,6 %)	8 (2,0 %)
Pulmonary oedema	9 (0,9 %)	9 (1,1 %)	3 (0,8 %)
Wheezing	4 (0,4 %)	4 (0,5 %)	1 (0,3 %)
Gastrointestinal disorders			
Nausea	90 (8,9 %)	73 (9,1 %)	36 (9,0 %)
Dry mouth	35 (3,5 %)	22 (2,8 %)	4 (1,0 %)
Vomiting	34 (3,4 %)	26 (3,3 %)	21 (5,3 %)
General disorders and administration site conditions			
Pyrexia	35 (3,5 %)	31 (3,9 %)	15 (3,8 %)
Hyperthermia	19 (1,9 %)	16 (2,0 %)	12 (3,0 %)
Chills	17 (1,7 %)	14 (1,8 %)	13 (3,3 %)
Peripheral oedema	4 (0,4 %)	2 (0,3 %)	2 (0,5 %)
Investigations			
Decreased urine output	6 (0,6 %)	6 (0,8 %)	0
Injury, poisoning and procedural complications			
Post-procedural haemorrhage	15 (1,5 %)	13 (1,6 %)	10 (2,5 %)

Adult conscious sedation

Adverse event information is derived from the two primary Phase III trials for conscious sedation in which 318 adult patients received PRECEDEX.

Treatment-emergent adverse events occurring at an incidence of > 2 % are provided in Table 2. The adverse reactions are displayed by system organ class. The majority of the adverse events were assessed as mild in severity. The most frequent adverse events were hypotension, bradycardia, and dry mouth (see section 4.4)

Table 2: Adverse events with an incidence > 2 % - Adult conscious sedation population

Body System (MedDRA) / Adverse Event	**PRECEDEX N = 318**
	n (%)
Cardiac disorders	
Bradycardia[3]	45 (14,2 %)
Tachycardia[4]	17 (5,3 %)
Vascular disorders	
Hypotension[1]	173 (54,4 %)
Hypertension[2]	41 (12,9 %)
Respiratory, thoracic and mediastinal disorders	
Respiratory depression[5]	117 (36,8 %)
Hypoxia[6]	7 (2,2 %)
Bradypnoea	5 (1,6 %)
Gastrointestinal disorders	
Nausea	10 (3,1 %)
Dry mouth	8 (2,5 %)

[1]. Hypotension was defined in absolute and relative terms as systolic blood pressure of < 80 mmHg or < 30 % lower than pre-study medicine 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 medicine infusion value or diastolic blood pressure of > 100 mmHg.

[3]. Bradycardia was defined in absolute and relative terms as < 40 bpm or < 30 % lower than pre-study medicine infusion value.

[4]. Tachycardia was defined in absolute and relative terms as > 120 bpm or > 30 % greater than pre-study medicine infusion value.

[5]. Respiratory depression was defined in absolute and relative terms as RR < 8 bpm or > 25 % decrease from baseline.

[6]. Hypoxia was defined in absolute and relative terms as SpO2 < 90 % or 10 % decrease from baseline.

Paediatric sedation for MRI imaging

Adverse reaction information is derived from a trial for sedation of paediatric procedural during a non-invasive procedure in which 122 paediatric patients 1 month to less than 17 years of age undergoing MRI scans received PRECEDEX. In paediatric patients 1 month to less than 2 years old, the median total dose for the PRECEDEX low, middle, and high dose treatment groups was 8,30; 18,90, and 22,75 mcg, respectively. The median duration of treatment ranged from 52,5 to 69 minutes across treatment groups. In paediatric patients 2 to less than 17 years old, the median total dose for the PRECEDEX low, middle, and high dose treatment groups was 21,30; 43,90, and 80,25 mcg, respectively. The median duration of treatment ranged from 56,5 to 66 minutes across treatment groups.

