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Orion Corporation, Orion Pharma
Global Pharmacovigilance and Patient Safety

RISK MANAGEMENT PLAN (RMP)

DEXMEDETOMIDINE

CONCENTRATE FOR SOLUTION FOR INFUSION, 100 MICROGRAMS/ML

DATA LOCK POINT 15-03-2021

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Orion Corporation
ORION PHARMA

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EU Risk Management Plan for Dexdor (dexmedetomidine hydrochloride)

RMP version to be assessed as part of this application:

RMP Version number:	9.1
Data lock point for this RMP:	21.1.2022
Date of final sign-off:	13.12.2021

Rationale for submitting an updated RMP:

Update according to Dexdor LEG procedure (EMEA/H/C/002268/LEG/016.3) and Dexdor PSUSA procedures EMEA/H/C/PSUSA/00000998/201903 and EMEA/H/C/PSUSA/00000998/202103.

Summary of significant changes in this RMP:

Reclassification of important potential risks of cardiac arrest and atrioventricular block to important identified risks. Addition of ´Increased mortality in younger ICU patients´ as an important potential risk in the summary of safety concerns; description of a DHPC in relation to risk mitigation

Addition of 'Rhabdomyolysis' as an important potential risk in the summary of safety concerns.

Deletion of 'Ischemic heart disease' and 'Respiratory depression' from the summary of safety concerns.

Version 9.1: The consolidated version of the RMP version 8 and 9 (Version 8 changes are highlighted in yellow)

Details of the currently approved RMP:

Version number: 7.2

Approved with procedure: EMEA/H/C/002268/II/0026

Date of approval (commission decision): 2.8.2018

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Dexmedetomidine hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Other hypnotics and sedatives (N05 CM18)
Marketing Authorisation <Holder> <Applicant>	Orion Corporation
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Dexdor
Marketing authorisation procedure	centralised
Brief description of the product	Chemical class Other hypnotics and sedatives (N05 CM18)
	Summary of mode of action Dexmedetomidine is a selective and specific alpha-2 adrenoceptor agonist. It is the pure dextro enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole.
	Important information about its composition None
Hyperlink to the Product Information	Product information is located in module 1.3.1
Indication(s) in the EEA	1. For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3) 2. For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

Dosage in the EEA	Indication 1. For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3). For hospital use only. Dexdor should be administered by healthcare professionals skilled in the management of patients requiring intensive care. Posology Patients already intubated and sedated may switch to dexmedetomidine with an initial infusion rate of 0.7 micrograms/kg/h which may then be adjusted stepwise within the dose range 0.2 to 1.4 micrograms/kg/h in order to achieve the desired level of sedation, depending on the patient's response. A lower starting infusion rate should be considered for frail patients. Dexmedetomidine is very potent and the infusion rate is given per hour. After dose adjustment, a new steady state sedation level may not be reached for up to one hour. Maximum dose The maximum dose of 1.4 micrograms/kg/h should not be exceeded. Patients failing to achieve an adequate level of sedation with the maximum dose of dexmedetomidine should be switched to an alternative sedative agent. Use of a loading dose of Dexdor in ICU sedation is not recommended and is associated with increased adverse reactions. Propofol or midazolam may be administered if needed until clinical effects of dexmedetomidine are established. Duration There is no experience in the use of Dexdor for more than 14 days. The use of Dexdor for longer than this period should be regularly reassessed. Indication 2. For sedation of non-intubated adult patients prior to and/or during dianostic or surgical procedures requiring sedation, i.e. procedural/awake sedation. Dexdor should be administered only by health care professionals skilled in the anaesthetic management of patients in the operating room or during diagnostic procedures. When Dexdor is administered for conscious sedation, patients should be continuously monitored by persons not involved in the conduct of the diagnostic or surgical procedure. Patients should be monitored continuously for early signs of hypotension, hypertension, bradycardia, respiratory depression, airway obstruction, apnoea, dyspnoea and/or oxygen desaturation (see section 4.8).

	Supplemental oxygen should be immediately available and provided when indicated. The oxygen saturation should be monitored by pulse oximetry. Dexdor is given as a loading infusion followed by maintenance infusion. Depending on the procedure concomitant local anaesthesia or analgesia may be needed in order to achieve the desired clinical effect. Additional analgesia or sedatives (e.g. opioids, midazolam or propofol) are recommended in case of painful procedures or if increased depth of sedation is necessary. The pharmacokinetic distribution half –life of Dexdor has been estimated to be around 6 min, which can be taken into consideration, together with the effects of other administered medications, when assessing the appropriate time needed for titration to desired clinical effect of Dexdor. Initiation of Procedural Sedation: - For adult patients: A loading infusion of 1.0 microgram/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 micrograms/kg given over 10 minutes may be suitable. Maintenance of Procedural Sedation: - For adult patients: The maintenance infusion is generally initiated at 0.6-0.7 microgram/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/hour. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

Pharmaceutical form(s) and strengths	Current (if applicable): Concentrate for solution for infusion, 100 micrograms/ml Proposed (if applicable): N/A
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

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

ICU sedation

Incidence and prevalence:

Rate of ICU admission and utilization per year for subjects from 18 to 44 years was 3.8 ICU admissions/ 1000 residents and 11.5 ICU days/ 1000 residents, for subjects from 45 to 64 years 11.9 admissions/ 1000 residents and 29.6 days/ 1000 residents, for subjects from 65 to 74 years 32.1 admissions/ 1000 residents and 82.8 days/ 1000 residents, for subjects from 75 to 84 years 51.1 admissions/ 1000 admissions and 154.2 days/ 1000 admissions and for subjects $\geqslant$ 85 years 58.2 admissions/ 1000 residents and 195.8 days/ 1000 residents (Seferian EG, Afessa B. Crit Care Med 2006; 34(8): 2113-9).

There was a large variation in ICU admission rates in a study of eight countries (6 European ones), the admissions per year varying from 216/100,000 population in the United Kingdom to 2353/100,000 in Germany. In France the figure is 426/100,000, in Netherlands 466/100,000 and in Belgium 1051/10000 (Wunsch H et al. Crit Care Med 2008; 36: 2787-2793). These variations are partly explained by different definitions of ICU. Prevalence information is not available.

Demographics of the target population – age, sex, race/ethnic origin:

In 851 consecutive mechanically ventilated patients with the age of at least 18 years who remained in university-affiliated, mixed medical-surgical ICUs for more than 48 hours, the mean age was 61.2 (±17.6) years and there were 42% of females and 58% of males (Rocker G, et al. Critical care medicine 2004; 32: 1149-1154).

Risk factors for the disease:

Not applicable. Patients treated in the ICU represent various heterogeneous backgrounds including operative, trauma and medical patients.

Main treatment options:

There are several treatments used for sedation in ICU, the most commonly used including propofol and midazolam.

Mortality and morbidity (natural history):

In ICU patients receiving mechanical ventilation, the hospital mortality has been reported to vary between 18% and 78%, with the long-term (1-4 years) mortality varying from 41 to 100% (Chelluri L et al. Archives of Internal Medicine 1995; 155: 1013-1022). In 851 consecutive mechanically ventilated patients with the age of at least 18 years who remained in university-affiliated, mixed medical-surgical ICUs for more than 48 hours, the mortality was 37.5% (Rocker G et al. Critical care medicine 2004; 32: 1149-1154). The overall mortality was 18.7% in a prospective, single-center, blinded study conducted in medical and respiratory intensive care unit of an academic health center (Guest TM et al. JAMA 1995; 273: 1945-49).

There was a very strong inverse correlation between ICU beds per capita and hospital mortality for ICU patients across countries in a study of Wunsch et al. (Wunsch H et al. Crit Care Med 2008; 36: 2787-2793).

Important co-morbidities:

In a 1-day prospective multicentre study of 13796 patients admitted to ICU, the type of ICU admission was medical in 28.2%, elective surgery in 23.3%, emergency surgery in 38.5% and trauma in 9.9%. The reason for admission was respiratory in 22.4%, cardiovascular in 22.0%, surveillance/ monitoring in 18.8%, neurologic in 14.6%, digestive/ liver in 9.5%, trauma in 8.1%, renal in 2.3% and other in 2.3% (Vincent J-L et al. JAMA 2009; 302: 2323-9).

The comorbid conditions of the patients included COPD in 16.7%, cancer in 15.1%, heart failure in 9.7%, diabetes mellitus in 9.7%, chronic renal failure in 9.1%, immunosupression in 4.3%, cirrhosis in 3.3%, hematologic cancer in 2.0% and HIV in 0.7%. 51% of the patients in ICU were considered infected, the infection was of respiratory origin in 64% (Vincent J-L, et al. JAMA 2009; 302: 2323-9).

The type of ICU admissions for 1369 patients was reported to be medical in 62.5%, surgical in 29.8% and trauma in 7.7% of patients admitted. The medical subgroups of subjects were cardiovascular in 35.6%, respiratory in 26.6%, neurologic in 14.6%, gastrointestinal in 10.5% and other in 12.6%. The surgical subgroups were gastrointestinal in 27.0%, respiratory in 22.1%, neurologic in 20.8%, cardiovascular in 19.1% and other in 11.0%. (ICUTracker, ICU Demographics, All patients and subpopulations January 1, 2004 – June 30, 2005. Medical Decisions Network, Medical Automation Systems).

Procedural sedation

Incidence, prevalence and demographics of the target population – age, sex, race/ethnic origin:

Procedural sedation is not a treatment on its own. The need for procedural sedation is linked to those diagnostic and therapeutic/surgical procedures where general anesthesia is not required, however patients need support in achieving comfort, controlling anxiety and pain during the procedure. Depending on the type of procedure, analgesia may be often controlled with local anesthetics, however, a systematic sedative might be required to achieve patient satisfaction and optimal settings for the procedure. In this respect procedural sedation mirrors the prevalence and incidence of the procedures themselves, where this way of aneshtesia is applicable. On overall level in the last two decades procedural sedation became the first choice in 10-30% of all the surgical procedures (Ghisi D et al. Minerva Anestesiol. 2005; 71 (9): 533-8)).

The use of procedural sedation is reported to be increasing (Saunders R et al. Ther Clin Risk Manag. 2018 Feb 28;14:393-401). Procedural sedation, or monitored anesthesia care (MAC), is used in a variety of ambulatory and in-hospital procedures. A systematic review from 2016, (Adams MA et al. Gastroenterol Hepatol 2016 Jun;12(6):361-70) studied monitored anesthesia care for endoscopic procedures and found an increase in the number of MAC procedures in thirteen eligible endoscopy studies from 0.4% to 71.2% in the US between year 2000 and 2011. In this review, a geographical variation in MAC utilization rates in the US was seen, illustrated by data from from 2000 to 2009 with the lowest rates (≤9%) of MAC use in the southwestern and western states and the highest in the northeastern states (41.9%; $p < 0.001$). In Canada, a marked increase in the percentage of MAC utilization from 8.4% to 19.1 % ($p<0.001$) in endoscopic procedures was recorded from 1993 to 2005. In most of the reviewed studies, increasing age was predictive of MAC use with an increase of the Odds Ratio with increasing age. Concerning race, the utilization of MAC was found to be more common in white patients in some of the studies. In one of the studies African American patients had a lower OR (0.76, 95%CI 0.610.94) of receiving MAC than white patients. This finding was repeated

in another study, but contradictory results were obtained in a study where the OR for MAC in African Americans was 1.37 (95%CI 1.22-1.54).

A recent study from the US (Chang B et al. J Patient Saf. 2018 Mar;14(1):9-16) examined The National Anesthesia Clinical Outcomes Registry database for all patient procedures from 2010 to 2013 consisting of 12 252 846 cases. Of these, 870 257(10.9%) patients received MAC in the Operating Room and 757 075 (20.2%) outside the Operating Room. Outside the Operating room 504 581 (32.6%) patients were recorded as belonging to the gastroenterology diagnosis group, 59 551 (34.3%) to cardiology, and 20 503(11.5%) to radiology, respectively.

Rabbitts et al (Anesth Analg. 2010 Oct;111(4):1011-5) published a survey study on ambulatory anesthesia for children in the US in 1996 and 2006. In this study data was extracted from The National Survey of Ambulatory Surgery database. In 1996, approximately 1.6 million children received ambulatory anesthesia. During 2006, a total of 2 300 651 (Standard Error [SE] 315 651) ambulatory anesthesia procedures were executed in children less than 15 years of age. Of these, MAC was administered to 44 462 (SE 10 149). 38 215 (SE 9823) of these patients were 5 to 14 years old. In 1996, the corresponding numbers were 53 943 (SE not given) and 39 351, respectively.

Because procedural sedation is not a treatment on its own, demographics fit the characteristics of the concerned procedures. I.e. in the two pivotal studies the types of surgeries/procedures were: orthopaedic, ophthalmic, plastic, vascular, breast biopsies and excision of lesions, and awake fibreoptic intubation. The two studies included 431 patients, age ranged between 18 and 93 year, mean age ranged 51.9 (SD15.3) – 56.8(SD16.5) year in the treatment groups. Sex distribution by treatment group varied between 49.3/50.7% and 28/72% female/male proportion, respectively, Ethnic origin in the MAC study was by treatment arms, Caucasian/Black/Asian/Hispanic/Other, in the 0.5 mcg/kg dexmedetomidine group, 67.9/17.2/0.7/13.4/0.7%; in the 1 mcg/kg dexmedetomidine group, 57.4/23.3/2.3/17.1/0%; in the placebo arm, 61.9/22.2/1.6/14.3/0%; in the AWAKE study, DEX arm, 52.7/18.2/0/29.1/0%; placebo arm, 74.0/10.0/0/16.0/0%. While Asian race was underrepresented in the pivotal studies conducted in the US, there are numerous publications from Asia in procedural sedation, where 99% of patients are with Asian origin.

Risk factors for the disease:

Not applicable. Patients undergo sedation for diagnostic or therapeutic procedures represent various heterogeneous backgrounds of health status and illness.

Main treatment options:

There are several treatments used for procedural sedation, the most commonly used including propofol, midazolam and opioids.

Mortality and morbidity (natural history):

Procedural sedation patient population is much diverse, and not characterisable by features of natural history of primary disease/morbidity. In general, procedural sedation is safe and risk of death is very low, i.e. a review of 55 articles evaluating the adverse effects in adults undergoing procedural sedation in the emergency department found no cases of death during 9652 procedures. (Bellolio MF et al, Acad Emerg Med. 2016; 23(2): 119-34).

Important co-morbidities:

Procedural/awake sedation encompasses a very heterogeneous collection of procedures and patients, managed by a wide variety of clinicians, thus likely comorbidities will be specific to each different clinical setting. Many patients can be expected to be essentially fit and well in some settings (e.g. certain

orthopaedic procedures), whereas in other cases all patients may have important systemic disease (e.g. cardiological procedures). In the phase 3 studies at least 75% of patients were ASA II or III meaning that they had some degree of systemic disease, while approximately 7% patients were ASA IV and had severe systemic disease considered a constant threat to life.

Part II: Module SII - Non-clinical part of the safety specification

Table SII.1: Safety concerns from nonclinical studies and their relevance to human usage (when applicable)

Key Safety findings (from non- clinical studies)	**Relevance to human usage**
Reproductive and developmental toxicity Dexmedetomidine had no effect on the male or female fertility in rat and no adverse effects were seen on gestation length or delivery. Body weight gain of offspring was decreased during lactation but otherwise there were no adverse effect on pup viability, physical growth and maturation or postnatal behavioural performances. Studies in lactating rats have shown that dexmedetomidine/ its metabolites are excreted in milk. Studies in pregnant animals indicate that dexmedetomidine is non-teratogenic. In rat studies, dexmedetomidine caused reduction in foetal/pup body weight which was associated with delayed skeletal ossification. No effect on foetal/pup body weight was seen in rabbit.	Recommendations to human usage are given in the SmPC for Dexdor in sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data.
Carcinogenicity and mutagenicity The absence of evidence of mutagenicity and preneoplastic changes in the data from subchronic studies obviate the need for carcinogenicity studies in the indication.	Appropriate statement is included in the SmPC for Dexdor in section 5.3 Preclinical safety data.

