SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
1. NAME OF THE MEDICINAL PRODUCT [Nationally approved name] 100 micrograms/ml concentrate for solution for infusion	--	--
2. QUALITATIVE AND QUANTITATIVE COMPOSITION Each 1 ml of concentrate contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine. Each 2 ml ampoule contains 200 micrograms of dexmedetomidine. Each 2 ml vial contains 200 micrograms of dexmedetomidine. Each 4 ml vial contains 400 micrograms of dexmedetomidine. Each 10 ml vial contains 1000 micrograms of dexmedetomidine. The concentration of the final solution after dilution should be either 4 micrograms/ml or 8 micrograms/ml. Excipient with known effect: ~~Each ml of concentrate contains less than 1 mmol (approximately 3.5 mg) sodium.~~This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'. For the full list of excipients, see section 6.1.	**(CMS):** Comment on PIL	To be in line with the changes made to the PIL due to (CMS) objections
3. PHARMACEUTICAL FORM Concentrate for solution for infusion (sterile concentrate). The concentrate is a clear, colourless solution, pH 4.5 - 7.0	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
4. CLINICAL PARTICULARS **4.1 Therapeutic indications** 1. For sedation of adult ICU (Intensive Care Unit) patients requiring 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.	--	--
4.2 Posology and method of administration **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). Posology ICU sedation** For hospital use only. [Nationally approved name] should be administered by healthcare professionals skilled in the management of patients requiring intensive care. 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. *(continued on next page)*	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) *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 [Nationally approved name] should be switched to an alternative sedative agent. Use of a loading dose of [Nationally approved name] 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 [Nationally approved name] are established. *Duration* There is no experience in the use of [Nationally approved name] for more than 14 days. The use of [Nationally approved name] for longer than this period should be regularly reassessed	--	--
Indication 2. For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation. [Nationally approved name] should be administered only by health care professionals skilled in the anaesthetic management of patients in the operating room or during diagnostic procedures. When [Nationally approved name] 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, apnoea, dyspnoe and/or oxygen desaturation (see section 4.8). Supplemental oxygen should be immediately available and provided when indicated. The oxygen saturation should be monitored. *(continued on next page)*	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) [Nationally approved name] is given as a loading infusion followed by maintenance infusion. Depending on the procedure concomitant local analgesia may be needed in order to achieve the desired clinical effect. Additional analgesia or sedatives (e.g. midazolam, propofol and opioids) are recommended in case of painful procedures or if deep sedation is necessary.*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. - **For awake fiberoptic intubation in adult patients:** A loading infusion of 1 microgram/kg over 10 minutes. - **For patients over 65 years of age:** A dose reduction should be considered. - **For adult patients with impaired hepatic function:** A dose reduction should be considered. *Maintenance of Procedural Sedation:* - **For adult patients:** The maintenance infusion is generally initiated at 0.6 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. - **For awake fiberoptic intubation in adult patients:** A maintenance infusion of 0.7 microgram/kg/hour is recommended until the endotracheal tube is secured. - **For patients over 65 years of age:** A dose reduction should be considered. **For adult patients with impaired hepatic function:** A dose reduction should be considered**.**	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
Special populations *Elderly:* A dose reduction should be considered. Please refer to section 4.4 . *Renal impairment:* No dose adjustment is required for patients with renal impairment. *Hepatic impairment:* [Nationally approved name] is metabolised in the liver and should be used with caution in patients with hepatic impairment. A reduced maintenance dose may be considered (see sections 4.4 and 5.2). *Paediatric population:* The safety and efficacy of [Nationally approved name] in children aged 0 to 18 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. Method of administration [Nationally approved name] must be administered only as a diluted intravenous infusion using a controlled infusion device. For instructions on dilution of the medicinal product before administration, see section 6.6. [Nationally approved name] should not be given as a bolus dose. See also general precautions, section 4.4.	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
4.3 Contraindications Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Advanced heart block (grade 2 or 3) unless paced. Uncontrolled hypotension. Acute cerebrovascular conditions.	--	--
4.4 Special warnings and precautions for use <u>Monitoring</u> Based on the indications, [Nationally approved name] is intended for use in an intensive care setting,operating roomandduring diagnostic procedures. The use in other environments is not recommended. All patients should have continuous cardiac monitoring during [Nationally approved name] infusion. The time to recovery after the use of dexmedetomidine was reported to be approximately one hour. When used in outpatients, based on the individual condition of the patient close monitoring is at least necessary for this period of time and medical supervision should continue for at least another hour to ensure the safety of the patient.	**(CMS):** -Monitoring Based on the indications, [Nationally approved name] is intended for use in an intensive care setting, operating room and during diagnostic procedures (stylistic matter):	The text is amended as desired; the missing space characters were added.