All-causality treatment-emergent adverse reactions occurring in the combined age group of paediatric patients during the procedure at an incidence of > 5 % are provided in Table 3. The most frequent treatment-emergent adverse events were bradypnea, bradycardia, hypertension, and hypotension (see section 4.4). In the combined age group and in each age group, increased incidence in bradycardia and hypertension was observed with increasing PRECEDEX dose. Mild transient withdrawal symptoms of emergence delirium or agitation occurred in 3 of 122 patients after discontinuation of PRECEDEX infusion (see section 4.4). All reported treatment emergent adverse reactions were mild to moderate in severity and the majority resolved without medical intervention. No individual in the study required airway intervention, including a jaw thrust or insertion of a nasal or oral airway. A similar profile was observed in the paediatric patients 1 month to less than 2 years old and in paediatric patients 2 to less than 17 years old. Prespecified criteria for the vital signs to be reported as adverse events are footnoted below the table.

Table 3: Treatment-emergent adverse events with incidence > 5 % paediatric patients during non-invasive procedure

	PRECEDEX Low Dose (N = 42)	**PRECEDEX Middle Dose (N = 42)**	**PRECEDEX High Dose (N = 38)**	**Total (N = 122)**
Number (%) of Paediatric Patients	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Adverse Event				
Cardiac disorders				
Bradycardia[2]	24 (57)	24 (57)	27 (71)	75 (62) 5
Tachycardia	3 (7)	1 (2)	1 (3)	(4)
Vascular disorders				
Hypertension[3]	11 (26)	17 (41)	18 (47)	46 (38)
Hypotension[4]	13 (31)	11 (26)	6 (16)	30 (25)
Diastolic Hypertension[3]	3 (7)	3 (7)	4 (11)	10 (8)
Systolic Hypertension[3]	1 (2)	5 (12)	3 (8)	9 (7)
Respiratory, thoracic and mediastinal disorders				
Bradypnea[1]	33 (79)	27 (64)	22 (58)	82 (67)
Hypoxia[5]	6 (14)	3 (7)	1 (3)	10 (8)

N = Number of paediatric patients evaluable for adverse events.

[1] Bradypnea was defined as respiratory rate < 1st centile of the age adjusted normal range.

[2] Bradycardia was defined as a decrease in HR of 30 % from baseline or absolute HR ≤ 1st centile of the age adjusted normal range.

[3] For paediatric patients 1 month to less than 1 year old, hypertension was defined as supine systolic blood pressure ≥ 104 mm/Hg and/or diastolic blood pressure ≥ 56 mmHg measurements. For paediatric patients 1 to less than 17 years old: hypertension was defined as supine systolic blood pressure and/or diastolic blood pressure measurements ≥ 95th percentile for gender, age, and height.

[4] Hypotension was defined as a decrease in systolic blood pressure ≥ 30 % from baseline.

[5] Hypoxia was defined as oxygen saturation < 90 % for any duration.

Post-marketing experience

Table 4: Adverse events experienced during post-approval use of PRECEDEX

Body system (WHOART)	**Preferred term**
Body as a whole – general disorders	Allergic reaction, ascites, fever, hyperpyrexia, hypovolaemia, light anaesthesia, oedema, peripheral oedema, pain, syncope, withdrawal syndrome, rigors
Cardiovascular disorders, General	Blood pressure fluctuation, circulatory failure, cyanosis, abnormal ECG, heart disorder, hypertension, aggravated hypertension, pulmonary hypertension, hypotension, postural hypotension, pulmonary hypertension, myocardial infarction
Central and peripheral nervous system disorders	Convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder
Gastrointestinal system disorders	Abdominal pain, diarrhoea, eructation, mucosal ulceration, nausea, vomiting