Conclusions on non-clinical data

There are no safety concerns that have not been adequately addressed by clinical data. No additional non-clinical data are considered to be needed.

Safety concerns
Important missing information: Pregnancy

Part II: Module SIII - Clinical trial exposure

A total of 61 completed clinical trials have been included in this RMP. The data on clinical trials are presented separately for the following three groups:

- Studies conducted in intensive care unit (ICU), presented as one grouping for all ICU studies, and in some sections separately for double-blind (DB) ICU studies
- Procedural sedation studies 2005-005 (MAC) and 2005-006 (AWAKE)
- Non-volunteer studies not conducted in the ICU (non-ICU), including also the procedural studies 2005-005 and 2005-006

These studies with a number of patients included in each treatment arm are presented in Table SIII.1 below.

Table SIII.1: Studies included in the RMP

Studies	Type of the study	Treatment and number of patients included
ICU -studies		
Placebo controlled double-blind studies		
W97-249	Part I: Open label study	Part I: Dexmedetomidine (n= 12)
	Part II: Randomised double-blind placebo-controlled study	Part II: Dexmedetomidine (n= 6) or placebo (n= 6)
W97-245	Part I: Open label study	Part I: Dexmedetomidine (n= 85)
	Part II: Randomised double-blind placebo-controlled study	Part II: Dexmedetomidine (n= 178) or placebo (n= 175)
W97-246	Part I: Open label study	Part I: Dexmedetomidine (n= 92)
	Part II: Randomised double-blind placebo-controlled study	Part II: Dexmedetomidine (n= 203) or placebo (n= 198)
W98-274	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 15) or placebo (n= 15)
Comparator controlled double-blind studies		
3005011	Randomised double-blind study with active comparator	Dexmedetomidine (n= 41) or midazolam (n= 16) or propofol (n= 28)
3005012	Randomised double-blind study with active comparator	Dexmedetomidine (n= 246) or propofol (n= 247)
3005013	Randomised double-blind study with active comparator	Dexmedetomidine (n= 247) or midazolam (n= 250)
2001-001	Randomised double-blind study with active comparator	Dexmedetomidine (n= 244) or midazolam (n=122)
Comparator controlled open studies		
W99-302	Randomised open label study with active comparator	Dexmedetomidine (n= 148) or propofol (n= 147)
W99-314	Randomised open label study with active comparator	Dexmedetomidine (n= 42) or propofol (n= 41)

Studies	Type of the study	Treatment and number of patients included
1999-016	Randomised open label study with active comparator	Dexmedetomidine (n= 14) or midazolam (n= 13)
Non-comparator controlled open studies		
W99-294	Randomised open label parallel-group study	Dexmedetomidine (n= 192)
W99-315	Randomised open label study	Dexmedetomidine (n= 84)
3005010	Randomised open label study	Dexmedetomidine (n= 221)
3005016	Non-randomised, open, non-controlled phase I study	Dexmedetomidine (n= 13)
W98-263/264	Open label study with an extension phase	Dexmedetomidine (n= 20)
Procedural sedation studies		
Placebo controlled double-blind studies		
2005-005	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 263) or placebo (n= 63)
2005-006	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 55) or placebo (n= 50)
Non-ICU studies		
2005-005	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 263) or placebo (n= 63)
2005-006	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 55) or placebo (n= 50)
3005001	Randomised single-blind placebo-controlled study	Dexmedetomidine (n= 33) or placebo (n= 16)
3005002	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 44) or placebo (n= 42)
3005003	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 22) or placebo (n= 19)
3005004	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 35 or placebo (n= 19)
3005006	Part I: Open feasibility study	Dexmedetomidine (n= 6)
	Part II: Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 44) or placebo (n= 43)
DEX-95-002	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 200) or placebo (n= 101)
DEX-95-004	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 205) or placebo (n= 101)
DEX-96-012	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 25) or placebo (n= 9)
DEX-96-016	Randomised open label placebo-controlled study	Dexmedetomidine (n= 29) or placebo (n= 15)
DEX-96-017	Part I: Open, dose of esmolol verification study	Dexmedetomidine (n= 14) or placebo (n= 6)

Studies	Type of the study	Treatment and number of patients included
	Part II: Randomised double-blind placebo-controlled study	
DEX-96-021	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 126) or placebo (n= 123)
DEX-96-023	Part I: Open label study	Dexmedetomidine (n= 4)
	Part II: Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 2)
DEX-9201	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 15) or placebo (n= 15)
DEX-9203	Randomised double-blind study with active comparator	Dexmedetomidine (n= 20) or midazolam (n= 20)
F-MPV-1440-CL-0288	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 8) or placebo (n= 8)
F-DEX-CL-0189-CHE	Part I: Open label study	
	Part II: Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 8) or placebo (n= 8)
F-DEX-CL-0189-NLD	Open label study	Dexmedetomidine (n= 9)
F-DEX-CL-0189-SF	Randomised double-blind placebo and active controlled study	Dexmedetomidine (n= 48) or fentanyl (n= 24) or placebo (n= 24)
F-DEX-CL-0190-FIN	Part I: Open label dose finding study	Dexmedetomidine (n= 4)
	Part II: Randomised double-blind study with active comparator	Dexmedetomidine (n= 10) or midazolam (n= 10)
F-DEX-CL-0192-USA	Randomised double-blind placebo-controlled dose escalation study	Dexmedetomidine (n= 18) or placebo (n= 6)
F-DEX-CL-0289-NLD	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 25) or placebo (n= 25)
F-DEX-CL-0289-SF	Randomised double-blind study with active control	Dexmedetomidine (n= 48) or oxycodone (n= 24) or diclofenac (n= 24)
F-DEX-CL-0290-FIN	Randomised double-blind study with active control	Dexmedetomidine and placebo (n= 64) or dexmedetomidine and fentanyl (n= 64) or midazolam and fentanyl (n= 64)
F-DEX-CL-0293-FIN	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 52) or placebo (n= 51)
F-DEX-CL-0389-SF	Part I: Double-blind placebo controlled dose-finding study	Dexmedetomidine (n= 15) or placebo (n= 5)
	Part II: Double-blind placebo and active controlled study	Dexmedetomidine (n= 35) or midazolam (n= 36) or placebo (n= 35)
F-DEX-CL-0390-FIN	Part I: Open label dose finding study	Dexmedetomidine (n= 15)
	Part II: Randomised double-blind blind placebo controlled study	Dexmedetomidine (n= 10) or placebo (n= 10)
F-DEX-CL-0392-FIN	Part I: Randomised, double-blind placebo controlled dose finding study	Dexmedetomidine (n= 24) or placebo (n= 8)
	Part II: Randomised double-blind placebo and active controlled study	Dexmedetomidine (n= 20) or diazepam (n= 20) or placebo (n= 20)
F-DEX-CL-0489-SF	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 15) or placebo (n= 15)
F-DEX-CL-0490-FIN	Part I: Open dose finding study	Dexmedetomidine (n= 11)
		Dexmedetomidine and atipamezole (n= 16)

Studies	Type of the study	Treatment and number of patients included
	Part II: Open dose finding study for atipamezole	Dexmedetomidine and atipamezole (n= 24)
		Dexmedetomidine and placebo (n= 24)
	Part III: Randomised double-blind placebo and active controlled study	Midazolam and placebo (n= 24)
		Total: dexmedetomidine (n=59) or midazolam (n= 24) or atipamezole (n= 16)
F-DEX-CL-0491-GBR	Randomised open non-comparative study	Dexmedetomidine (n= 49)
DEX-CL-0492-FIN	Part I: Open label dose verification study	
	Part II: Randomised double-blind placebo-controlled study	Total: Dexmedetomidine (n= 5) or placebo (n= 2)
F-DEX-CL-0589-SF	Randomised double-blind placebo and active treatment controlled study	Dexmedetomidine (n= 59) or oxycodone (n= 20) or placebo (n= 20)
F-DEX-CL-0592-FIN	Part I: Open label dose verification study	Dexmedetomidine (n= 9)
	Part II: Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 40) or placebo (n= 40)
F-DEX-CL-0689-SF	Part I: Open label study	
	Part II: Randomised double-blind placebo-controlled study	Dexmedetomidine and dexmedetomidine (n= 15)
		Dexmedetomidine and placebo (n= 15)
		Placebo and placebo (n= 15)
F-DEX-CL-0791-DEU	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 27) or placebo (n= 28)
F-DEX-CL-0890-FIN	Part I: Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 30) or placebo (n= 12)
	Part II: Randomised double-blind placebo-controlled study with active control	Dexmedetomidine (n= 30) or midazolam (n= 30) or placebo (n= 30)
F-DEX-CL-0990-FIN	Randomised double-blind placebo-controlled study with active control	Dexmedetomidine (n= 34) or midazolam (n= 32) or placebo (n= 33)
F-DEX-CL-1089-SF	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 15) or placebo (n= 15)
F-DEX-CL-1090-FIN	Randomised double-blind study with active control	Dexmedetomidine and placebo (n= 64) or dexmedetomidine and fentanyl (n= 64) or midazolam and fentanyl (n= 64)
F-DEX-CL-1189-SF	Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 17) or placebo (n= 12)
F-DEX-CL-1289-SF	Part I: Open dose finding study	
	Part II: Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 15) or placebo (n= 15)
F-MPV-1440-CL-0188	Part I: Open randomised dose finding study	Dexmedetomidine (n= 20)
	Part II: Randomised double-blind placebo-controlled study	Dexmedetomidine (n= 19) or placebo (n= 20)
PT931	Open non-randomised non-comparative study	Dexmedetomidine (n= 10)

The exposures in clinical trials are presented for all ICU studies, DB ICU studies, procedural studies and non-ICU studies separately for the duration and dose of infusion Tables SIII.2 and Table SIII.3, respectively, for age group and gender in Table SIII.4, and for different ethnic origins in Table SIII.5. Clinical trial exposure in certain special populations is shown in Table SIII.6 for the ICU population. This table shows the number of persons included in the ICU population clinical trials that had certain medical

conditions (e.g. hepatic or renal failure) in their medical history searched with MedDRA SMQs and *ad hoc* –search categories specified in Annex 7: Other supporting data. Clinical trial exposure in special populations in procedural sedation studies is not presented in Table SIII.6, as medical history for these studies is not in the pooled dataset.

Clinical trial exposure by duration

Table SIII.2a: Clinical trial exposure by duration in all ICU studies

Duration of treatment	Persons (n, (%))	Person time (subject days)
≤24 hours	1473 (70.0)	830.0
>24 hours	242 (11.5)	369.2
>48 hours	124 (5.9)	320.1
>72 hours	98 (4.7)	347.5
>96 hours	46 (2.2)	210.6
>120 hours	90 (4.3)	598.8
> 240 hours	22 (1.0)	267.9
Unknown	8 (0.4)	0.0
Total	2103	2944.1

Table SIII.2b: Clinical trial exposure by duration in DB ICU studies

Duration of treatment	Persons (n, (%))	Person time (subject days)
≤24 hours	791 (57.8)	512.9
>24 hours	223 (16.3)	345.8
>48 hours	116 (8.5)	301.0
>72 hours	93 (6.8)	329.9
>96 hours	44 (3.2)	202.0
>120 hours	102 (7.5)	789.4
Total	1369	2481.0

Table SIII.2c: Clinical trial exposure by duration in procedural studies

Duration of treatment	Persons (n, (%))	Person time (subject days)
<=1 H	111 (34.9)	3.1
<=2 H	137 (43.1)	8.0
<=3 H	47 (14.8)	4.9
<=4 H	17 (5.3)	2.4
<=5 H	4 (1.3)	0.8
<=6 H	1 (0.3)	0.2
<=7 H	1 (0.3)	0.3
Total	318	19.6

Table SIII.2d: Clinical trial exposure by duration in Non-ICU studies

Duration of treatment	Persons	Person time (subject days)
≤24 hours	1267 (56.8)	214.1
>24 hours	2 (0.1)	3.1
>48 hours	37 (1.7)	83.6
>72 hours		
>96 hours		
>120 hours		
Unknown	924 (41.4)	0.0
Total	2230	300.7

Clinical trial exposure by dose

Table SIII.3a: Clinical trial exposure by dose in all ICU studies

Dose/hour	Persons (n, (%))	Person time (subject days)
≤0.7 mcg/kg/hour	1519 (72.2)	1528.6
>0.7 to 1.1 mcg/kg/hour	370 (17.6)	801.0
>1.1 mcg/kg/hour	201 (9.6)	611.7
Unknown	13 (0.6)	2.8
Total	2103	2944.1

Table SIII.3b: Clinical trial exposure by dose in DB ICU studies

Dose/hour	Persons (n, (%))	Person time (subjects days)
≤0.7 mcg/kg/hour	877 (64.1)	1162.5
>0.7 to 1.1 mcg/kg/hour	308 (22.5)	766.9
>1.1 mcg/kg/hour	182 (13.3)	550.8
Unknown	2 (0.1)	0.7
Total	1369	2480.9

Table SIII.3c: Clinical trial exposure by dose in procedural studies

Dose/hour	Persons (n, (%))	Person time (subject days)
≤0.7 mcg/kg/hour	39 (12.3)	3.9
>0.7 to 1.1 mcg/kg/hour	97 (30.5)	7.8
>1.1 mcg/kg/hour	182 (57.2)	7.9
Total	318	19.6

Table SIII.3d: Clinical trial exposure by dose in all Non-ICU studies

Dose/hour	Persons (n, (%))	Person time (subjects days)
≤0.7 mcg/kg/hour	597 (26.8)	194.4
>0.7 to 1.1 mcg/kg/hour	132 (5.9)	10.4
>1.1 mcg/kg/hour	275 (12.3)	12.9
Unknown	1226 (55.0)	83.1
Total	2230	300.7

Clinical trial exposure by age group and gender*

Table SIII.4a: Clinical trial exposure by age group and gender in all ICU studies

Age group and gender	Persons (n)			Person time (subject days)		
	Female	Male	Total	Female	Male	Total
≤65 years	318	894	1212	497.5	1101.1	1598.6
>65 years	184	420	604	321.3	494.3	815.6
>75 years	118	161	279	237.3	292.4	529.7
Total	620	1475	2095	1056.1	1887.8	2943.9

Table SIII.4b: Clinical trial exposure by age group and gender in DB ICU studies

Age group and gender	Persons (n)			Person time (subject days)		
	Female	Male	Total	Female	Male	Total
≤65 years	223	538	761	439.8	879.7	1319.5
>65 years	147	255	402	303.3	384.4	687.7
>75 years	92	114	206	210.7	263.2	473.9

Table SIII.4b: Clinical trial exposure by age group and gender in DB ICU studies

Age group and gender	Persons (n)			Person time (subject days)		
	Female	Male	Total	Female	Male	Total
Total	462	907	1369	953.8	1527.3	2481.1

Table SIII.4c: Clinical trial exposure by age group and gender in procedural studies

Age group and gender	Persons (n)			Person time (subject days)		
	Female	Male	Total	Female	Male	Total
≤65 years	113	117	230	6.7	7.1	13.8
>65 years	24	35	59	1.6	2.1	3.7
>75 years	15	14	29	1.3	0.9	2.2
Total	152	166	318	9.6	10.1	19.7

Table SIII.4d: Clinical trial exposure by age group and gender in Non-ICU studies

Age group and gender	Persons (n)			Person time (subject days)		
	Female	Male	Total	Female	Male	Total
≤65 years	432	521	953	47.1	132.9	180.0
>65 years	79	202	281	15.7	89.6	105.3
>75 years	31	34	65	4.1	8.8	12.9
Unknown	1	1	2	0.0	2.0	2.0
Total	543	758	1301	66.9	2333	300.2

*Subject included if study treatment duration (gender and age) is known

Clinical trial exposure by ethnic origin*

Table SIII.5a: Clinical trial exposure by ethnic origin in all ICU studies

Ethnic origin	Persons (n)	Person time (subject days)
Caucasian	1877	2652.8
Black	50	112.7
Asian	52	48.2
Hispanic	91	92.1
Other	24	37.9
Unknown	1	0.3

Table SIII.5b: Clinical trial exposure by ethnic origin in DB ICU studies

Ethnic origin	Persons (n)	Person time (subject days)
Caucasian	1290	2275.3
Black	32	99.6
Asian	13	16.7
Hispanic	23	65.2
Other	11	24.3

Table SIII.5c: Clinical trial exposure by ethnic origin in procedural studies

Ethnic origin	Persons (n)	Person time (subject days)
Caucasian	194	11.6
Black	63	4.2
Asian	4	0.4
Hispanic	56	3.4
Other	1	0.0

Table SIII.5d: Clinical trial exposure by ethnic origin in Non-ICU studies

Ethnic origin	Persons (n)	Person time (subject days)
Caucasian	920	242.2

Table SIII.5c: Clinical trial exposure by ethnic origin in procedural studies

Ethnic origin	Persons (n)	Person time (subject days)
Caucasian	194	11.6
Black	63	4.2
Asian	4	0.4
Hispanic	56	3.4
Other	1	0.0

Table SIII.5d: Clinical trial exposure by ethnic origin in Non-ICU studies

Ethnic origin	Persons (n)	Person time (subject days)
Black	143	25.0
Asian	9	1.5
Hispanic	87	16.5
Other	8	1.3
Unknown	139	14.2

*Subject included if study treatment duration is known

Clinical trial exposure by special population*

Table SIII.6: Clinical trial exposure by special population, All ICU studies

Population	Persons	Person time (subject days)
Hepatic failure	47	126.4
Renal failure	301	861.3
Ischaemic heart disease	162	435.1
Cardiac or vascular abnormality	642	1763.9
Nervous system disorder	182	487.7
Diabetes mellitus	299	804.3
Sepsis	286	907.2

*Medical history is available for studies 1999016, 2001-001, 3005011, 3005012, 3005013 and 3005016 (n= 805)

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Data from 16 studies conducted in the ICU setting and from 45 non-volunteer studies conducted outside the ICU have been pooled together to form a basis for the adverse event data. Eight of the 16 ICU studies were double-blind (4 placebo-controlled and 4 comparator-controlled) and 8 open-label (3 comparator-controlled and 5 non-comparator –controlled). These data include a total of 2103 and 2230 patients exposed to dexmedetomidine in and outside the ICU, respectively.