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
General precautions [Nationally approved name] should not be given as bolus dose. At ICU also a loading dose is not recommended. Users should generally be ready to use an alternative sedative for acute control of agitation, in ICU patients especially during the first few hours of treatment. Some patients receiving [Nationally approved name] have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms. [Nationally approved name] should not be used as an induction agent for intubation or to provide sedation during muscle relaxant use. Dexmedetomidine lacks the anticonvulsant action of some other sedatives and so will not suppress underlying seizure activity. Care should be taken if combining dexmedetomidine with other substances with sedative or cardiovascular actions as additive effects may occur. [Nationally approved name] is not recommended for patient controlled sedation. Adequate data is not available. When [Nationally approved name] is used in outpatients the effects of dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient should be considered when advising patients on: *(continued on next page*	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) • The advisability of being accompanied on leaving the place of administration • The timing of recommencement of skilled or hazardous tasks such as driving • The use of other agents that may sedate (e.g, benzodiazepines, opioids, alcohol.) Elderly Caution should be exercised when administering dexmedetomidine to elderly patients. Elderly patients over 65 years of age are more prone to hypotension with the administration of dexmedetomidine. A dose reduction should be considered. Please refer to section 4.2.	**(CMS):** -Subheading Elderly should be written as a new paragraph	The text is amended as desired; the missing line break was added.
Cardio-vascular effects and precautions [Nationally approved name] reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension (see section 5.1). [Nationally approved name] normally does not cause deep sedation and patients may be easily roused. [Nationally approved name] is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation or with severe cardiovascular instability. Caution should be exercised when administering dexmedetomidine to patients with pre-existing bradycardia. Data on the effects of [Nationally approved name] in patients with heart rate <60 are very limited and particular care should be taken with such patients. Bradycardia does not normally require treatment, but has commonly responded to anti-cholinergic medicine or dose reduction where needed. Patients with high physical fitness and slow resting heart rate may be particularly sensitive to bradycardic effects of alpha-2	--	--

receptor agonists and cases of transient sinus arrest have been reported. *(continued on next page)*		
Initial Proposed SmPC plus proposed revisions (using track-changes function)	**Objections/Points for consideration raised by Member States**	**Company response (with cross reference to the response document when applicable)**
(continued) The hypotensive effects of [Nationally approved name] may be of greater significance in those patients with pre-existing hypotension (especially if not responsive to vasopressors), hypovolaemia, chronic hypotension or reduced functional reserve such as patients with severe ventricular dysfunction and the elderly and special care is warranted in these cases (see section 4.3). Hypotension does not normally require specific treatment but, where needed, users should be ready to intervene with dose reduction, fluids and/or vasoconstrictors. Patients with impaired peripheral autonomic activity (e.g. due to spinal cord injury) may have more pronounced haemodynamic changes after starting [Nationally approved name] and so should be treated with care. Transient hypertension has been observed primarily during the loading dose in association with the peripheral vasoconstrictive effects of dexmedetomidine and a loading dose in ICU sedation is not recommended. Treatment of hypertension has generally not been necessary but decreasing the continuous infusion rate may be advisable. Local vasoconstriction at higher concentration may be of greater significance in patients with ischaemic heart disease or severe cerebrovascular disease who should be monitored closely. Dose reduction or discontinuation should be considered in a patient developing signs of myocardial or cerebral ischaemia. *(continued on next page)*	--	--
Initial Proposed SmPC plus proposed revisions (using track-changes function)	**Objections/Points for consideration**	**Company response (with cross**