Heart rate and rhythm disorders	Dysrhythmia, atrial dysrhythmia, atrial fibrillation, AV block, bradycardia, bundle branch block, cardiac arrest, extrasystoles, heart block, hypoxia, supraventricular tachycardia,T wave inversion, tachycardia, ventricular dysrhythmia, ventricular tachycardia
Liver and biliary system disorders	Increased AG ratio, increased GGT, abnormal hepatic function, hyperbilirubinaemia, increased aspartate transaminase (AST), increased alanine transaminase (ALT), jaundice
Metabolic and nutritional disorders	Acidosis, lactic acidosis, respiratory acidosis, diabetes mellitus, hyperglycaemia, hypoglycaemia, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphatase, increased non-protein nitrogen (NPN), thirst
Musculoskeletal system disorders	Muscle weakness
Myo-, endo-, pericardial & valve disorders	Angina pectoris, myocardial infarction, myocardial ischaemia
Platelet, bleeding & clotting disorders	Coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia

Psychiatric disorders	Agitation, anxiety, confusion, delirium, depression, hallucination, illusion, nervousness
Red blood cell disorders	Anaemia
Renal disorders	Increased blood urea, oliguria
Resistance mechanism disorders	Infection, fungal infection, sepsis
Respiratory system disorders	Adult respiratory distress syndrome, apnoea, bronchial obstruction, bronchospasm, coughing, dyspnoea, emphysema, haemoptysis, hypercapnia, hypoventilation, hypoxia, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, pulmonary oedema, respiratory depression, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Skin and appendages disorders	Rash erythematous, increased sweating
Urinary system disorders	Haematuria, acute renal failure, abnormal renal function, urinary retention
Vascular (extracardiac) disorders	Haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation
Vision disorders	Diplopia, photopsia, abnormal vision
White cell & RES disorders	Leukocytosis

Withdrawal

ICU sedation (adult)

Although not specifically studied, withdrawal symptoms similar to those reported for another alpha$_2$ adrenergic medicine (clonidine) may result when PRECEDEX is administered in excess of 24 hours and stopped abruptly. These symptoms include nervousness, agitation and headache (see section 4.8) accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

Conscious sedation

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

In paediatric patients, mild transient withdrawal symptoms of emergence delirium or agitation were seen after discontinuation of short-term infusions of PRECEDEX (< 2 hours).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit / risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

First-degree AV block and second-degree heart block may occur.

Bradycardia, with or without hypotension, and cardiac arrest may occur.

Because PRECEDEX has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. In clinical trials, atropine and glycopyrrolate were effective in the treatment of PRECEDEX-induced bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other Analgesics

Mechanism of action

Dexmedetomidine is an alpha$_2$-adrenoreceptor agonist.

The sedative actions of dexmedetomidine are believed to be mediated primarily by post-synaptic alpha$_2$-adrenoreceptors, which in turn act on inhibitory pertussis-toxin-sensitive G protein, thereby increasing conductance through potassium channels. The site of the sedative effects of dexmedetomidine has been attributed to the locus ceruleus. The analgesic actions are believed to be mediated by a similar mechanism of action at the brain and spinal cord level.

Alpha$_2$ selectivity is demonstrated following low and medium doses given slowly. Alpha$_2$ and alpha$_1$ activity is seen following rapid administration. Dexmedetomidine has no affinity for beta adrenergic, muscarinic, dopaminergic, or serotonin receptors.

5.2 Pharmacokinetic properties

Distribution

Following administration, dexmedetomidine exhibits the following pharmacokinetic characteristics: rapid distribution phase with a distribution half-life ($t_{½\,\alpha}$) of about six minutes; terminal elimination half-life ($t_{½}$) of approximately two hours; steady-state volume of distribution (V_{ss}) of approximately 118 L. Clearance has an estimated value of about 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female human individuals: the average binding was 94 % and constant across the different concentrations tested. Protein

binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was statistically significantly decreased in individuals with hepatic impairment compared with healthy individuals.

Dexmedetomidine is unlikely to cause clinically significant changes in the plasma protein binding of fentanyl, ketorolac, theophylline, digoxin, lidocaine, phenytoin, warfarin, ibuprofen and propranolol.