There is a long post-marketing experience reaching up to 13 million patient days with dexmedetomidine worldwide since 1999.

The exclusion criteria for the ICU studies included in the RMP are shown in Table SIV.1 and Table SIV.2 below. The exclusion criteria for the procedural sedation studies are shown in Table SIV.3.

Table SIV.1: Table of the exclusion criteria for the comparator controlled double-blind studies

	3005011	3005012	3005013	2001-001
Exclusion Criteria				
Acute severe neurological disorder	X	X	X	X[1]
Uncompensated acute circulatory failure at time of randomisation (mean arterial pressure < 55 mmHg despite volume and vasopressors	X	X	X	
Severe bradycardia (HR < 50 bpm)	X	X	X	X
AV conduction block II-III (unless pacemaker installed)	X	X	X	X
Severe hepatic impairment bilirubin > 101 µmol/l	X	X	X	
Child Pugh score > 9				X
Required neuromuscular blocking agents during study period except for insertion of endotracheal tube	X	X	X	X
Loss of hearing or vision or any other condition which would interfere with RASS assessment	X	X	X	
Burn injuries or other injuries requiring anaesthesia or surgery		X	X	X
Use of alpha-2 agonists or alpha-2 antagonists at randomisation	X			
Use of alpha-2 agonists or alpha-2 antagonists within 24h prior to randomisation		X	X	
Known allergy to study drugs	X	X	X	X
Sedation for therapeutic indications rather than to tolerate ventilator e.g. epilepsy		X	X	
Unlikely to require continuous sedation e.g. Guillain-Barre syndrome		X	X	
Unlikely to be weaned from mechanical ventilation e.g. advanced Amytrophic Lateral Sclerosis		X	X	
Distal paraplegia		X	X	
Positive pregnancy test or currently lactating	X	X	X	X
Participation in a trial with experimental drug in last 30 days	X	X	X	X
Concurrent participation in any other interventional study	X	X	X	
Previous participation in this study	X	X	X	X
Any other condition which in the Investigators opinion would make it detrimental for the subject to participate in the study		X	X	X
Unstable angina, acute MI, LVEF < 30%, HR < 50bpm, SBP < 90mmHg, conduction abnormalities except 1st degree A-V block, rate controlled AF.				X
Dialysis				X
Seizure, drug dependence, psychiatric illness, incarceration, life expectancy < 60 days.				X

[1]Serious CNS pathology/trauma

Table SIV.2: Exclusion criteria by protocol for the placebo controlled double-blind studies, open label studies and studies of the loading dose (ICU studies)

	W97-249	W97-245	W97-246	W98-274	1999-016	W99-302	W99-314	W99-294	W99-315	3005010	W263/264	3005016
Exclusion criteria												
Serious CNS trauma	X	X	X	X	X	X	X	X	X	X	X	X
Intracranial surgery during current hospitalisation	X	X	X	X				X	X	X	X	X
Required neuromuscular blocking agents during study period except for insertion of endotracheal tube	X	X	X		X			X	X	X	X	X[1]
Required epidural or spinal analgesia during ICU stay	X	X	X		X	X	X	X	X	X	X	
Burn injuries or other conditions requiring regular anaesthesia or surgery												X

	W97-249	W97-245	W97-246	W98-274	1999-016	W99-302	W99-314	W99-294	W99-315	3005010	W263/264	3005016
Exclusion criteria												
Opiates or benzodiazepines contraindicated	X	X	X		X				X **			
Opiates or propofol contraindicated				X		X	X	X		X	X	
Serious allergy to any medicine likely to be administered during study	X	X	X	X	X	X	X	X	X	X	X	X
Grossly obese	X	X	X	X	X	X		X		X	X	
Currently hospitalised for drug overdose	X	X	X	X							X	
Alpha-2 agonists or alpha-2 antagonists contraindicated	X	X	X	X	X			X	X	X	X	X
Current or in last 30 days treated with alpha-2 agonists or alpha-2 antagonists	X	X	X	X	X	X	X	X	X	X	X	X
Participation in a trial with experimental drug in last 30 days	X	X	X	X	X	X	X	X	X	X	X	X
Terminally ill, life duration no more than 24 hours	X	X	X	X							X	
Had or were expected to have treatment withdrawn or withheld due to poor prognosis												X
Unable to undergo any procedure required by protocol		X	X	X	X	X	X	X	X	X		X
Demonstrated tolerance to standard sedating medication		X	X	X				X	X	X		
Receiving sedation for therapeutic indications rather than to tolerate the ventilator (e.g. epilepsy)												X
Unlikely to require continuous sedation during mechanical ventilation (e.g. Guillain-Barré syndrome)												X
Unlikely to be weaned from mechanical ventilation												X
Previously received dexmedetomidine		X	X		X	X	X	X	X	X	X	
Unstable/uncontrolled diabetes		X	X	X							X	
Excessive bleeding likely to require re-surgery		X	X	X				X	X	X	X	
Had received midazolam for maintenance of anaesthesia		X										
Ejection fraction less than 30%						X						
Clinically significant arrhythmia or other cardiac condition or factor which, in investigators opinion, may have increased risk to patient or precluded obtaining satisfactory data		X	X	X						X	X	
Any other factor which, in investigators opinion, may have increased risk to patient or precluded obtaining satisfactory data e.g. dobutamine > 8 µg/kg.min or epinephrine > 4 µg/min.						X	X					
Any other factor which, in investigators opinion, may have increased risk to patient or precluded obtaining satisfactory data e.g. high vagal tone									X			
Pre-existing severe bradycardia disorders, pre-existing severe ventricular dysfunction							X		X			
Unstable angina, acute MI, LVEF < 30%, HR < 50bpm, SBP < 90mmHg, conduction abnormalities except 1st degree A-V block, rate controlled AF.					X							
Uncompensated acute circulatory failure at screening (severe hypotension with MAP												X

	W97-249	W97-245	W97-246	W98-274	1999-016	W99-302	W99-314	W99-294	W99-315	3005010	W263/264	3005016
Exclusion criteria												
< 55 mmHg despite vasopressor and inotrope therapy)												
HR < 50 beats/min for longer than 5 min between screening and starting study treatment												X
AV-conduction block II-III (unless pacemaker installed)												X
Hospitalised due to burns, transplantation or received chemotherapeutic agent within last 3 months.					X							
Severe hepatic failure				X						X		X
Renal impairment										X		
Positive pregnancy test or currently lactating												X
Child Pugh 9 or greater,, required dialysis, known HIV, ARC or AIDS, active hepatitis, seizure disorder, substance abuse, psychiatric illness, incarceration or terminally ill.					X							

* recommended only, ** opiates only, 1 need for continuous muscle relaxation

Table SIV.3: Table of the exclusion criteria for the placebo controlled double-blind studies in procedural sedation

	2005-005	2005-0006
Exclusion criteria		
Previous exposure to any experimental drug within 30 days prior to study drug administration	X	X
Previously enrolled in this study	X	
Subject received general anesthesia within 7 days prior to study entry	X	
Subject required endotracheal intubation or laryngeal mask airway (LMA)	X	
Central nervous system (CNS) disease with an anticipated potential for increased intracranial pressure	X	
Central nervous system (CNS) disease with an anticipated increased intracranial pressure or cerebrospinal fluid (CSF) leak		X
Uncontrolled seizure disorder and/or known psychiatric illness that could confound a normal response to sedative treatment	X	X
Presence of acute alcohol intoxication		X
Subject required epidural or spinal anesthesia	X	
Subject had received treatment with an α-2-agonist or antagonist within 14 days prior to the scheduled surgery/procedure	X	
Current (within 14 days of study entry) treatment with an α-2-agonist or antagonist		X
Subject for whom benzodiazepines, DEX, or other α-2-agonists were contraindicated	X	X
Subject for whom opiates were contraindicated	X	
Subject received an intravenous (IV) or by mouth (PO) opioid within 1 hour or intramuscularly within 4 hours of the start of study drug administration		X
Subject had received an IV opioid within 1 hour, or PO/IM opioid within 4 hours, of the start of study drug administration	X	
Subject had known elevated SGPT (ALT) and/or SGOT (AST) values of > 2 times the upper limit of normal (ULN) within the 2 months prior to screening, and/or a history of liver failure	X	

	2005-005	2005-0006
Exclusion criteria		
Subject had elevated alanine aminotransferase (SGPT or ALT) and/or aspartate aminotransferase (SGOT or AST) values of ≥ 2 times the upper limit of normal (ULN)		X
Subject had acute unstable angina, acute myocardial infarction documented by laboratory findings in the past 6 weeks, heart rate < 50 bpm, SBP < 90 mmHg, or third-degree heart block unless the subject had a pacemaker	X	X
Subject had any other condition or factor, which, in the Investigator's opinion, could increase the risk to the subject	X	X

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.4: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Please see the Table SIII.6 'Clinical trial exposure by special population, All ICU studies' for available data in patients with hepatic impairment, renal impairment, ischaemic heart disease and cardiac or vascular abnormality. No data available for immunocompromised patients and for patients with a disease severity different from inclusion criteria in clinical trials
Population with relevant different ethnic origin	Please see the tables SIII.5a-d 'Clinical trial exposure by ethnic origin' for data on exposure in different ethnic groups
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not included in the clinical development program

Populations not-studied that are considered as missing information are included in Table SIV.5 below.

Table SIV.5: Important missing information

Safety concerns due to limitations of the clinical trial programme		**Outstanding concern?**
Safety concern	**Comment**	**Yes/No**
Pregnancy	Clinical trial data on the use of dexmedetomidine in pregnant or lactating women are very limited, and the information received from spontaneous reports is very limited concerning foetal effects of dexmedetomidine	Yes

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The calculations are based on the World Health Organisation (WHO) defined daily dose (DDD) of 1 000 µg. For Dexdor the exposure estimates are based on Orion ex-factory sales and for Precedex estimates are based on audited pharmacy and/or wholesaler sales of dexmedetomidine received from the IMS Health Midas Database.

At the time of the marketing authorisation application for Dexdor, the total patient exposure to medicinal products containing dexmedetomidine was estimated to be more than 1,5 million patient days until the end of April 2010.

SV.1.2 Exposure

The estimated cumulative post-marketing patient exposure to Dexdor during the period September 2011 - February 2019 is estimated as 4 196 558 patient days equalling to 11 497 patient years.

For dexmedetomidine product Precedex sold by Hospira, a Pfizer company, sales data is available dating back to the first quarter of 2005. The cumulative post-marketing exposure until February 2019 is estimated as 12 556 783 patient days equalling to 34 379 patient years.

Based on these figures presented above the cumulative exposure to both dexmedetomidine products Dexdor and Precedex can be estimated to exceed 16 million patient days.

Table SV.1: Cumulative post-marketing patient exposure for Dexdor and Precedex.

Product	**Period**	**Patient days**	**Patient years**
Dexdor	Sep 2011 – Feb 2019	4 196 558	11 497
Precedex	Dec 1999 – Feb 2019	12 556 783	34 379
	TOTAL	**16 753 341**	**45 876**

A drug utilisation study to investigate the use of dexmedetomidine in clinical practice in EU has been completed (study 3005021, DexDUS). Based on this retrospective review of 2000 patients at 16 hospitals in 4 EU countries, 36.6% of the administrations were given for use that deviated in some way (indication, dose, location of use or age group) from the original SmPC recommendations. The most common use that deviated from the original SmPC recommendations was perioperative use (15.5% of administrations). In addition, 5.8% of administrations were given to paediatric patients, of which the vast majority occurred in an ICU environment. Uses other than ICU sedation were normally conducted with an appropriate level of patient monitoring and with the recommended adult dose.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

No ICSRs including misuse for illegal purposes were found from the Drug Safety database including the post-marketing data.

Dexdor is intended for use only at hospital by persons skilled in the management of patients in intensive care. The MAH considers that the potential for Dexdor to be misused for illegal purposes is very low.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable as not an initial submission.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

According to the Dexdor LEG 16.3 procedure (EMEA/H/C/002268/LEG/016.3) conclusion:

- "Increased mortality in younger ICU patients" is a new important potential risk

According to the Dexdor PSUSA procedure EMEA/H/C/PSUSA/00000998/202103, the following changes to the safety concerns have been made:

- Ischemic heart disease and Respiratory depression, both previously classified as important potential risks, have been removed from the summary of safety oncerns
- Rhabdomyolysis is a new important potential risk

Dexdor PSUSA procedure (EMEA/H/C/PSUSA/00000998/201903) product information amendments were requested by RMS regarding important potential risks of AV block and cardiac arrest. Along with these amendments AV block and cardiac arrest were reclassified as important identified risks.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

The following important identified risks are presented below in more detail: atrioventricular block, cardiac arrest, bradycardia, hypotension, hypertension, hyperglycaemia and withdrawal syndrome.

In addition, the following important potential risks are presented: cortisol suppression, convulsions, hypothermia, torsade de pointes/QT prolongation, overdose, off-label use, increased mortality in younger ICU patients and rhabdomyolysis. There are no data to confirm positive causal relationship between dexmedetomidine and these events. The selection for potential risks was based on the following:

- Based on the CHMP Day 120 List of Questions, the list of important potential risks was expanded to include also cortisol suppression, convulsions, hypothermia, respiratory depression, tachypnoeic potential, overdose, and off-label use, and the scope of the potential risk of atrioventricular block was widened to also cover atrioventricular block grade I. Cortisol suppression was considered as a potential imidazole class effect. Convulsions, hypothermia and respiratory depression have been reported to be adverse effects of clonidine, another alpha-2-adrenergic receptor agonist, when given in high doses. Taphypnoeic potential was deleted from the list of the RMP version 6 due to lack of any supporting data. Respiratory depression was deleted from the list in the RMP version 9 based on Dexdor PSUSA procedure EMEA/H/C/PSUSA/00000998/202103 conclusion.