SmPC - Tabular presentation of proposed changes

	raised by Member States	reference to the response document when applicable)
(continued) Patients with hepatic impairment Care should be taken in severe hepatic impairment as excessive dosing may increase the risk of adverse reactions, over-sedation or prolonged effect as a result of reduced dexmedetomidine clearance. Patients with neurological disorders Experience of [Nationally approved name] in severe neurological disorders such as head injury and after neurosurgery is limited and it should be used with caution here, especially if deep sedation is required. [Nationally approved name] may reduce cerebral blood flow and intracranial pressure and this should be considered when selecting therapy. Other Alpha-2 agonists have rarely been associated with withdrawal reactions when stopped abruptly after prolonged use. This possibility should be considered if the patient develops agitation and hypertension shortly after stopping dexmedetomidine. It is not known whether dexmedetomidine is safe to use in malignant hyperthermia-sensitive individuals therefore it is not recommended. [Nationally approved name] treatment should be discontinued in the event of a sustained unexplained fever. Excipient with known effect: Each ml of concentrate contains less than 1 mmol (approximately 3.5 mg) sodium.	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
4.5 Interaction with other medicinal products and other forms of interaction Interaction studies have only been performed in adults. Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, including sedative, anaesthetic and cardiorespiratory effects. Specific studies have confirmed enhanced effects with isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with dexmedetomidine, a reduction in dosage of dexmedetomidine or the concomitant anaesthetic, sedative, hypnotic or opioid may be required. Inhibition of CYP enzymes including CYP2B6 by dexmedetomidine has been studied in human liver microsome incubations. In vitro study suggests that interaction potential in vivo exists between dexmedetomidine and substrates with dominant CYP2B6 metabolism. Induction of dexmedetomidine *in vitro* was observed on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4, and induction *in vivo* cannot be excluded. The clinical significance is unknown. The possibility of enhanced hypotensive and bradycardic effects should be considered in patients receiving other medicinal products causing these effects, for example beta blockers, although additional effects in an interaction study with esmolol were modest.	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
4.6 Fertility, pregnancy and lactation Pregnancy There are no adequate data from the use of dexmedetomidine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). [Nationally approved name] is not recommended during pregnancy and in women of childbearing potential not using contraception. Breastfeeding Available data in the rat have shown excretion of dexmedetomidine or metabolites in milk. A risk to infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue dexmedetomidine therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. Fertility In the rat fertility study, dexmedetomidine had no effect on male or female fertility. **4.7 Effects on ability to drive and use machines** [Nationally approved name] has major impact on the ability to drive and use machines.	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
4.8 Undesirable effects Summary of the safety profile Indication 1: Sedation of adult ICU (Intensive Care Unit) patients: The most frequently reported adverse reactions with dexmedetomidine in ICU sedation are hypotension, hypertension and bradycardia, occurring in approximately 25%, 15% and 13% of ICU patients respectively. Hypotension and bradycardia were also the most frequent dexmedetomidine-related serious adverse reactions occurring in 1.7% and 0.9% of randomised Intensive Care Unit (ICU) patients respectively. Indication 2: Procedural/awake sedation The most frequently reported adverse reactions with dexmedetomidine in procedural sedation are: - Hypotension (54 % in dexmedetomidine-group vs. 30 % in placebo-group) - Respiratory depression (37 % in dexmedetomidine-group vs. 32 % in placebo-group) - Bradycardia (14 % in dexmedetomidine-group vs. 4 % in placebo-group)	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
Tabulated list of adverse reactions The adverse reactions listed in Table 1 have been accumulated from pooled data of clinical trials in intensive care consisting of 3,137 randomised patients (1,879 treated with dexmedetomidine, 864 treated with active comparators, and 394 treated with placebo) and from pooled data of clinical trials conducted in procedural sedation with 431 randomised patients (381 treated with dexmedetomine and 113 treated with placebo). The frequency of adverse reactions listed below is defined using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. *(continued on next page)*	--	--

SmPC - Tabular presentation of proposed changes

<table>
<tr><th>Initial Proposed SmPC plus proposed revisions (using track-changes function)</th><th>Objections/Points for consideration raised by Member States</th><th>Company response (with cross reference to the response document when applicable)</th></tr>
<tr><td>