Elimination

Dexmedetomidine is eliminated almost exclusively by metabolism with 95 % of a radio-labelled dose being excreted in the urine and 4 % in the faeces. Approximately 34 % of the excreted metabolites are products of N-glucuronidation.

Special populations

Hepatic impairment

In adult individuals with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values were lower than in healthy individuals. The mean clearance values for individuals with mild, moderate, and severe hepatic impairment were 74 %, 64 % and 53 % respectively, of those observed in the normal healthy adult individuals. Mean clearances for free medicine were 59 %, 51 %, and 32 % respectively, of those observed in the normal healthy adult individuals.

Although dexmedetomidine is dosed to effect, it may be necessary to consider dose reduction depending on the degree of hepatic impairment (see section 4.2 and section 4.4).

Renal impairment

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{½}$, CL and V_{ss}) were not different in individuals with severe renal impairment (Cr Cl: < 30 mL/min) compared with healthy individuals.

Gender

No difference in dexmedetomidine pharmacokinetics due to gender was observed.

Elderly population

The pharmacokinetic profile of dexmedetomidine was not altered by age. The elderly are more sensitive to the effects of dexmedetomidine. In clinical trials, there was a higher incidence of bradycardia and hypotension in elderly patients (> 65 years of age).

Paediatric population

A population pharmacokinetic (PK) analysis was conducted with data collected from mechanically ventilated paediatric patients less than 17 years of age from 4 clinical studies. A linear 2-compartment model was found to best characterize the pooled dexmedetomidine concentration data. Mean PK parameters for each age group are summarized in Table 5.

Table 5: Geometric mean point estimates and 95 % confidence intervals of pk parameters by paediatric age group

Age Group	N	CL (L/h)	Vc (L)
1 to less than 6 months of age	14	6,94 (5,46; 8,81)	4,34 (3,25; 5,81)
6 to less than 12 months of age	15	8,15 (7,01; 9,47)	7,29 (5,57; 9,53)
12 to less than 24 months of age	13	10,76 (9,09; 12,74)	7,35 (5,59; 9,67)
2 to less than 6 years of age	26	15,89 (14,00; 18,04)	13,78 (10,66; 17,83)
6 to less than 17 years of age	28	24,45 (19,34; 30,92)	24,47 (17,06; 35,10)

Abbreviations: CL = plasma clearance, Vc = volume of the central compartment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

Sodium chloride

6.2 Incompatibilities

PRECEDEX must not be mixed with other medicines or diluents except those mentioned in section 6.6.

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

6.3 Shelf life

36 months.

Once diluted, the diluted solution should be used immediately. If not used immediately, the diluted solution may be stored at 2 °C – 8 °C during the 24 hour “in use” period. Discard any unused diluted solution after 24 hours.

6.4 Special precautions for storage

PRECEDEX should be stored in the original container at room temperature (at or below 25 °C). Do not refrigerate.

6.5 Nature and contents of container

Available in colourless 2 mL glass vials in packs of 5 and 25.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Directions for use

A controlled infusion device should be used to administer PRECEDEX.

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration. Do not use if medicine is discoloured or if precipitate matter is present.

Vials are intended for single patient use only.

Preparation of solution

Strict aseptic technique must always be maintained during handling of PRECEDEX infusion.

Preparation of infusion solutions is the same, whether for the loading dose or for the maintenance dose.

To prepare the infusion, withdraw 2 mL of PRECEDEX concentrate and add to 48 mL of 0,9 % sodium chloride solution to total 50 mL. Shake gently to mix well.

After dilution, PRECEDEX is intended for immediate use and should be discarded after 24 hours.

Administration with other fluids

PRECEDEX has been shown to be compatible when administered with the following intravenous fluids and medicines: Lactated Ringers, 5 % Dextrose in Water, 0,9 % Sodium Chloride in Water, 20 % Mannitol, thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine HCl, atropine sulphate, midazolam, morphine sulphate, fentanyl citrate and a plasma-substitute (i.e. Haemacel).

7. HOLDER OF CERTIFICATE OF REGISTRATION

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