- Safety signals of ventricular tachycardia and QT prolongation were detected based on case reports received during the periods of the 1st and 3rd PSUR, respectively. Although the non-clinical and clinical trial data no not provide evidence to support a positive causal relationship, there are several ICSRs in the cumulative post-marketing data where the role of dexmedetomidine in contributing to the development of ventricular tachycardia and QT prolongation cannot be ruled out. These events are considered as an important potential risk named as torsade de pointes/QT prolongation.

- Safety signal of "increased mortality in patients treated with Early Goal Directed Sedation protocol under the median age of 63.7 years" was detected during the period of the 11th PSUR based on the investigator initiated study SPICE III. The signal was evaluated further by PRAC in a LEG procedure and "increased mortality in younger ICU patients" was considered to be an important potential risk for Dexdor to be included in the RMP.

- A safety signal of rhabdomyolysis was detected during the period of the 13th PSUR based on cumulative number of post-marketing reports along with some well-documented cases with temporal association with rhabdomyolysis and possibly dexmedetomidine-induced hyperthermia. Based on the available data on dexmedetomidine and rhabdomyolysis, it was concluded that there is currently not enough evidence to state a causal association. Rhabdomyolysis is considered as an important potential risk for Dexdor.

For risks added in the RMP versions 1-8, the frequencies of the risks during dexmedetomidine treatment with 95% confidence intervals (calculations were performed without logarithmic transformation) are presented separately for the clinical trials in all ICU, DB ICU, procedural sedation and non-ICU population (non-ICU population contains also the procedural sedation population).

Additional information on characteristics of the risks is shown for the ICU population and procedural sedation population (data on characteristics are not available for other populations). Proportion of subjects having serious events as well as the numbers of subjects experiencing each grade of severity of the event are shown for the whole ICU population and for the procedural sedation population. Seriousness and severity are presented as proportion (percent) of patients having the event for each separate subgroup (serious, mild, moderate and severe). Furthermore, the distribution of subjects experiencing different outcomes for the events is shown for those ICU studies where these data were available (studies 3005011, 3005012, 3005013 and 3005016). The outcomes are presented as proportion (percent) of patients in the whole study population having the specific outcome for the specific risk.

The new risks added in the version 9 of the RMP are presented according to the GVP Module V Revision 2 template, and the clinical data for these risks is presented according to the data used in the signal assessment.

In addition, the numbers of ICSRs are presented for the post-marketing data. The post-marketing data include spontaneous ICSRs (reports from healthcare professionals, consumers and regulatory authorities and those identified in the literature) and reports from clinical studies with a positive causal relationship received for dexmedetomidine by the MAH as well as those received from partner company Pfizer/Hospira from the time of the first authorisation of dexmedetomidine, Precedex, in the US on December 17th, 1999 until the data lock point of Mar 15th, 2021.

The AE and ADR searches have been performed with a specified MedDRA searches - either with an SMQ or a customised ad hoc –search. All the search categories including the individual MedDRA terms are shown in Annex 7: Other supporting data.

Important Identified Risk	**Atrioventricular block**
Frequency with 95 % CI	The frequencies and characteristics of atrioventricular block are shown separately for: 1. all atrioventricular blocks excluding atrioventricular block first degree, and for 2. atrioventricular block first degree only. **All ICU studies** Atrioventricular block excluding first degree: Dexmedetomidine (n= 2103): 0.3% (0.1, 0.6) Active comparators (n= 864): 0.8% (0.2, 1.4) Midazolam (n= 401): 0.7% (-0.1, 1.6) Propofol (n= 463): 0.9% (0, 1.7) Placebo (n= 394): 0.3% (-0.2, 0.8) Atrioventricular block first degree: Dexmedetomidine (n= 2103): 0.8% (0.4, 1.1) Active comparators (n= 864): 0.6% (0.1, 1.1) Midazolam (n= 401): 0.5% (-0.2, 1.1) Propofol (n= 463): 0.6% (-0.1, 1.4) Placebo (n= 394): 0% **Double-blind comparator controlled studies** Atrioventricular block excluding first degree: Dexmedetomidine (n= 758): 0.5% (0, 1) Active comparators (n= 663): 0.8% (0.1, 1.4) Midazolam (n= 388): 0.5% (-0.2, 1.2) Propofol (n= 275): 1.1% (-0.1, 2.3) Atrioventricular block first degree: Dexmedetomidine (n= 758): 1.7% (0.8, 2.6) Active comparators (n= 663): 0.8% (0.1, 1.4) Midazolam (n= 388): 0.5% (-0.2, 1.2) Propofol (n= 275): 1.1% (-0.1, 2.3) **Placebo controlled double-blind studies** Atrioventricular block excluding first degree: Dexmedetomidine (n= 591): 0.3% (-0.1, 0.8) Placebo (n= 394): 0.3% (-0.2, 0.8)

Important Identified Risk	**Atrioventricular block**
	Atrioventricular block first degree: Dexmedetomidine (n= 591): 0.3% (-0.1, 0.8) Placebo (n= 394): 0% **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 0 % Placebo (n= 113): 0% If also events that occurred during the 48-hour follow-up period are taken into account, the incidence of atrioventricular block (PT Atrioventricular block first degree) was 0.6% for dexmedetomidine and 0% for placebo **Non-ICU studies** Atrioventricular block excluding first degree: Dexmedetomidine (n= 2230): 0.4% (0.1, 0.7) Active comparators (n= 280): 0% Placebo (n= 1079): 0.1% (-0.1, 0.3) Other (n= 128): 0% Atrioventricular block first degree: Dexmedetomidine (n= 2230): 0.0% (0, 0.1) Active comparators (n= 280): 0% Placebo (n= 1079): 0.1% (-0.1, 0.3) Other (n= 128): 0%
Seriousness/outcomes	In 29% of subjects experiencing atrioventricular block other than first degree in the dexmedetomidine treatment arm in the ICU population, the event was reported as serious. All the cases of atriventricular block first degree were non-serious. The only outcome reported for atrioventricular block other than first degree was resolved in the cases retrieved from the data of 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016. The outcome for atriventricular block first degree in these studies was resolved in 10 (1.8%), other in 3 (0.5%) and unchanged in 1 (0.2%) subject.
Severity and nature of risk	Of the 7 subjects experiencing atrioventricular block other than first degree in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 3 (43%), moderate in 2 (29%) and as severe in 2 (29%). The severity of atrioventricular block first degree was mild in 15 (94%) and moderate in one (6%) subject.
Background incidence/prevalence	**ICU sedation**: Of 756 patients screened in a medical-cardiological-postoperative ICU at a university hospital, 2

Important Identified Risk	**Atrioventricular block**
	(0.3%) experienced atrioventricular block second degree and 7 (0.9%) atrioventricular block third degree (Reinelt P et al. Intensive Care Med 2001; 27: 1466-1473). **Procedural sedation**: Data not available.
Risk groups or risk factors	Cardiovascularly compromised patients.
Potential mechanisms	Dexmedetomidine may increase PR interval which could be considered as a risk for atrioventricular conduction block. The effect on PR interval in combined studies 3005011, 3005012 and 3005013 was modest; mean change from baseline was 6.06 msec (95% CIs, 5.06, 7.07) for dexmedetomidine, 1.5 msec (0.16, 2.84) for midazolam and 0.15 msec (-1.04, 1.34) for propofol. By comparison, a classical inhibitor of AV conduction, verapamil IR 80mg tid, increased PR interval by approximately 50msec mean and verapamil SR 240 mg od increased PR interval by 38 msec mean (Fuenmayor NT et al. Drugs 1992; 44: 1-11).
Preventability	Ongoing cardiac ECG monitoring and continuous attention of medical and nursing staff experienced in care of patients needing intensive care, or skilled in the anaesthetic management of patients in the operating room or during diagnostic procedures.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), the event was serious in minority of the patients. Most of the cases were graded as mild or moderate, and almost all the events resolved.
Evidence source	This risk is based on theoretical mechanism of action and postmarketing data
Post-marketing data	91 reports (82 serious and 9 non-serious), of which 2 originated from a clinical trial.
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Identified Risk	**Cardiac arrest**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 0.4% (0.1, 0.6) Active comparators (n= 864): 0.3% (0, 0.7) Midazolam (n= 401): 0.7% (-0.1, 1.6) Propofol (n= 463): 0% Placebo (n= 394): 0.3% (-0.2, 0.8) **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 0.5% (0, 1) Active comparators (n= 663): 0.5% (-0.1, 1)

Important Identified Risk	**Cardiac arrest**
	Midazolam (n= 388): 0.8% (-0.1, 1.6) Propofol (n= 275): 0% **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 0.5% (-0.1, 1.1) Placebo (n= 394): 0.3% (-0.2, 0.8) **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 0% Placebo (n= 113): 0% **Non-ICU studies** Dexmedetomidine (n= 2230): 0.4% (0.1, 0.7) Active comparators (n= 280): 0% Placebo (n= 1079): 0.2% (-0.1, 0.4) Other (n= 128): 0%
Seriousness/outcomes	All the events of cardiac arrest in the dexmedetomidine treatment arm in the ICU population were serious. Of the 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016, the outcome of cardiac arrest was resolved in 3 (0.5%) and fatal in 1 (0.2%) subject.
Severity and nature of risk	The event was reported as severe in all the subjects experiencing cardiac arrest in the dexmedetomidine treatment arm in the ICU population.
Background incidence/prevalence	**ICU sedation**: A prospective study by Skrifvars et al. reports that 0.6% of adult patients treated in the ICU had cardiac arrest during ICU-treatment (22 patients out of total 3931 ICU-patients) (Skrifvars MB et al. Resuscitation 2012; 83: 728-733). **Procedural sedation**: A retrospective study by Goudra et al reports that the overall incidence of cardiac arrest (defined as an event with cessation of pumping action of the heart requiring cardiopulmonary resuscitation) during or after the procedure in patients undergoing gastrointestinal (GI) endoscopic procedures was 6.069 per 10,000 procedures with propofol sedation and 0.666 per 10,000 procedures with non–propofol-based sedation (total of 20 cardiac arrests reported in 73,029 GI endoscopic procedures performed) (Goudra B et al. Saudi J Gastroenterol. 2015; 21(6): 400-11).
Risk groups or risk factors	Patients with pre-existing bradycardia, especially in connection with high physical fitness (see Identified risk Bradycardia). Patients with medical history of cardiac conduction or structural disorders. Usage in paediatric population. Vagal stimulation. Usage of bolus/loading dose.

Important Identified Risk	**Cardiac arrest**
Potential mechanisms	Progressive bradycardia possibly related to excessive parasympathetic activity may occasionally lead to a brief sinus pause/asystole.
Preventability	Continuous cardiac monitoring
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), cardiac arrest was serious and severe in all of the patients affected. Based on the clinical trial and the post-marketing data, the event usually resolves rapidly with basic resuscitation and adrenaline or atropine.
Evidence source	The risk is based on postmarketing data.
Post-marketing data	228 reports (all serious), of which 8 originated from a clinical trial.
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Identified Risk	**Bradycardia**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 13.3% (11.9, 14.8) Active comparators (n= 864): 9.0% (7.1, 10.9) Midazolam (n= 401): 11.5% (8.4, 14.6) Propofol (n= 463): 6.9% (4.6, 9.2) Placebo (n= 394): 3.0% (1.3, 4.7) **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 24.9% (21.9, 28) Active comparators (n= 663): 11.0% (8.6, 13.4) Midazolam (n= 388): 11.3% (8.2, 14.5) Propofol (n= 275): 10.5% (6.9, 14.2) **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 8.6% (6.4, 10.9) Placebo (n= 394): 3.0% (1.3, 4.7) **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 10.7 % (7.3, 14.1) Placebo (n= 113): 2.7% (-0.3, 5.6) If also events that occurred during the 48-hour follow-up period are taken into account, the incidence of bradycardia (PTs Bradycardia and Sinus bradycardia) was 14.2 % for dexmedetomidine and 3.5% for placebo. **Non-ICU studies**

Important Identified Risk	**Bradycardia**
	Dexmedetomidine (n= 2230): 6.9% (5.8, 7.9) Active comparators (n= 280): 2.5% (0.7, 4.3) Placebo (n= 1079): 2.6% (1.6, 3.5) Other (n= 128): 0.8% (-0.7, 2.3)
Seriousness/outcomes	In 8% of subjects experiencing bradycardia in the dexmedetomidine treatment arm in the ICU population, the event was reported as serious. Of the 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016, the outcome of bradycardia was fatal in 2 (0.4%) subjects (however, the event was not necessarily the main cause of death), unchanged in 1 (0.2%), improved in 1 (0.2%), resolved in 84 (15%) and other in 4 (0.7%) subjects. In all subjects experiencing bradycardia in the dexmedetomidine treatment arm in the procedural sedation population, the event was reported as non-serious.
Severity and nature of risk	Of the 280 subjects experiencing bradycardia in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 184 (66%), moderate in 87 (31%) and as severe in 22 (8%). Of the 34 subjects experiencing bradycardia in the dexmedetomidine treatment arm during the treatment in the procedural sedation population, the event was reported as mild in 26 (76%) and moderate in 8 (24%).
Background incidence/prevalence	**ICU sedation**: Of 756 patients screened in a medical-cardiological-postoperative ICU at a university hospital, 133 (18%) were identified as experiencing arrhythmias. These 133 patients experienced 310 arrhythmia episodes of which 32 (10%) were bradycardias (fewer than 40 beats per minute) (Reinelt P et al. Intensive Care Med 2001; 27: 1466-1473). When comparing this incidence of bradycardia to dexmedetomidine, the vital sign data in the active comparator controlled ICU studies can be used instead of the AE frequencies presented above. Based on these data, the frequency of bradycardia with heart rate <40 beats per minute was 0.9% in the dexmedetomidine treatment arm. In 2820 patients admitted to a general ICU for more than 24 hours, the prevalence of atrial bradyarrhythmias was 11% (Artucia H and Pereira M. Critical Care Medicine 1990; 18: 1383-1388). **Procedural sedation**: In a systematic review and meta-analysis in adults undergoing procedural sedation in the emergency department, there were 11 events of bradycardia in 837 sedations on 837 patients (6.5 per 1,000 sedations, 95% CI = 1.1 to 11.8). (Bellolio MF et al. Acad Emerg Med. 2016; 23(2): 119-34)) In a retrospective analysis of adult patients who received procedural sedation and analgesia at an academic tertiary care center, 2% of the 101 trauma patients and 3% of

Important Identified Risk	**Bradycardia**
	the 4223 non-trauma patients experienced bradycardia (heart rate ≤50 beats/min). (Green RS et al. J Emerg Trauma Shock. 2015; 8(4): 210-5
Risk groups or risk factors	Patients with severe bradycardia or advanced heart block (Grade 2/3 AV Block unless paced) and patients with high physical fitness and slow resting heart rate may be at greater risk.
Potential mechanisms	When a loading dose is administered, dexmedetomidine produces a direct vasoconstriction in the peripheral vasculature (mediated by postsynaptic alpha-2 adrenoceptors in blood vessel smooth muscle) which is initially unopposed by the hypotensive central effects. In this case, bradycardia is believed to be due to a baroreceptor reflex reduction in heart rate secondary to direct vasoconstriction and mild hypertension. If no loading dose is given or at 30 minutes after the loading dose, the predominant effect is centrally mediated reduction in heart rate. This is believed to be due to the effect of dexmedetomidine causing sympatholysis and a consequent reduction in heart rate.
Preventability	Continuous cardiac monitoring
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), bradycardia was typically non-serious and mild. Although the vast majority of cases of bradycardia resolved, isolated cases resulting in death were also reported. In some patients bradycardia has led to cardiac arrest (see Potential risk Cardiac arrest). Based on the clinical trial data in the procedural sedation population (see above), bradycardia was typically non-serious and mild.
Evidence source	The risk is based on data from randomised clinical trials
Post-marketing data	1067 reports (748 serious and 319 non-serious), of which 73 originated from a clinical trial).
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Identified Risk	**Hypotension**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 26.4% (24.6, 28.3) Active comparators (n= 864): 20.3% (17.6, 22.9) Midazolam (n= 401): 25.9% (21.6, 30.2) Propofol (n= 463): 15.3% (12.1, 18.6) Placebo (n= 394): 12.2% (9, 15.4) **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 29.3% (26.1, 32.5)