(continued)

Table 1: Adverse reactions (Indication 1 and Indication 2)

<table>
<tr><th>MedDRA System Organ Class (SOC)</th><th>Very common</th><th>Common</th><th>Uncommon</th><th>Rare</th></tr>
<tr><td>Metabolism and nutrition disorders</td><td></td><td>Hyperglycaemia, Hypoglycaemia *</td><td>Metabolic acidosis *, hypoalbuminaemia *</td><td></td></tr>
<tr><td>Psychiatric disorder</td><td></td><td>Agitation *</td><td>Hallucination *</td><td></td></tr>
<tr><td>Cardiac disorders</td><td>Bradycardia</td><td>Myocardial ischaemia or infarction *,

Tachycardia</td><td>Atrioventricular block first degree, cardiac output decreased *</td><td></td></tr>
<tr><td>Vascular disorders</td><td>Hypotension , hypertension</td><td></td><td></td><td></td></tr>
<tr><td>Respiratory, thoracic and mediastinal disorders</td><td>Respiratory depression</td><td></td><td>Dyspnoea *, apnoea *</td><td></td></tr>
<tr><td>Gastrointestinal</td><td></td><td>Nausea, vomiting,</td><td>Abdominal</td><td></td></tr>
</table>

</td><td>--</td><td>--</td></tr>
</table>

disorders		dry mouth	distension *			
General disorders and administration site conditions		Withdrawal syndrome, hyperthermia *	Drug ineffective, thirst *			

* Adverse reactions reported only for indication 1

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
Description of selected adverse reactions Clinically significant hypotension or bradycardia should be treated as described in section 4.4. In relatively healthy non-ICU subjects treated with dexmedetomidine, bradycardia has occasionally led to sinus arrest or pause. The symptoms responded to leg raising and anticholinergics such as atropine or glycopyrrolate. In isolated cases bradycardia has progressed to periods of asystole in patients with pre-existing bradycardia. Hypertension has been associated with the use of a loading dose at ICU use and this reaction can be reduced by avoiding such a loading dose or reducing the infusion rate or size of the loading dose. Paediatric population Children > 1 month post-natal, predominantly post-operative, have been evaluated for treatment up to 24 hours in the ICU and demonstrated a similar safety profile as in adults. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to maintenance doses ≤ 0.2 micrograms/kg/h. A single case of hypothermic bradycardia in a neonate has been reported in the literature. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
4.9 Overdose Symptoms Several cases of dexmedetomidine overdose have been reported both in the clinical trial and the post-marketing data. The reported highest infusion rates of dexmedetomidine in these cases have reached up to 60 µg/kg/h for 36 minutes and 30 µg/kg/h for 15 minutes in a 20-month-old child and in an adult, respectively. The most common adverse reactions reported in conjunction with overdose in these cases included bradycardia, hypotension, oversedation, somnolence and cardiac arrest. Management In cases of overdose with clinical symptoms, dexmedetomidine infusion should be reduced or stopped. Expected effects are primarily cardiovascular and should be treated as clinically indicated (see section 4.4). At high concentration hypertension may be more prominent than hypotension. In clinical studies, cases of sinus arrest reversed spontaneously or responded to treatment with atropine and glycopyrrolate. Resuscitation was required in isolated cases of severe overdose resulting in cardiac arrest.	--	--
5. PHARMACOLOGICAL PROPERTIES **5.1 Pharmacodynamic properties** Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives, ATC code: N05CM18 *(continued on next page)*	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) Dexmedetomidine is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has analgesic and anesthetic/analgesic-sparing effects. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstricting effects prevail leading to an increase in systemic vascular resistance and blood pressure, while the bradycardic effect is further emphasised. Dexmedetomidine is relatively free from respiratory depressive effects when given as monotherapy to healthy subjects. Physiologic responses mediated by α2 adrenoreceptors vary with location. From an anaesthesiology viewpoint, neuronal hyperpolarization is a key element in the mechanism of action of α2-adrenoceptor agonists centrally and peripherally. In general, presynaptic activation of the α2 adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of α2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can produce analgesia, sedation, and anxiolysis. Dexmedetomidine combines all these effects, thus avoiding some of the side effects of multiagent therapies. At least 3 different α-2 isoreceptors have been defined both by pharmacologic studies (affinity for different a2 antagonists) and by biological probes. *(continued on next page)*		

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) The α2-adrenergic receptor mediates its effects by activating guanine-nucleotide regulatory binding proteins (G proteins). Activated G proteins modulate cellular activity by signalling a second messenger system or by modulating ion channel activity. The second messenger system, when activated, leads to the inhibition of adenylate cyclase, which, in turn, results in decreased formation of 3,5-cyclic adenosine monophosphate (cAMP). Specific cAMP-dependent kinases modify the activity of target proteins by controlling their phosphorylation status. Modulation of ion channel activity leads to hyperpolarization of the cell membrane. Efflux of potassium through an activated channel hyperpolarizes the excitable membrane and provides an effective means of suppressing neuronal firing. Stimulation of the α2 adrenoceptor also suppresses calcium entry into the nerve terminal, which may be responsible for its inhibitory effect on secretion of neurotransmitters. From an anaesthesiologist viewpoint, neuronal hyperpolarization is a key element in the mechanism of action of α2-adrenoceptor agonists. In general, presynaptic activation of the α2 adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of α2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can produce analgesia, sedation, and anxiolytics. Dexmedetomidine combines all these effects, thus avoiding some of the side effects of multiagent therapies. Dexmedetomidine is a α2-adrenoceptor agonist with dose-dependent α2-adrenoceptor selectivity *(continued on next page)*		

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) Indication 1: Sedation of adult ICU (Intensive Care Unit) patients In placebo controlled trials in a post-operative ICU population previously intubated and sedated with midazolam or propofol, dexmedetomidine significantly reduced the requirement for both rescue sedative (midazolam or propofol) and opioids during sedation for up to 24 hours. Most dexmedetomidine patients required no additional sedative treatment. Patients could be successfully extubated without stopping the dexmedetomidine infusion. Dexmedetomidine was similar to midazolam (Ratio 1.07; 95% CI 0.971, 1.176) and propofol (Ratio 1.00; 95% CI 0.922, 1.075) on the time in target sedation range in a predominantly medical population requiring prolonged light to moderate sedation (RASS 0 to -3) in the ICU for up to 14 days, reduced the duration of mechanical ventilation compared to midazolam and reduced the time to extubation compared to midazolam and propofol. Compared to both propofol and midazolam, patients were more easily roused, more cooperative and better able to communicate whether or not they had pain. Dexmedetomidine treated patients had more frequent hypotension and bradycardia but less tachycardia than those receiving midazolam and more frequent tachycardia but similar hypotension to propofol-treated patients. Delirium measured by the CAM-ICU scale was reduced in a study compared to midazolam and delirium-related adverse events were lower on dexmedetomidine compared to propofol. Those patients who withdrew due to insufficient sedation were switched to either propofol or midazolam. The risk of insufficient sedation was increased in patients who were difficult to sedate with standard care immediately prior to switching. *(continued on next page)*		
Initial Proposed SmPC plus proposed revisions (using track-changes function)	**Objections/Points for consideration**	**Company response (with cross**