Important Identified Risk	**Hypotension**
	Active comparators (n= 663): 21.7% (18.6, 24.9) Midazolam (n= 388): 25.8% (21.4, 30.1) Propofol (n= 275): 16.0% (11.7, 20.3) **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 27.4% (23.8, 31) Placebo (n= 394): 12.2% (9, 15.4) **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 37.7 % (32.4, 43.1) Placebo (n= 113): 17.7% (10.7, 24.7) If also events that occurred during the 48-hour follow-up period are taken into account, the incidence of hypotension (PTs Hypotension, Procedural hypotension and Diastolic hypotension) was 54.7% for dexmedetomidine and 30.1% for placebo **Non-ICU studies** Dexmedetomidine (n= 2230): 15.9% (14.4, 17.4) Active comparators (n= 280): 13.9% (9.9, 18) Placebo (n= 1079): 12.7% (10.7, 14.7) Other (n= 128): 10.2% (4.9, 15.4)
Seriousness/outcomes	In 9% of subjects experiencing hypotension in the dexmedetomidine treatment arm in the ICU population, the event was reported as serious. Of the 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016, the outcome of hypotension was fatal in 9 (1.6%) subjects (however, the event was not necessarily the main cause of death), unchanged in 2 (0.4%), improved in 2 (0.4%), resolved in 83 (15%) and other in 2 (0.4%) subjects. In the dexmedetomidine treatment arm in the procedural sedation population, none of the events of hypotension during the study drug infusion were serious, but one event of hypotension during the follow-up was reported as serious.
Severity and nature of risk	Of the 556 subjects experiencing hypotension in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 255 (46%), moderate in 276 (50%) and as severe in 62 (11%). Of the 120 subjects experiencing hypotension in the dexmedetomidine treatment arm during the treatment in the procedural sedation population, the event was reported as mild in 97 (81%), moderate in 23 (19%) and as severe in 1 (1%).
Background incidence/prevalence	**ICU sedation**: Based on a prospective, single-center, blinded study conducted in medical and respiratory intensive care unit of an academic health center, hypotension (mean arterial pressure

Important Identified Risk	**Hypotension**
	<65 mmHg) occurred in 49.5% of patients without cardiac injury (Guest TM et al. JAMA 1995; 273: 1945-49). **Procedural sedation**: In a systematic review and meta-analysis in adults undergoing procedural sedation in the emergency department, the incidence of hypotension (different definitions for hypotension in different studies) was 15.2 per 1,000 sedations (95% CI = 10.7 to 19.7) in 5,801 sedations on 5,801 patients. (Bellolio MF et al. Acad Emerg Med. 2016; 23(2): 119-34) In a retrospective analysis of adult patients who received procedural sedation and analgesia at an academic tertiary care center, 20% of the 101 trauma patients and 16% of the 4223 non-trauma patients experienced hypotension (systolic blood ≤100 mm Hg). (Green RS et al. J Emerg Trauma Shock. 2015; 8(4): 210-5
Risk groups or risk factors	Hypotension might be expected to be more common in patients with hypovolaemia or chronic hypotension.
Potential mechanisms	Hypotension is believed to be due to the effect of dexmedetomidine causing sympatholysis and a consequent reduction in heart rate and vasodilation. The blood pressure response is biphasic – at therapeutic doses dexmedetomidine overall causes hypotension but as doses increase the blood pressure increases, presumably due to a higher contribution from direct vasoconstriction.
Preventability	Frequent blood pressure monitoring Caution and careful titration of dose in patients with preexisting low blood pressure despite volume and vasopressors, and in patients with other drugs reducing blood pressure.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), hypotension was typically non-serious and mild or moderate. The vast majority of cases of hypotension resolved. Based on the clinical trial data in the procedural sedation population (see above), hypotension was typically non-serious and mild.
Evidence source	The risk is based on data from randomised clinical trials
Post-marketing data	1010 reports (548 serious and 462 non-serious), of which 90 originated from a clinical trial.
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Identified Risk	**Hypertension**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 15.1% (13.6, 16.7)

Important Identified Risk	**Hypertension**
	Active comparators (n= 864): 15.5% (13.1, 17.9) Midazolam (n= 401): 25.4% (21.2, 29.7) Propofol (n= 463): 6.9% (4.6, 9.2) Placebo (n= 394): 16.5% (12.8, 20.2) **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 21.7% (18.8, 24.6) Active comparators (n= 663): 18.9% (15.9, 21.8) Midazolam (n= 388): 26.0% (21.7, 30.4) Propofol (n= 275): 8.7% (5.4, 12.1) **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 14.4% (11.6, 17.2) Placebo (n= 394): 16.5% (12.8, 20.2) **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 11.6 % (8.1, 15.2) Placebo (n= 113): 20.4% (12.9, 27.8) **Non-ICU studies** Dexmedetomidine (n= 2230): 4.1% (3.3, 5) Active comparators (n= 280): 0% Placebo (n= 1079): 7.9% (5.7, 8.8) Other (n= 128): 0%
Seriousness/outcomes	In 3% of subjects experiencing hypertension in the dexmedetomidine treatment arm in the ICU population, the event was reported as serious. In the 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016, the outcome of hypertension was unchanged in 3 (0.5%), improved in 3 (0.5%), resolved in 57 (10%) and other in 3 (0.5%) subjects. In all subjects experiencing hypertension in the dexmedetomidine treatment arm in the procedural sedation population, the event was reported as non-serious.
Severity and nature of risk	Of the 318 subjects experiencing hypertension in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 176 (55%), moderate in 139 (44%) and as severe in 21 (7%). Of the 37 subjects experiencing hypertension in the dexmedetomidine treatment arm during the treatment in the procedural sedation population, the event was reported as mild in 29 (78%) and moderate in 8 (22%).
Background incidence/prevalence	**ICU sedation**: Data not available. **Procedural sedation**: In a prospective, observational project erolling a consecutive sample of adult and paediatric patients who

Important Identified Risk	**Hypertension**
	received parenteral sedation for a procedure in the emergency department, 42 (1.6%) cases of hypertension (systolic BP >180 mmHg), were reported in enrolled 2623 patients. (Taylor DM. Emerg Med Australas. 201; 23(4): 466-73
Risk groups or risk factors	Hypertension might be expected to be more common in patients with chronic hypertension or peripheral autonomic dysfunction.
Potential mechanisms	When a loading dose is administered, dexmedetomidine produces a direct vasoconstriction in the peripheral vasculature (mediated by postsynaptic alpha-2 adrenoceptors in blood vessel smooth muscle) which is initially unopposed by the hypotensive central effects. If no loading dose is given or at 30 minutes after the loading dose, the predominant effect is centrally mediated reduction in blood pressure. This is believed to be due to the effect of dexmedetomidine on the locus coeruleus which causes sympatholysis and a consequent reduction in heart rate and vasodilation. The blood pressure response is biphasic – at therapeutic doses dexmedetomidine overall causes hypotension but as doses increase the blood pressure increases, presumably due to a higher contribution from direct vasoconstriction.
Preventability	Frequent blood pressure monitoring. Reduction of loading dose or decreasing the continuous infusion rate.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), hypertension was typically non-serious and mild or moderate. The outcome in the vast majority of cases of hypertension was resolved. Based on the clinical trial data in the procedural sedation population (see above), hypertension was typically non-serious and mild.
Evidence source	The risk is based on data from randomised clinical trials
Post-marketing data	235 reports (104 serious and 131 non-serious), of which 19 originated from a clinical trial.
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Identified Risk	**Hyperglycaemia**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 2.0% (1.4, 2.6) Active comparators (n= 864): 1.6% (0.8, 2.5) Midazolam (n= 401): 2.0% (0.6, 3.4) Propofol (n= 463): 1.3% (0.3, 2.3) Placebo (n= 394): 1.3% (0.2, 2.4) **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 3.2% (2.0, 4.5)

Important Identified Risk	**Hyperglycaemia**
	Active comparators (n= 663): 1.2% (0.4, 2.0) Midazolam (n= 388): 1.8% (0.5, 3.1) Propofol (n= 275): 0.4% (-0.3, 1.1) **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 1.5% (0.5, 2.5) Placebo (n= 394): 1.3% (0.2, 2.4) **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 0% Placebo (n= 113): 0% If also events that occurred during the 48-hour follow-up period are taken into account, the incidence of hyperglycaemia (PT Hyperglycaemia) was 0.6% for dexmedetomidine and 0% for placebo **Non-ICU studies** Dexmedetomidine (n= 2230): 0.4% (0.1, 0.7) Active comparators (n= 280): 0% Placebo (n= 1079): 0.6% (0.2, 1.1) Other (n= 128): 0%
Seriousness/outcomes	In 2% of subjects experiencing hyperglycaemia in the dexmedetomidine treatment arm in the ICU population, the event was reported as serious. Of the 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016, the outcome of hyperglycaemia was fatal in 1 (0.2%) subject (however, the event was not necessarily the main cause of death), improved in 1 (0.2%), resolved in 5 (0.9%) and other in 1 (0.2%) subjects.
Severity and nature of risk	Of the 42 subjects experiencing hyperglycaemia in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 21 (50%) and as moderate in 21 (50%). None of the events was graded as severe.
Background incidence/prevalence	**ICU sedation**: In a glycaemic survey consisting of 1 010 705 patients in 126 US hospitals, the prevalence of hyperglycaemia (>180 mg/dl) in the ICU was 46.0% (Cook CB et al. J Hosp Med 2009; 4: E7-E14). In non-diabetic patients who sustain an acute myocardial infarction, the reported rate of stress hyperglycaemia varies from 3% to 71% (Capes SE et al. Lancet 2000; 355: 773-778). Hyperglycaemia has been noted in approximately 50% of non-diabetic ICU patients with sepsis (Frankeneld DC et al. Journal of Parenteral and Enteral Nutrition 1994; 18: 398-403). **Procedural sedation**: Data not available.
Risk groups or risk factors	Patients with diabetes mellitus

Important Identified Risk	**Hyperglycaemia**
Potential mechanisms	Transient inhibition of insulin secretion in pancreatic β-cells.
Preventability	Blood glucose is routinely monitored in ICU patients and closely managed with exogenous insulin in most patients.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), hyperglycaemia was typically non-serious and mild or moderate. Majority of cases of hyperglycaemia resolved.
Evidence source	The risk is based on data from randomised clinical trials
Post-marketing data	3 spontaneous reports (1 serious and 2 non-serious).
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Identified Risk	**Withdrawal syndrome**
Frequency with 95 % CI	**All ICU studies during 48-hour follow-up** Dexmedetomidine (n= 2103): 1.5% (1.0, 2.0) Active comparators (n= 864): 2.0% (1.0, 2.9) Midazolam (n= 401): 2.5% (1, 4) Propofol (n= 463): 1.5% (0.4, 2.6) **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 4.0% (2.6, 5.4) Active comparators (n= 663): 2.6% (1.4, 3.8) Midazolam (n= 388): 2.6% (1, 4.2) Propofol (n= 275): 2.5% (0.7, 4.4) **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 0% Placebo (n= 113): 0%
Seriousness/outcomes	In 3% of subjects experiencing withdrawal syndrome during 48-hour follow-up in the dexmedetomidine treatment arm in the ICU population, the event was reported as serious. In the 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016, the outcome of withdrawal syndrome during 48-hour follow-up was deteriorated in 1 (0.2%), improved in 1 (0.2%), resolved in 24 (4.4%) and other in 1 (0.2%) subject.
Severity and nature of risk	Of the 31 subjects experiencing withdrawal syndrome during 48-hour follow-up in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 18 (58%) and as moderate in 13 (42%). None of the events was graded as severe.
Background incidence/prevalence	**ICU sedation:** The frequency of having signs and symptoms of withdrawal was 3.4% in adult burn patients with inhalation

Important Identified Risk	**Withdrawal syndrome**
	injury receiving mechanical ventilation with continuous infusions of lorazepam or midazolam for greater than 7 days (Brown C et al. Am Surg 2000; 66: 367– 71). **Procedural sedation**: Data not available.
Risk groups or risk factors	Patients treated with alpha-2 agonists for a long period of time have rarely been shown to develop withdrawal syndrome after the treatment has been stopped abruptly.
Potential mechanisms	Rebound hypertension and tachycardia on withdrawal might be expected. Stopping the drug after prolonged use might result in a withdrawal syndrome in the form of excessive sympathetic activation such as anxiety, hyperhidrosis and tremor.
Preventability	Tapering of dexmedetomidine rather than abrupt cessation in ICU sedation.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), withdrawal syndrome was typically non-serious and mild. The outcome in vast majority of cases of withdrawal syndrome was resolved.
Evidence source	The risk is based on data from randomised clinical trials
Post-marketing data	122 reports (55 serious and 67 non-serious), of which 2 originated from a clinical trial.
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Potential Risk	**Cortisol suppression**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 0.2% (0, 0.4) (adrenal insufficiency) Active comparators (n= 864): 0% Midazolam (n= 401): 0% Propofol (n= 463): 0% Placebo (n= 394): 0% **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 0.5% (0, 1.0) (adrenal insuffuciency) Active comparators (n= 663): 0% Midazolam (n= 388): 0% Propofol (n= 275): 0% **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 0% Placebo (n= 394): 0%

Important Potential Risk	**Cortisol suppression**
	Procedural sedation, placebo controlled double-blind studies Dexmedetomidine (n= 318): 0% Placebo (n= 113): 0% **Non-ICU studies** Dexmedetomidine (n= 2230): 0% Active comparators (n= 280): 0% Placebo (n= 1079): 0% Other (n= 128): 0%
Seriousness/outcomes	All the events of cortisol suppression in the dexmedetomidine treatment arm in the ICU population were non-serious.The only outcome reported for cortisol suppression was resolved in 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016.
Severity and nature of risk	Of the 4 subjects experiencing cortisol suppression in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 1 (25%) and moderate in 3 (75%). There was no increase in the frequency of low cortisol values on dexmedetomidine in the ICU studies 3005012, 3005013 and 2001-001, compared to midazolam and propofol.
Background incidence/prevalence	**ICU sedation**: Based on the measurement of serum cortisol levels with or without ACTH stimulation test, the incidence of adrenal insufficiency has been reported to vary greatly between 0.66% - 35% in pro- and restrospective studies conducted in the ICU population (Barquist E and Kirton O. J Trauma 1997; 42: 27-31, Morris JA et al. J Am Coll Surg 2007; 204: 885-892, Dimopoulou I et al. Intensive Care Med 2007; 33: 2116–2121, Rivers EP et al. Chest 2001; 119: 889-96). **Procedural sedation**: Data not available.
Risk groups or risk factors	Features that have been associated with cortisol suppression in the scientific literature include sepsis and/or shock, high lactate, hypoalbuminaemia, high percentage of eosinophils, low sodium and glucose, low platelets, severe underlying disease or organ failure, and use of antifungal agents.
Potential mechanisms	Compounds with an imidazole structure are recognised to have the potential to reduce cortisol release from the adrenals. The mechanism seems to be by reversible inhibition of 11-β hydroxylase activity, hence blocking conversion of 11-deoxycortisol to active cortisol. A number of drugs have been shown to have this effect, especially ketoconazole and etomidate (which has multiple potential mechanisms of cortisol suppression).In addition, sedative drugs may reduce the stress response to surgery with consequent smaller increase in total cortisol.