SmPC - Tabular presentation of proposed changes

	raised by Member States	reference to the response document when applicable)
(continued) Evidence of paediatric efficacy was seen in a dose-controlled ICU study in a largely post-operative population aged 1 month to ≤ 17 years. Approximately 50% of patients treated with dexmedetomidine did not require rescue addition of midazolam during a median treatment period of 20.3 hours, not exceeding 24 hours. Data on treatment for > 24 hours is not available. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to low doses (≤ 0.2 micrograms/kg/h) (see sections 5.2 and 4.4). New-born infants may be particularly sensitive to the bradycardic effects of dexmedetomidine in the presence of hypothermia and in conditions of heart rate-dependent cardiac output. In double blind comparator controlled ICU studies the incidence of cortisol suppression in patients treated with dexmedetomidine (n=778) was 0.5% compared with 0% in patients treated with either midazolam (n=338) or propofol (n=275). The event was reported as mild in 1 and moderate in 3 cases.	--	--
<u>Indication 2: Procedural/awake sedation</u> The safety and efficacy of dexmedetomidine for sedation of non-intubated patients prior to and/or during surgical and diagnostic procedures was evaluated in two randomized, double-blind, placebo-controlled multicenter clinical trials. *(continued on next page)*	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) ▪ Study 1 evaluated the sedative properties of dexmedetomidine in patients having a variety of elective surgeries/procedures performed under monitored anesthesia care by comparing the percent of patients not requiring rescue midazolam to achieve a specified level of sedation using the standardized Observer's Assessment of Alertness/Sedation Scale. Patients were randomized to receive a loading infusion of either dexmedetomidine 1 µg/kg (n=129), dexmedetomidine 0.5 µg/kg (n=134), or placebo (normal saline) (n=63) given over 10 minutes and followed by a maintenance infusion started at 0.6 µg/kg/h. The maintenance infusion of study drug could be titrated from 0.2 mµ/kg/h to 1 µg/kg/h to achieve the targeted sedation score (Observer's Assessment of Alertness/Sedation Scale ≤4). Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an Observer's Assessment of Alertness/Sedation Scale ≤4. After achieving the desired level of sedation, a local or regional anesthetic block was performed. Demographic characteristics were similar between the dexmedetomidine and placebo groups. Efficacy results showed that dexmedetomidine was more effective than the placebo group when used to sedate non-intubated patients. 54 % of the patients receiving dexmedetomidine 1 µg/kg and 40 % the patients receiving 0.5 µg/kg dexmedetomidine did not require midazoloam rescue vs. 3 % of patients receiving the placebo. *(continued on next page)*		

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) ▪ Study 2 evaluated dexmedetomidine in patients undergoing awake fiberoptic intubation prior to a surgical or diagnostic procedure. The sedative properties of dexmedetomidine were evaluated by comparing the percent of patients requiring rescue midazolam to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale score ≥2. Patients were ▪ randomized to receive a loading infusion of dexmedetomidine 1 µg/kg (n=55)or placebo (normal saline) (n=50) given over 10 minutes and followed by a fixed maintenance infusion of 0.7 mµg/kg/h. After achieving the desired level of sedation, topicalisation of the airway occurred. Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain a Ramsay Sedation Scale ≥2. Demographic characteristics were similar between the dexmedetomidine and placebo groups. Efficacy results showed that dexmedetomidine was more effective than the placebo group when used to sedate non-intubated patients. 53 % of the patients receiving dexmedetomidine 1 µg/kg did not require midazoloam rescue vs. 14 % of patients receiving the placebo		

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
5.2 Pharmacokinetic properties The pharmacokinetics of dexmedetomidine has been assessed following short term IV administration in healthy volunteers and long term infusion in ICU population. <u>Distribution</u> Dexmedetomidine exhibits a two-compartment disposition model. In healthy volunteers it exhibits a rapid distribution phase with a central estimate of the distribution half-life ($t_{1/2\alpha}$) of about 6 minutes. The mean estimate of the terminal elimination half-life ($t_{1/2}$) is approximately 1.9 to 2.5 h (min 1.35, max 3.68 h) and the mean estimate of the steady-state volume of distribution (Vss) is approximately 1.16 to 2.16 l/kg (90 to 151 litres). Plasma clearance (Cl) has a mean estimated value of 0.46 to 0.73 l/h/kg (35.7 to 51.1 l/h). The mean body weight associated with these Vss and Cl estimates was 69 kg. Plasma pharmacokinetics of dexmedetomidine is similar in the ICU population following infusion >24 h. The estimated pharmacokinetic parameters are: $t_{1/2}$ approximately 1.5 hours, Vss approximately 93 litres and Cl approximately 43 l/h. The pharmacokinetics of dexmedetomidine is linear in the dosing range from 0.2 to 1.4 µg/kg/h and it does not accumulate in treatments lasting up to 14 days. Dexmedetomidine is 94% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.85 to 85 ng/ml. Dexmedetomidine binds to both human serum albumin and Alpha-1-acid glycoprotein with serum albumin as the major binding protein of dexmedetomidine in plasma.	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
Biotransformation and Elimination Dexmedetomidine is eliminated by extensive metabolism in the liver. There are three types of initial metabolic reactions; direct N-glucuronidation, direct N-methylation and cytochrome P450 catalysed oxidation. The most abundant circulating dexmedetomidine metabolites are two isomeric N-glucuronides. Metabolite H-1, N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide, is also a major circulating product of dexmedetomidine biotransformation. Cytochrome P-450 catalyses the formation of two minor circulating metabolites, 3-hydroxymethyl dexmedetomidine produced by hydroxylation at the 3-methyl group of dexmedetomidine and H-3 produced by oxidation in the imidazole ring. Available data suggest that the formation of the oxidised metabolites is mediated by several CYP forms (CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19). These metabolites have negligible pharmacological activity. Following IV administration of radiolabelled dexmedetomidine an average 95% of radioactivity was recovered in the urine and 4% in the faeces after nine days. The major urinary metabolites are the two isomeric N-glucuronides, which together accounted for approximately 34% of the dose and N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide that accounted for 14.51% of the dose. The minor metabolites dexmedetomidine carboxylic acid, 3-hydroxymethyl dexmedetomidine and its O-glucuronide individually comprised 1.11 to 7.66% of the dose. Less than 1% of unchanged parent drug was recovered in the urine. Approximately 28% of the urinary metabolites are unidentified minor metabolites.	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
Special Populations No major pharmacokinetic differences have been observed based on gender or age. Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment compared with healthy subjects. The mean percentage of unbound dexmedetomidine in plasma ranged from 8.5% in healthy subjects to 17.9% in subjects with severe hepatic impairment. Subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C) had decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. The mean plasma clearance values of unbound dexmedetomidine for subjects with mild, moderate, and severe hepatic impairment were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively. The mean $t_{1/2}$ for the subjects with mild, moderate or severe hepatic impairment was prolonged to 3.9, 5.4, and 7.4 hours, respectively. Although dexmedetomidine is administered to effect, it may be necessary to consider initial/maintenance dose reduction in patients with hepatic impairment depending on the degree of impairment and the response. The pharmacokinetics of dexmedetomidine in subjects with severe renal impairment (creatinine clearance <30 ml/min) is not altered relative to healthy subjects. Data in new-born infants (28 - 44 weeks gestation) to children 17 years of age are limited. Dexmedetomidine half life in children (1 month to 17 years) appears similar to that seen in adults, but in new-born infants (under 1 month) it appears higher. In the age groups 1 month to 6 years, body weight-adjusted plasma clearance appeared higher but decreased in older children. Body weight-adjusted plasma clearance in new-born infants (under 1 month) appeared lower (0.9 l/h/kg) than in the older groups due to immaturity. The available data is summarised in the following table; *(continued on next page)*	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)

(continued)

		Mean (95% CI)	
Age	N	Cl (l/h/kg)	$t_{1/2}$ (h)
Under 1 month	28	0.93 (0.76, 1.14)	4.47 (3.81, 5.25)
1 to < 6 months	14	1.21 (0.99, 1.48)	2.05 (1.59, 2.65)
6 to < 12 months	15	1.11 (0.94, 1.31)	2.01 (1.81, 2.22)
12 to < 24 months	13	1.06 (0.87, 1.29)	1.97 (1.62, 2.39)
2 to < 6 years	26	1.11 (1.00, 1.23)	1.75 (1.57, 1.96)
6 to < 17 years	28	0.80 (0.69, 0.92)	2.03 (1.78, 2.31)