Important Potential Risk	**Cortisol suppression**
Preventability	Relative adrenal insufficiency is common in critically ill patients and so routinely tested in patients with possible symptoms (unresponsive hypotension) or treated empirically with exogenous steroids.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), cortisol suppression was not serious or severe in any of the patients affected. In 3 of the 4 cases the outcome of the event was reported as recovered, for one case the outcome was not presented, and evidence of clinically relevant cortisol suppression was not found in the clinical trials.
Evidence source	The risk is based on a potential imidazole class effect.
Post-marketing data	1 spontaneous report (serious).
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Potential Risk	**Convulsions**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 0.2% (0, 0.4) Active comparators (n= 864): 0.3% (0, 0.7) Midazolam (n= 401): 0.5% (-0.2, 1.2) Propofol (n= 463): 0.2% (-0.2, 0.6) Placebo (n= 394): 0% **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 0.6% (0.1, 1.2) Active comparators (n= 663): 0.5% (-0.1, 1) Midazolam (n= 388): 0.5% (-0.2, 1.2) Propofol (n= 275): 0.4% (-0.3, 1.1) **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 0 % Placebo (n= 394): 0% **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 0% Placebo (n= 113): 0% **Non-ICU studies** Dexmedetomidine (n= 2230): 0% (0, 0.1) Active comparators (n= 280): 0% Placebo (n= 1079): 0% Other (n= 128): 0%
Seriousness/outcomes	In none of subjects experiencing convulsion in the dexmedetomidine treatment arm in the ICU population, the event was reported as serious. Of the 547 subjects treated with

Important Potential Risk	**Convulsions**
	dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016, the outcome of convulsion was resolved in 3 (0.5%) subjects and unknown in 1 subject (0.2%).
Severity and nature of risk	Of the 5 subjects experiencing convulsion in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 1 (20%), moderate in 2 (40%) and as severe in 2 (40%).
Background incidence/prevalence	**ICU sedation**: In a series of 27,723 patients admitted to medical and surgical intensive care units at Mayo Clinic Rochester hospitals during June 1981 to February 1992, 213 (0.8%) patients had at least one episode of generalized tonic-clonic seizures (Wijdicks E and Sharbrough FW. Neurology 1993; 43: 1042-1044). **Procedural sedation**: Data not available.
Risk groups or risk factors	No specific groups known. However, dexmedetomidine lacks the aniconvulsant action of some other sedatives and so will not suppress underlying seizure activity.
Potential mechanisms	Dexmedetomidine is not suspected to cause convulsions as such. However, the motor aspects of convulsions are unlikely to be blocked by dexmedetomidine, unlike by general anaesthetics such as propofol, and therefore seizure activity would normally be apparent and not masked.
Preventability	The incidence of convulsion is not increased in the general ICU population on dexmedetomidine at the indicated dose. The SmPC warning regarding status epilepticus should ensure such patients have adequate anti-convulsant treatment.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), convulsions were not serious in any of the patients affected but were severe in 40% of the patients. In 3 of the 4 cases the outcome of the event was reported as recovered, for one case the outcome was not presented.
Evidence source	The risk has been reported to be an adverse effect of clonidine, another alpha-2-adrenergic receptor agonist, when given in high doses.
Post-marketing data	56 reports (all serious, of these 3 originated from a clinical trial).
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Potential Risk	**Hypothermia**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 0.2% (0, 0.4) Active comparators (n= 864): 0.2% (-0.1, 0.6) Midazolam (n= 401): 0.5% (-0.2, 1.2)

Important Potential Risk	**Hypothermia**
	Propofol (n= 463): 0% Placebo (n= 394): 0% **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 0.5% (0, 1) Active comparators (n= 663): 0.3% (-0.1, 0.7) Midazolam (n= 388): 0.5% (-0.2, 1.2) Propofol (n= 275): 0% **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 0% Placebo (n= 394): 0% **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 0% Placebo (n= 113): 0% **Non-ICU studies** Dexmedetomidine (n= 2230): 0.3% (0.1, 0.5) Active comparators (n= 280): 0% Placebo (n= 1079): 0.2% (-0.1, 0.4) Other (n= 128): 0%
Seriousness/outcomes	All the events of hypothermia in the dexmedetomidine treatment arm in the ICU population were non-serious. Of the 547 subjects treated with dexmedetomidine in the ICU studies 3005011, 3005012, 3005013 and 3005016, the outcome of hypothermia was resolved in 3 (0.5%) subjects.
Severity and nature of risk	In all the 5 (100%) subjects experiencing hypothermia in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild.
Background incidence/prevalence	**ICU sedation**: In a retrospective review of 5050 consecutive postoperative patients of a general ICU of a tertiary hospital, 35% of patients were hypothermic and 6% were severely hypothermic in the first 24 h after surgery (Karalapillai D et al. Anaesthesia 2009; 64: 968-972). **Procedural sedation**:In a prospective observational study in a tertiary-care hospital, hypothermia (<36.0°C) was present after 23.3% (n = 93; 95% CI 19.2%-27.4%) of the 399 procedures performed with procedural sedation and analgesia in a cardiac catheterization laboratory.(Conway A et al. J Cardiothorac Vasc Anesth. 2015; 29(5): 1285-90).
Risk groups or risk factors	Small reductions in body temperature are unlikely to be of clinical relevance however neonates may be at greater risk of developing significant hypothermia and associated bradyarrhythmia, and this is identified in the SmPC.

Important Potential Risk	**Hypothermia**
Potential mechanisms	Alpha2 agonists are recognised to reduce body temperature (demonstrated clearly with high doses of dexmedetomidine in animal studies) and dexmedetomidine has been proposed for this reason in management of therapeutic hypothermia.
Preventability	Regular monitoring of body temperature.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), hypothermia was mild in all the subjects affected.
Evidence source	The risk has been reported to be an adverse effect of clonidine, another alpha-2-adrenergic receptor agonist, when given in high doses
Post-marketing data	6 spontaneous reports (4 serious and 2 non-serious).
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Potential Risk	**Torsade de pointes/QT prolongation**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 0.6% (0.2, 0.9) Active comparators (n= 864): 2.3% (1.3, 3.3) Midazolam (n= 401): 1.2% (0.2, 2.3) Propofol (n= 463): 3.2% (1.6, 4.9) Placebo (n= 394): 0.5% (-0.2, 1.2) **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 1.0% (0.3, 1.7) Active comparators (n= 663): 1.7% (0.7, 2.6) Midazolam (n= 388): 1.0% (0, 2) Propofol (n= 275): 2.5% (0.7, 4.4) **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 0.2% (-0.2, 0.5) Placebo (n= 394): 0.5% (-0.2, 1.2) **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 0.3% (-0.3, 0.9) Placebo (n= 113): 0% **Non-ICU studies** Dexmedetomidine (n= 2230): 0.1% (0, 0.2) Active comparators (n= 280): 0% Placebo (n= 1079): 0.3% (0, 0.6) Other (n= 128): 0%

Important Potential Risk	**Torsade de pointes/QT prolongation**
Seriousness/outcomes	None of the subjects in the dexmedetomidine treatment arm in the ICU population experienced an event of Torsade de Pointes (TdP) during the study treatment infusion. In 33% of the subjects experiencing other events than TdP included in the SMQ Torsade de Pointes/QT Prolongation, narrow, the event was reported as serious. The outcome was resolved in all the patients experiencing other events than TdP events belonging to this SMQ. The one subject experiencing an event belonging to the SMQ Torsade de Pointes/QT Prolongation in the procedural sedation population, experienced ventricular tachycardia. This event was assessed non-serious.
Severity and nature of risk	Of the 12 subjects experiencing other events than TdP included in the SMQ Torsade de Pointes/QT Prolongation, narrow, in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 7 (58%), moderate in 1 (8%) and as severe in 4 (33%). The ventricular tachycardia belonging to the SMQ Torsade de Pointes/QT Prolongation in the procedural sedation population, was reported as mild.
Background incidence/prevalence	**ICU sedation**: Of 756 patients screened in a medical-cardiological-postoperative ICU at a university hospital, 133 (18%) were identified as experiencing arrhythmias. Five of these 133 patients (4%) were diagnosed with Torsade de pointes (Reinelt et al. Intensice Care Med 2001; 27: 1466-73). **Procedural sedation**: Data not available.
Risk groups or risk factors	QTc prolongation is unlikely to occur due to dexmedetomidine based on the preclinical data and data from the clinical trials. Rate dependent ECG intervals including PR and uncorrected QT intervals may appear to increase during dexmedetomidine infusion in keeping with its known bradycardic effect. However, there is no evidence of increases in the corrected QT (QTc) on dexmedetomidine using either Bazett or Fridericia corrections, and neither was there clinical evidence of increase in relevant rhythm disturbances. No TdP was attributed to dexmedetomidine in the ICU controlled studies. TdP is a recognised hazard of concomitant medication used in the ICU such as haloperidol; this risk is managed by continuous ecg monitoring and rapid treatment of TdP in the ICU.
Potential mechanisms	Dexmedetomidine induces bradycardia and some slowing of atrioventricular and ventricular conduction but has not been shown to have any proarrhythmic (torsadogenic) effects on action potential or ventricular repolarisation.
Preventability	Continuous cardiac monitoring

Important Potential Risk	**Torsade de pointes/QT prolongation**
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population the events included in the SMQ Torsade de Pointes/QT Prolongation most commonly were non-serious and mild (no TdPs occurred). All the patients for whom the information was available recovered from the event. Based on the clinical trial data in the procedural sedation population (see above), the event belonging to the SMQ Torsade de Pointes/QT Prolongation (ventricular tachycardia) was non-serious and mild.
Evidence source	The risk is based on postmarketing data.
Post-marketing data	38 reports (36 serious, of which one originated from clinical trials and 2 non-serious)
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Potential Risk	**Overdose**
Frequency with 95 % CI	**All ICU studies** Dexmedetomidine (n= 2103): 0.1% (0, 0.3) Active comparators (n= 864): 0% Midazolam (n= 401): 0% Propofol (n= 463): 0% Placebo (n= 394): 0% **Double-blind comparator controlled ICU studies** Dexmedetomidine (n= 778): 0% Active comparators (n= 663): 0% Midazolam (n= 388): 0% Propofol (n= 275): 0% **Placebo controlled double-blind ICU studies** Dexmedetomidine (n= 591): 0.5% (-0.1, 1.1) Placebo (n= 394): 0% **Procedural sedation, placebo controlled double-blind studies** Dexmedetomidine (n= 318): 0% Placebo (n= 113): 0% **Non-ICU studies** Dexmedetomidine (n= 2230): 0% (0, 0.1) Active comparators (n= 280): 0% Placebo (n= 1079): 0% Other (n= 128): 0%
Seriousness/outcomes	In all of the 3 subjects (100%) experiencing overdose in the dexmedetomidine treatment arm in the ICU population, the event was reported as serious. No events of overdose ocurred

Important Potential Risk	**Overdose**
	the ICU studies 3005011, 3005012, 3005013 and 3005016, and therefore the outcome of overdose was not available.
Severity and nature of risk	Of the 3 subjects experiencing overdose in the dexmedetomidine treatment arm in the ICU population, the event was reported as mild in 2 (67%) and moderate in 1 (33%).
Background incidence/prevalence	Based on claims filed under 'anaesthesia' recorded in the NHS Litigation Authority database between 1995 and 2007, 39% of drug administration errors included wrong dose. Ninety two percent of these alleged overdose (Cranshaw J et al. Anaesthesia 2009; 64: 1317-1323).
Risk groups or risk factors	Lack of familiarity or standard procedure with a drug increases the risk of such errors.
Potential mechanisms	Accidental overdose due to medication errors leading to incorrect infusion rate including administration of erroneous amount of dexmedetomidine in micrograms (e.g. ten fold higher), specifying erroneous time over which the specific amount of dexmedetomidine should have been administered (e.g. a minute instead of an hour resulting in 60-fold higher dose) or administration of undiluted dexmedetomidine.
Preventability	Clear instructions regarding infusion rate and dilution, and follow-up of them.
Potential impact on individual patient and public health	Based on the clinical trial data in the ICU population (see above), overdose was assessed as serious in all 3 subjects experiencing overdose, but the severity of the event was assessed as mild in 2 and moderate in 1 subjects.
Evidence source	The risk is based on reported medication errors resulting in overdose.
Post-marketing data	115 spontaneous reports (47 serious and 68 non-serious).
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important Potential Risk	**Off-label use**
Frequency with 95 % CI	No events of off-label use were reported in clinical studies.
Seriousness/outcomes	No events of off-label use were reported in clinical studies.
Severity and nature of risk	No events of off-label use were reported in clinical studies.
Background incidence/prevalence	**ICU sedation**: Based on a review of the literature on the paediatric off-label use, drugs were prescribed off-label in 18-55% of patients in neonatal and paediatric ICUs located in the EU (Lindell-Osuagwu L et al. J Clin Pharm Ther 2009; 34: 277-87). According to a prospective study of patients admitted to a neonatal ICU in a University Hospital in Finland, 79% of patients were prescribed at least one drug for off-label use or unlicensed drug (Lindell-Osuagwu L et al. J Clin Pharm Ther 2009; 34: 277-87). Based on a study comparing list of medications dispensed in pediatric ICU to Food and Drug Administration (FDA)

Important Potential Risk	**Off-label use**
	approvals for use in children, 24.2% of the medications dispensed were not FDA approved for any pediatric age group (Yang CP et al. Pediatr Crit Care Med 2011; 12: 1-5). According to a study on medical prescriptions of adult patients consecutively admitted in surgical ICU in France, 25.6% of the prescriptions were considered off-label (Albaladejo P et al. Presse Med 2001; 30: 1484-8). **Procedural sedation**: Data not available.
Risk groups or risk factors	Paediatric patients, off-label routes of administration (e.g. intranasal administration or use as an adjunct with local anesthetic in peripheral blocks)
Potential mechanisms	Not applicable
Preventability	The SmPC clearly identifies the appropriate clinical environment and patient population.
Potential impact on individual patient and public health	There are many literature reports and published studies of off-label use of dexmedetomidine in children in ICU sedation, during procedural sedation and perioperatively which generally have not identified specific new risks. Hypothermia may increase the risk of bradycardia in neonates and a specific warning is included in the SmPC to cover this. No specific safety concerns have been identified concerning the off-label routes of administration, either. The public health impact is therefore believed by the MAH to be small provided the general precautions specified in the SmPC are observed. However, as with all drugs the potential for unexpected reactions when the drug is used in off-label indications remains.
Evidence source	The risk is based on recognised off-label use of dexmedetomidine, including off-label use in children.
Post-marketing data	761 reports (275 serious and 486 non-serious) of which 6 originated from a clinical trial.
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important potential risk	**Rhabdomyolysis**
Potential mechanisms	Not known.
Evidence source(s) and strength of evidence	This risk is based on post-marketing data.

<table>
<tr><td>Important potential risk</td><td>Rhabdomyolysis</td></tr>
<tr><td>Characterisation of the risk</td><td><u>Clinical data</u>
<table>
<tr><td colspan="4">Incidence of Rhabdomyolysis after study treatment start - All studies</td></tr>
<tr><td></td><td>All DEX (N=4333)
Subjects/(%)</td><td>Comparators (N=1144)
Subjects/(%)</td><td>PLACEBO (N=1473)
Subjects/(%)</td></tr>
<tr><td>Total</td><td>2 (0.0)</td><td>2 (0.2)</td><td>2 (0.1)</td></tr>
<tr><td>95% CI for Total incidence</td><td>(0, 0.1)</td><td>(-0.1, 0.4)</td><td>(-0.1, 0.3)</td></tr>
<tr><td>PT Rhabdomyolysis</td><td>2 (0.0)</td><td>1 (0.1)</td><td>1 (0.1)</td></tr>
<tr><td>PT Muscle necrosis</td><td></td><td>1 (0.1)</td><td>1 (0.1)</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Severity</td><td>Subjects</td><td>Subjects</td><td>Subjects</td></tr>
<tr><td>Mild</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Moderate</td><td>0</td><td>1</td><td>2</td></tr>
<tr><td>Severe</td><td>2</td><td>1</td><td>0</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="4">Number of subjects with serious events</td></tr>
<tr><td></td><td>0</td><td>1</td><td>0</td></tr>
</table>
All the events in the dexmedetomidine and the comparator groups occurred in the double-blinded comparator controlled ICU-studies. All the events in placebo patients occurred in the non-ICU studies.

<u>Postmarketing data</u>

23 reports (21 serious and 2 non-serious), of which 1 originated from a clinical trial).</td></tr>
<tr><td>Risk factors and risk groups</td><td>Features that have been associated with rhabdomyolysis in the scientific literature in general include e.g. direct muscle injury, prolonged compression during immobility (for example time-consuming surgery without adequate periodic patient mobilization or self-induced intoxication), strenuous muscular activity, seizures, electrolyte imbalances, hyperthermia, neuroleptic malignant syndrome and numerous bacterial, viral, fungal and protozoal infections.</td></tr>
<tr><td>Preventability</td><td>Rhabdomyolysis can be detected at an early stage by monitoring serum creatine kinase values.</td></tr>
<tr><td>Impact on the risk-benefit balance of the product</td><td>Rhabdomyolysis can lead to acute kidney injury and have serious consequences if not treated. The prognosis is usually good if treated early and aggressively.</td></tr>
</table>

Important potential risk	**Rhabdomyolysis**
Public health impact	The incidence of rhabdomyolysis in clinical studies and the number of postmarketing reports is low. The public health impact is considered to be low.
MedDRA terms	For detailed MedDRA search criteria, please refer to Annex 7.

Important potential risk	**Increased mortality in younger ICU patients**
Potential mechanisms	Not known.
Evidence source(s) and strength of evidence	This risk is based on data from the academy sponsored, randomised, controlled, open-label clinical trial SPICE III
Characterisation of the risk	Data from SPICE III study In the SPICE III pragmatic randomised controlled trial of 3,904 critically ill adult ICU patients there was no overall difference in 90-day mortality between the dexmedetomidine and usual care group (mortality 29.1% in both groups), but a heterogeneity of effect from age on mortality was observed. Dexmedetomidine was associated with an increased mortality in the age-group ≤65 years (odds ratio 1.26; 95% credibility interval 1.02 to 1.56) compared to alternative sedatives. While the mechanism is unclear, this heterogeneity of effect on mortality from age was most prominent in cases with early use of dexmedetomidine in high dose to achieve deep sedation in patients admitted for other reasons than post-operative care and increased with increasing APACHE II scores. The effect on mortality was not detectable when dexmedetomidine was used for light sedation. Orion Clinical data In the analysis of Orion clinical database the cut-off value used for age was 63.7 years, as the first publication of SPICE III results reported heterogeneity between treatment groups and an age above or below the median (63.7 years) with respect to 90-day mortality.

Death by age in the pivotal ICU studies

Study	**DEX**	**Control**	**Absolute risk difference**	**95% Confidence limits**
3005012				
Total	46 (18.7%)	48 (19.4%)	-0.7*	-7.7, 6.2
Younger than 63.7 years	11 (9.3%)	9 (8.1%)	1.2	-6.1, 8.5
Age 63.7 or older	35 (27.3%)	39 (28.7%)	-1.3*	-12.2, 9.5

	Study 3005013				
	Total	69 (27.9%)	54 (21.6%)	6.3	-1.2, 13.9
	Younger than 63.7 years	16 (14.3%)	11 (9.3%)	4.3	-3.4, 13.3
	Age 63.7 or older	53 (39.3%)	43 (32.6%)	6.7	-4.8, 18.2
	Study 2001-001				
	Total	59 (24.2%)	34 (27.9%)	-3.7*	-13.3, 5.9
	Younger than 63.7 years	23 (18.3%)	9 (16.1%)	2.2	-9.6, 13.9
	Age 63.7 or older	36 (30.5%)	25 (37.9%)	-7.4*	-21.7, 7.0
	*Negative difference favours DEX Postmarketing data Not applicable, this risk cannot be evaluated based on post-marketing reports				
Risk factors and risk groups	The heterogeneity of effect on mortality from age was most prominent in cases with early use of dexmedetomidine in high dose to achieve deep sedation in patients admitted for other reasons than post-operative care and increased with increasing APACHE II scores.				
Preventability	Dexdor is not indicated for deep sedation (RASS -4 and -5), as described in the SmPC sections 4.1. and 4.4. A DHPC will be distributed to inform the prescribers of this risk (see section V.2)				
Impact on the risk-benefit balance of the product	In the SPICE III study, the heterogeneity of effect on mortality from age was most prominent in cases with early use of dexmedetomidine in high dose to achieve deep sedation in patients admitted for other reasons than post-operative care and increased with increasing APACHE II scores. Without knowing the data behind the 3rd SPICE publication it is not possible to assess whether this affects the risk-benefit balance of Dexdor when used according to the authorised indication.				
Public health impact	No statistically significant difference in mortality between age groups has been seen in company sponsored studies or in published literature relevant to the authorised indication. Therefore the public health impact is expected to be low when Dexdor is used according to the authorised indication.				
MedDRA terms	Not applicable				

SVII.3.2. Presentation of the missing information

Missing information: Pregnancy

Evidence source:

There are no or limited amount of data from the use of dexmedetomidine in pregnant women. Studies in animals have shown reproductive toxicity.In the reproductive toxicity studies, no teratogenic effects were observed in the rat or rabbit. In the rabbit study intravenous administration of the maximum dose, 96 µg/kg/day, produced exposures that are similar to those observed clinically. In the rat, subcutaneous administration at the maximum dose, 200 µg/kg/day, caused an increase in embryofetal death and reduced the fetal body weight. These effects were associated with clear maternal toxicity. Reduced fetal body weight was noted also in the rat fertility study at dose 18 µg/kg/day and was accompanied with delayed ossification at dose 54 µg/kg/day. The observed exposure levels in the rat are below the clinical exposure range.

Population in need of further characterisation: Pregnant females

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Atrioventricular block Cardiac arrest Bradycardia Hypotension Hypertension Hyperglycaemia Withdrawal syndrome
Important potential risks	Cortisol suppression Convulsions Hypothermia Torsade de pointes/QT prolongation Overdose Off-label use Rhabdomyolysis Increased mortality in younger ICU patients
Missing information	Pregnancy

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for certain important potential risks:

For certain potential risks there are templates to be used to create follow-up queries for the individual case safety reports received for these risks. The purpose of these follow-up query templates is to obtain

structured information on individual case safety reports received for these risks.The templates used to create follow-up queries are provided in Annex 4.

III.2 Additional pharmacovigilance activities

None proposed currently.

III.3 Summary Table of additional Pharmacovigilance activities

There are no on-going and planned additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

Not applicable. Dexmedetomidine has been on the market for almost 17 years with the post-marketing exposure exceeding thirteen million patient days.

There is no need for conducting further post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

V.1 Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Atrioventricular block	Routine risk communication: *SmPC sections 4.3, 4.4, 4,8* *PL sections 2, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: - Contraindication of advanced heart block in section 4.3 - Advice that all patients should have continuous cardiac monitoring during Dexdor infusion included in section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.

Cardiac arrest	Routine risk communication: *SmPC sections 4.4, 4.8, 4.9* *PL sections 2, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: - Advice that all patients should have continuous cardiac monitoring during Dexdor infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Bradycardia	Routine risk communication: *SmPC sections 4.2, 4.4, 4.5, 4.8.* *PL sections 2, 3, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: – As described in section 4.2 early signs of bradycardia should be monitored by persons not involved in the conduct of the diagnostic or surgical procedure (indication 2.). – Advice that all patients should have continuous cardiac monitoring during Dexdor infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Hypotension	Routine risk communication: *SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8.* *PL sections 2, 3, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: - As described in section 4.2 early signs of hypotension should be monitored by persons not involved in the conduct of the diagnostic or surgical procedure (indication 2.). The use of a loading dose during

	procedural sedation may increase the risk for hypotension in the elderly. - Contraindication of uncontrolled hypotension in section 4.3 - Advice on the length of monitoring when used in an outpatient setting included in section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Hypertension	Routine risk communication: *SmPC sections 4.2, 4.4, 4.8* *PL sections 3, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: - As described in section 4.2 early signs of hypertension should be monitored by persons not involved in the conduct of the diagnostic or surgical procedure (indication 2.) Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Hyperglycaemia	Routine risk communication: *SmPC section 4.8* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: - None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Withdrawal syndrome	Routine risk communication: *SmPC sections 4.4, 4.8* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk:

	- None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Cortisol suppression	Routine risk communication: SmPC section 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: - None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Convulsions	Routine risk communication: SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: - None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Hypothermia	Routine risk communication: Not included in the SmPC. Routine risk minimisation activities recommending specific clinical measures to address the risk: - None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Torsade de pointes/QT prolongation	Routine risk communication: Not included in the SmPC. Routine risk minimisation activities recommending specific clinical measures to address the risk:

	- None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Overdose	Routine risk communication: SmPC sections 4.2, 4.9, 6.6 PL section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: - None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Off-label use	Routine risk communication: *SmPC sections 4.1, 4.2, 4.4* *PL sections 1, 3* Routine risk minimisation activities recommending specific clinical measures to address the risk: - Indications and instructions for administration included in sections 4.1 and 4.2, respectively - Use in only ICU, operating room and during diagnostic procedures emphasised in section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Rhabdomyolysis	Routine risk communication: Not included in the SmPC. Routine risk minimisation activities recommending specific clinical measures to address the risk: - None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription

	For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Increased mortality in younger ICU patients	Routine risk communication: *SmPC section 4.4* Routine risk minimisation activities recommending specific clinical measures to address the risk: - Section 4.4. includes advice to weigh the findings of increased mortality in the age-group ≤65 years in the SPICE III trial against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in younger patients Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.
Pregnancy	Routine risk communication: *SmPC section 4.6* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: - Advice that Dexdor should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexmedetomidine included in section 4.6 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription For hospital use only in indication 1. In indication 2 to be used only by health care professionals skilled in the anaesthetic management of patients.

V.2 Additional risk minimisation measures

Direct Healthcare Professional Communication

Objectives:

To inform prescribers about the finding of increased risk of mortality in ICU patients ≤ 65 years when dexmedetomidine is used to provide deep sedation

The risks addressed with the DHPC: Increased mortality in younger ICU patients.

Rationale for the additional risk minimisation activity:

Dissemination of a DHPC has been required in the the Dexdor LEG 16.3 procedure (EMEA/H/C/002268/LEG/016.3).

Target audience and planned distribution path:

Target recipients will be intensive care specialists and anesthesiologists in all EU countries, except Malta, where Dexdor is not on the market. The details of the communication plan will be agreed with each national competent authority prior to the distribution of the materials. The distribution path will include mailing of the printed material and/or electronic access to the material.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be measured with process indicators regarding the extent of implementation of the DHPC communication plan.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Atrioventricular block	Routine risk minimisation measures: *SmPC sections 4.3, 4.4, 4.8* *PL sections 2, 4* Contraindication of advanced heart block in section 4.3 Advice that all patients should have continuous cardiac monitoring during Dexdor infusion included in section 4.4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac arrest	Routine risk minimisation measures: *SmPC sections 4.4, 4.8, 4.9* *PL section 2, 4* Advice that all patients should have continuous cardiac monitoring during	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Dexdor infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4. Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Bradycardia	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.5, 4.8.* *PL sections 2, 3, 4* As described in section 4.2 early signs of bradycardia should be monitored (indication 2.) Advice that all patients should have continuous cardiac monitoring during Dexdor infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypotension	Routine risk minimisation measures: *SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8.* *PL sections 2, 3, 4* As described in section 4.2 early signs of hypotension should be monitored (indication 2.). The use of a loading dose during procedural sedation may increase the risk for hypotension in the elderly. Contraindication of uncontrolled hypotension in section 4.3 Advice on the length of monitoring when used in an outpatient setting included in section 4.4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypertension	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.8* *PL sections 3, 4*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	As described in section 4.2 early signs of hypertension should be monitored (indication 2.) Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hyperglycaemia	Routine risk minimisation measures: *SmPC section 4.8* *PL section 4* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Withdrawal syndrome	Routine risk minimisation measures: *SmPC sections 4.4, 4.8* *PL section 4* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cortisol suppresion	Routine risk minimisation measures: *SmPC section 5.1* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Convulsions	Routine risk minimisation measures: *SmPC section 4.4* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypothermia	Routine risk minimisation measures: Not included in the SmPC Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Torsade de pointes/QT prolongation	Routine risk minimisation measures: Not included in the SmPC. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Overdose	Routine risk minimisation measures: *SmPC sections 4.2, 4.9, 6.6* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Off-label use	Routine risk minimisation measures: *SmPC sections 4.1, 4.2, 4.4* *PL section 1 ,3* Indications and instructions for administration included in sections 4.1 and 4.2, respectively Use in only ICU, operating room and during diagnostic procedures emphasised in section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Rhabdomyolysis	Routine risk minimisation measures: Not included in the SmPC. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Increased mortality in younger ICU patients	Routine risk minimisation measures: *SmPC section 4.4 where advice is given to weigh the findings of increased mortality in the age-group ≤65 years seen in the SPICE III trial against the expected clinical benefit of dexmedetomidine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

	Additional risk minimisation measures: *DHPC dissemination*	

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Pregnancy	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* Advice that Dexdor should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexmedetomidine included in section 4.6 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Dexdor (dexmedetomidine hydrochloride)

This is a summary of the risk management plan (RMP) for Dexdor. The RMP details important risks of Dexdor, how these risks can be minimised, and how more information will be obtained about Dexdor's risks and uncertainties (missing information).

Dexdor's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Dexdor should be used.

This summary of the RMP for Dexdor should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Dexdor's RMP.

I. The medicine and what it is used for

Dexdor is authorised for sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3) and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation (see SmPC for the full indication). It contains dexmedetomidine hydrochloride as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Dexdor's benefits can be found in Dexdor's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage .

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Dexdor, together with measures to minimise such risks and the proposed studies for learning more about Dexdor's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Dexdor is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Dexdor are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Dexdor. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Atrioventricular block Cardiac arrest Bradycardia Hypotension Hypertension Hyperglycaemia Withdrawal syndrome
Important potential risks	Cortisol suppression Convulsions Hypothermia Torsade de pointes/QT prolongation Overdose Off-label use Increased mortality in younger ICU patients Rhabdomyolysis
Missing information	Pregnancy

II.B Summary of important risks

Important identified risk : Atrioventricular block	
Evidence for linking the risk to the medicine	This risk is based on theoretical mechanism of action and postmarketing data.
Risk factors and risk groups	Cardiovascularly compromised patients.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.4, 4.8* *PL sections 2, 4* Contraindication of advanced heart block in section 4.3 Advice that all patients should have continuous cardiac monitoring during Dexdor infusion included in section 4.4.
Important identified risk : Cardiac arrest	
Evidence for linking the risk to the medicine	The risk is based on postmarketing data.
Risk factors and risk groups	Patients with pre-existing bradycardia, especially in connection with high physical fitness (see Identified risk Bradycardia). Patients with medical history of cardiac conduction or structural disorders. Usage in paediatric population. Vagal stimulation. Usage of bolus/loading dose.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4, 4.8, 4.9* *PL section 2, 4* Advice that all patients should have continuous cardiac monitoring during Dexdor infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4.

Important identified risk : Bradycardia	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Patients with severe bradycardia or advanced heart block (Grade 2/3 AV Block unless paced) and patients with high physical fitness and slow resting heart rate may be at greater risk.)
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.5, 4.8.* *PL sections 2, 3, 4* As described in section 4.2 early signs of bradycardia should be monitored (indication 2.) Advice that all patients should have continuous cardiac monitoring during Dexdor infusion and advice on the length of

	monitoring when used in an outpatient setting included in section 4.4.

Important identified risk : Hypotension	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Hypotension might be expected to be more common in patients with hypovolaemia or chronic hypotension.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8.* *PL sections 2, 3, 4* As described in section 4.2 early signs of hypotension should be monitored (indication 2.). The use of a loading dose during procedural sedation may increase the risk for hypotension in the elderly. Contraindication of uncontrolled hypotension in section 4.3 Advice on the length of monitoring when used in an outpatient setting included in section 4.4.

Important identified risk : Hypertension	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Hypertension might be expected to be more common in patients with chronic hypertension or peripheral autonomic dysfunction.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.8* *PL sections 3, 4* As described in section 4.2 early signs of hypertension should be monitored (indication 2.)