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
5.3 Preclinical safety data Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity. In the reproductive toxicity studies, dexmedetomidine had no effect on male or female fertility in the rat, and no teratogenic effects were observed in the rat or rabbit. In the rabbit study intravenous administration of the maximum dose, 96 µg/kg/day, produced exposures that are similar to those observed clinically. In the rat, subcutaneous administration at the maximum dose, 200 µg/kg/day, caused an increase in embryofoetal death and reduced the foetal body weight. These effects were associated with clear maternal toxicity. Reduced foetal body weight was noted also in the rat fertility study at dose 18 µg/kg/day and was accompanied with delayed ossification at dose 54 µg/kg/day. The observed exposure levels in the rat are below the clinical exposure range.	--	--
6. PHARMACEUTICAL PARTICULARS **6.1 List of excipients** Sodium chloride Water for injections **6.2 Incompatibilities** This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Compatibility studies have shown potential for adsorption of dexmedetomidine to some types of natural rubber. Although dexmedetomidine is dosed to effect, it is advisable to use components with synthetic or coated natural rubber gaskets.	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
6.3 Shelf life 2 years *After dilution* Chemical and physical stability of the diluted infusion (Infusion Solution Stability) has been demonstrated for 48 hours at 25°C and at refrigerated conditions (2 °C – 8 °C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2° to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. **6.4 Special precautions for storage** This medicinal product does not require any special temperature storage conditions. Keep the ampoules or vials in the outer carton in order to protect from light. For storage conditions after dilution of the medicinal product, see section 6.3	--	--
6.5 Nature and contents of container 2 ml Type I colourless glass ampoules 2, 5 or 10 ml Type I colourless glass vials (with filling volumes of 2, 4 and 10 ml), bromobutyl rubber closure with fluoropolymer coating *(continued on next page)*	--	--

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) *Pack sizes* 5 x 2 ml ampoules 25 x 2 ml ampoules 5 x 2 ml vials 4 x 4 ml vials 5 x 4 ml vials 4 x 10 ml vials 5 x 10 ml vials Not all pack sizes may be marketed.		

SmPC - Tabular presentation of proposed changes

<table>
<tr><th>Initial Proposed SmPC plus proposed revisions (using track-changes function)</th><th>Objections/Points for consideration raised by Member States</th><th>Company response (with cross reference to the response document when applicable)</th></tr>
<tr><td>

6.6 Special precautions for disposal and other handling

Ampoules and vials are intended for single patient use only.

Preparation of solution

[Nationally approved name] can be diluted in glucose 50 mg/ml (5%), Ringers, mannitol or sodium chloride 9 mg/ml (0.9%) solution for injection to achieve the required concentration of either 4 micrograms/ml or 8 micrograms/ml prior to administration. Please see below in tabulated form the volumes needed to prepare the infusion.

In case the required concentration is 4 micrograms/ml:

Volume of [Nationally approved name] 100 micrograms/ml concentrate for solution for infusion	Volume of diluent	Total volume of infusion
2 ml	48 ml	50 ml
4 ml	96 ml	100 ml
10 ml	240 ml	250 ml
20 ml	480 ml	500 ml

(continued on next page)

</td><td>--</td><td>--</td></tr>
</table>

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)

(continued)

In case the required concentration is 8 micrograms/ml:

Volume of [Nationally approved name] 100 micrograms/ml concentrate for solution for infusion	Volume of diluent	Total volume of infusion
4 ml	46 ml	50 ml
8 ml	92 ml	100 ml
20 ml	230 ml	250 ml
40 ml	460 ml	500 ml

The solution should be shaken gently to mix well.

[Nationally approved name] should be inspected visually for particulate matter and discoloration prior to administration.

(continued on next page)

SmPC - Tabular presentation of proposed changes

Initial Proposed SmPC plus proposed revisions (using track-changes function)	Objections/Points for consideration raised by Member States	Company response (with cross reference to the response document when applicable)
(continued) [Nationally approved name] has been shown to be compatible when administered with the following intravenous fluids and medicinal products: Lactated Ringers, 5% glucose solution, sodium chloride 9 mg/ml (0.9%) solution for injection, mannitol 200 mg/ml (20%), thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, rocuronium bromide, glycopyrrolate bromide, phenylephrine HCl, atropine sulfate, dopamine, noradrenaline, dobutamine, midazolam, morphine sulfate, fentanyl citrate, and a plasma-substitute. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.		
7. MARKETING AUTHORISATION HOLDER [to be completed nationally] **8. MARKETING AUTHORISATION NUMBER(S)** [to be completed nationally] **9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION** [to be completed nationally] **10. DATE OF REVISION OF THE TEXT** [to be completed nationally]	--	--