Important identified risk : Hyperglycaemia	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Patients with diabetes mellitus
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8* *PL section 4*

Important identified risk : Withdrawal syndrome	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials

Risk factors and risk groups	Patients treated with alpha-2 agonists for a long period of time have rarely been shown to develop withdrawal syndrome after the treatment has been stopped abruptly.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4, 4.8* *PL section 4*

Important potential risk : Cortisol suppression	
Evidence for linking the risk to the medicine	The risk is based on a potential imidazole class effect.
Risk factors and risk groups	Features that have been associated with cortisol suppression in the scientific literature include sepsis and/or shock, high lactate, hypoalbuminaemia, high percentage of eosinophils, low sodium and glucose, low platelets, severe underlying disease or organ failure, and use of antifungal agents.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 5.1*

Important potential risk : Convulsions	
Evidence for linking the risk to the medicine	The risk has been reported to be an adverse effect of clonidine, another alpha-2-adrenergic receptor agonist, when given in high doses.
Risk factors and risk groups	No specific groups known. However, dexmedetomidine lacks the aniconvulsant action of some other sedatives and so will not suppress underlying seizure activity.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4*

Important potential risk : Hypothermia	
Evidence for linking the risk to the medicine	The risk has been reported to be an adverse effect of clonidine, another alpha-2-adrenergic receptor agonist, when given in high doses
Risk factors and risk groups	Small reductions in body temperature are unlikely to be of clinical relevance however neonates may be at greater risk of developing significant hypothermia and associated bradyarrhythmia, and this is identified in the SmPC.
Risk minimisation measures	Routine risk minimisation measures: Not included in the SmPC

Important potential risk : Torsade de pointes/QT prolongation	
Evidence for linking the risk to the medicine	The risk is based on postmarketing data.
Risk factors and risk groups	QTc prolongation is unlikely to occur due to dexmedetomidine based on the preclinical data and data from the clinical trials. Rate dependent ECG intervals including PR and uncorrected QT intervals may appear to increase during dexmedetomidine infusion in keeping with its known bradycardic effect. However,

	there is no evidence of increases in the corrected QT (QTc) on dexmedetomidine using either Bazett or Fridericia corrections, and neither was there clinical evidence of increase in relevant rhythm disturbances. No TdP was attributed to dexmedetomidine in the ICU controlled studies. TdP is a recognised hazard of concomitant medication used in the ICU such as haloperidol; this risk is managed by continuous ecg monitoring and rapid treatment of TdP in the ICU.
Risk minimisation measures	Routine risk minimisation measures: Not included in the SmPC

Important potential risk : Overdose	
Evidence for linking the risk to the medicine	The risk is based on reported medication errors resulting in overdose.
Risk factors and risk groups	Lack of familiarity or standard procedure with a drug increases the risk of such errors.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.9, 6.6*

Important potential risk : Rhabdomyolysis	
Evidence for linking the risk to the medicine	The risk is based on postmarketing data.
Risk factors and risk groups	Features that have been associated with rhabdomyolysis in the scientific literature in general include e.g. direct muscle injury, prolonged compression during immobility (for example time-consuming surgery without adequate periodic patient mobilization or self-induced intoxication), strenuous muscular activity, seizures, electrolyte imbalances, hyperthermia, neuroleptic malignant syndrome and numerous bacterial, viral, fungal and protozoal infections.
Risk minimisation measures	No risk minimisation measures

Important potential risk : Increased mortality in younger ICU patients	
Evidence for linking the risk to the medicine	This risk is based on data from the academy sponsored, randomised, controlled, open-label clinical trial SPICE III
Risk factors and risk groups	The heterogeneity of effect on mortality from age was most prominent in cases with early use of dexmedetomidine in high dose to achieve deep sedation in patients admitted for other reasons than post-operative care and increased with increasing APACHE II scores.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where advice is given to weigh the findings of increased mortality in the age-group ≤65 years seen in the SPICE III trial against the expected clinical benefit of dexmedetomidine* Additional risk minimisation measures: *DHPC dissemination*

Important potential risk : Off-label use	
Evidence for linking the risk to the medicine	The risk is based on recognised off-label use of dexmedetomidine, including off-label use in children.
Risk factors and risk groups	Paediatric patients, off-label routes of administration (e.g. intranasal administration or use as an adjunct with local anesthetic in peripheral blocks)
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.1, 4.2, 4.4* *PL section 1, 3* Indications and instructions for administration included in sections 4.1 and 4.2, respectively Use in only ICU, operating room and during diagnostic procedures emphasised in section 4.4

Missing information : Pregnancy	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* Advice that Dexdor should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexmedetomidine included in section 4.6

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Dexdor.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Dexdor.

Annex 4 - Specific adverse drug reaction follow-up forms

The templates used to create follow-up queries for the individual case safety reports received for the potential risks are listed below.

Atrioventricular block

- Please provide patient's concomitant diseases and medical history relevant for the event (e.g. cardiac conduction disorders)
- Please provide patient demographics (e.g. gender and age) and indication for which dexmedetomidine was used
- Please provide detailed information on the dosing of dexmedetomidine (treatment start time, dose/infusion rate, duration of treatment and time of discontinuation)
- Please provide a list of medications that were used concomitantly with dexmedetomidine including name, dose and dosing frequency/rate
- Please provide description of the event including ECG findings (e.g. PR interval), signs and symptoms, final diagnosis (at least the grade of AV block), onset time of first symptoms/signs, course of action as well as treatment and outcome of the event
- Was dexmedetomidine thought to be causally related to the development of AV block?
- Was treatment with dexmedetomidine discontinued or infusion rate decreased due to atrioventricular block or some other adverse reaction? If yes, did the event abate?
- Did the patient have any other factors in addition to treatment with dexmedetomidine that might have contributed to the development of the event, e.g. other medications or diseases?
- Was dexmedetomidine re-introduced? If yes, did the reaction reoccur?

Cortisol suppression

- Please provide patient's concomitant diseases and medical history relevant for the event (e.g. adrenal insufficiency or conditions that might have contributed to abnormal cortisol secretion such as sepsis or some severe underlying disease/organ failure)
- Please provide patient demographics (e.g. gender and age) and indication for which dexmedetomidine was used
- Please provide detailed information on the dosing of dexmedetomidine (treatment start time, dose/infusion rate, duration of treatment and time of discontinuation)
- Please provide a list of medications that were used concomitantly with dexmedetomidine including name, dose and dosing frequency/rate
- Please provide description of the event including laboratory data on cortisol levels and other applicable tests (e.g. ACTH stimulation test), signs and symptoms, onset time of first symptoms/signs, course of action as well as treatment and outcome of the event
- Was dexmedetomidine thought to be causally related to the development of cortisol suppression?
- Was treatment with dexmedetomidine discontinued or infusion rate decreased due to cortisol suppression or some other adverse reaction? If yes, did the event abate?

- Did the patient have any other factors in addition to treatment with dexmedetomidine that might have contributed to the development of the event, e.g. other medications or diseases?
- Was dexmedetomidine re-introduced? If yes, did the reaction reoccur?

Convulsions

- Please provide patient's concomitant diseases and medical history relevant for the event (e.g. history of convulsions or conditions that might have contributed to the development of convulsions)
- Please provide patient demographics (e.g. gender and age) and indication for which dexmedetomidine was used
- Please provide detailed information on the dosing of dexmedetomidine (treatment start time, dose/infusion rate, duration of treatment and time of discontinuation)
- Please provide a list of medications that were used concomitantly with dexmedetomidine including name, dose and dosing frequency/rate
- Please provide description of the event including abnormal diagnostic findings (e.g. EEG), signs and symptoms, onset time of first symptoms/signs, course of action as well as treatment and outcome of the event
- Was dexmedetomidine thought to be causally related to the development of convulsions?
- Was treatment with dexmedetomidine discontinued or infusion rate decreased due to convulsions or some other adverse reaction? If yes, did the event abate?
- Did the patient have any other factors in addition to treatment with dexmedetomidine that might have contributed to the development of the event, e.g. underlying diseases or addition or discontinuation of concomitant medications?
- Was dexmedetomidine re-introduced? If yes, did the reaction reoccur?

Hypothermia

- Please provide patient's concomitant diseases and medical history relevant for the event
- Please provide patient demographics (e.g. gender and age) and indication for which dexmedetomidine was used
- Please provide detailed information on the dosing of dexmedetomidine (treatment start time, dose/infusion rate, duration of treatment and time of discontinuation)
- Please provide a list of medications that were used concomitantly with dexmedetomidine including name, dose and dosing frequency/rate
- Please provide description of the event including abnormal diagnostic findings (e.g. body temperature , heart rate), signs and symptoms, onset time of first symptoms/signs, course of action as well as treatment and outcome of the event
- Was dexmedetomidine thought to be causally related to the development of hypothermia?
- Was treatment with dexmedetomidine discontinued or infusion rate decreased due to hypothermia or some other adverse reaction? If yes, did the event abate?
- Did the patient have any other factors in addition to treatment with dexmedetomidine that might have contributed to the development of the event, e.g. other medications or diseases?
- Was dexmedetomidine re-introduced? If yes, did the reaction reoccur?

Cardiac arrest

- Please provide patient's concomitant diseases and medical history relevant for the event (e.g. cardiac conduction and structural disorders)
- Please provide patient demographics (e.g. gender and age) and indication for which dexmedetomidine was used
- Please provide detailed information on the dosing of dexmedetomidine (treatment start time, dose/infusion rate, duration of treatment and time of discontinuation)
- Was bolus/loading dose used? If yes, please provide details
- Please provide a list of medications that were used concomitantly with dexmedetomidine including name, dose and dosing frequency/rate
- Please provide description of the event including ECG findings, signs and symptoms, final diagnosis, onset time of first symptoms/signs, course of action as well as treatment and outcome of the event
- Was dexmedetomidine thought to be causally related to the development of cardiac arrest?
- Was treatment with dexmedetomidine discontinued or infusion rate decreased due to cardiac arrest or some other adverse reaction? If yes, did the event abate?
- Did the patient have any other factors in addition to treatment with dexmedetomidine that might have contributed to the development of the event, e.g. surgical procedures, other medications or diseases?
- Was dexmedetomidine re-introduced? If yes, did the reaction reoccur?

TdP/QT prolongation

- Please provide patient's concomitant diseases and medical history relevant for the event (e.g. cardiac conduction and structural disorders)
- Please provide patient demographics (e.g. gender and age) and indication for which dexmedetomidine was used
- Please provide detailed information on the dosing of dexmedetomidine (treatment start time, dose/infusion rate, duration of treatment and time of discontinuation)
- Was bolus/loading dose used? If yes, please provide details
- Please provide a list of medications that were used concomitantly with dexmedetomidine including name, dose and dosing frequency/rate
- Please provide description of the event including ECG findings (including corrected QT times), signs and symptoms, final diagnosis, onset time of first symptoms/signs, course of action as well as treatment and outcome of the event
- Was dexmedetomidine thought to be causally related to the development of the event?
- Was treatment with dexmedetomidine discontinued or infusion rate decreased due to the event? If yes, did the event abate?
- Did the patient have any other factors in addition to treatment with dexmedetomidine that might have contributed to the development of the event, e.g. other medications or diseases?

- Was dexmedetomidine re-introduced? If yes, did the reaction reoccur?

Overdose

- Please provide patient details including gender, age and weight, and indication for which dexmedetomidine was used
- Please provide detailed information on the dosing of dexmedetomidine (treatment start time, dose/infusion rate, duration of treatment and time of discontinuation)
- What was considered to be the reason for the overdose of dexmedetomidine: intentional dose increase or accidental overdose due to medication error? If latter, please provide detailed description of the medication error.
- Did the overdose of dexmedetomidine lead to any adverse reactions? If yes, please provide description of those reactions including abnormal diagnostic findings, signs and symptoms, onset time of first symptoms/signs, course of action as well as treatment and outcome of the events
- Was the infusion rate of dexmedetomidine altered or treatment discontinued due to overdose or due to possibly resulting adverse reactions?
- How was the dexmedetomidine overdose treated?
- Please provide the final outcome
- Please provide a list of medications that were used concomitantly with dexmedetomidine including name, dose and dosing frequency/rate

Off-label use

- Please provide patient details including gender, age and weight
- Please provide the indication for which and circumstances where dexmedetomidine was used off-label
- Please provide detailed information on the dosing of dexmedetomidine (treatment start time, dose/infusion rate, duration of treatment and time of discontinuation)
- Please provide a list of medications that were used concomitantly with dexmedetomidine including name, dose and dosing frequency/rate
- Did the off-label use of dexmedetomidine lead to any adverse reactions? If yes, please provide description of those reactions including abnormal diagnostic findings, signs and symptoms, onset time of first symptoms/signs, course of action as well as treatment and outcome of the events

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

DHPC: Increased mortality in younger ICU patients

Dexmedetomidine (Dexdor®): Evidence for increased risk of mortality in ICU patients ≤65 years when dexmedetomidine is used to provide deep sedation

Dear Healthcare professional,

Orion Corporation in agreement with the European Medicines Agency and the <*National Competent Authority* > would like to inform you of the following:

Summary

- **The SPICE III study was a randomised clinical trial comparing the effect of sedation with dexmedetomidine on all cause mortality with the effect of "usual standard of care" in 3,904 critically ill adult ICU patients. The study showed no difference in 90-day mortality overall between the dexmedetomidine and the usual care group (mortality 29.1% in both groups).**
- **The study showed an effect of age on risk of mortality. Dexmedetomidine was associated with an increased risk of mortality in the age-group ≤65 years compared with alternative sedatives (odds ratio 1.26; 95% credibility interval 1.02 to 1.56). The mechanism is not known.**
- **This heterogeneity of effect on mortality from age was most prominent in cases with early use of dexmedetomidine in high dose to achieve deep sedation in patients admitted for other reasons than post-operative care and increased with increasing APACHE II scores.**
- **The effect on mortality was not detectable when dexmedetomidine was used for light sedation.**
- **These findings should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in younger patients.**
- **Dexmedetomidine is not authorised for sedation deeper than RASS -3 in patients receiving intensive care**

Background on the safety concern

Dexmedetomidine (Dexdor®) is indicated for:

- sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).
- sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

The academy sponsored SPICE III trial enrolled 4000 ICU patients needing mechanical ventilation, who were randomly allocated to receive sedation with either dexmedetomidine as primary sedative or with standard of care (propofol, midazolam). The target sedation range was not limited to Dexdor approved indication in ICU sedation (RASS 0 to -3), deeper sedation levels (RASS -4 and -5) were also allowed. The administration of Dexdor was continued as clinically required for up to 28 days after randomization.[1]

Altogether 3904 patients were included in an intention-to-treat analysis. The study showed no difference in 90-day mortality overall between the dexmedetomidine and the usual care group (mortality 29.1% in both groups). The median age of patients included in the analysis was 63.7 years. Among patients under the median age 976 patients received dexmedetomidine as primary sedative. Out of them 219 died within 90-days after randomization (22.4%). Among patients under the median age 975 patients were sedated according to usual care (propofol, midazolam). Out of them 176 died within 90-days after randomization (18.1%).[1]

In subsequent analyses heterogeneity of treatment effect of Dexdor has been identified.[2,3] An increased risk of 90-day mortality (odds ratio 1.26 [95% CrI 1.02-1.56]) was observed among patients ≤ 65 years of age. While the mechanism is yet unclear, the heterogeneity of effect on mortality from age was most prominent in cases with early use of dexmedetomidine in high dose to achieve deep sedation in patients admitted for other reasons than post-operative care and increased with increasing APACHE II scores.

These findings should be weighed against the expected clinical benefit of Dexdor, when administered according to the recommendations in the product information, compared to alternative sedatives in patients 65 years of age or younger.

The effect on mortality was not detectable when dexmedetomidine was used for light sedation or in patients > 65 years old.

The mechanism by which dexmedetomidine might increase the risk of death in ICU patients aged ≤65 years is not known.

Dexmedetomidine is not authorised for sedation deeper than RASS -3 in patients receiving intensive care.

A warning has been added to the product information describing the evidence, and risk factors, for increased risk of mortality in ICU patients ≤65 years of age.

Call for reporting

Reporting suspected adverse reactions 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 *[include the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system*

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

TO BE COMPLETED LOCALLY

Annexes (if applicable)

References

1. SHEHABI, Yahya, et al. Early sedation with dexmedetomidine in critically ill patients. *New England Journal of Medicine*, 2019, 380.26: 2506-2517.

2. SHEHABI, Yahya, et al. Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial. *Intensive care medicine*, 2021, 47.4: 455-466.

3. SHEHABI, Yahya, et al. unpublished data (2021)