ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dexdor 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The concentrate is a clear, colourless solution, pH 4.5 – 7.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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 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.

Special populations

Elderly

No dose adjustment is normally required for elderly patients.

Renal impairment

No dose adjustment is required for patients with renal impairment.

Hepatic impairment

Dexmedetomidine is metabolised in the liver and should be used with caution in patients with hepatic impairment. A reduced maintenance dose may be considered (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Dexdor 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

Dexdor must be administered only as a diluted intravenous infusion using a controlled infusion device. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Advanced heart block (grade 2 or 3) unless paced.

Uncontrolled hypotension.

Acute cerebrovascular conditions.

4.4 Special warnings and precautions for use

Monitoring

Dexdor is intended for use in an intensive care setting and use in other environments is not recommended. All patients should have continuous cardiac monitoring during Dexdor infusion. Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea (see section 4.8).

General precautions

Since Dexdor should not be administered by loading or bolus dose, users should be ready to use an alternative sedative for acute control of agitation or during procedures, especially during the first few hours of treatment.

Some patients receiving Dexdor 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.

Dexdor 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.

Cardio-vascular effects and precautions

Dexmedetomidine reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension (see section 5.1). Dexmedetomidine normally does not cause deep sedation and patients may be easily roused. Dexmedetomidine is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation or with severe cardiovascular instability.

Caution should be exercised when administering dexmedetomidine to patients with pre-existing bradycardia. Data on the effects of Dexdor 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.

The hypotensive effects of dexmedetomidine 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 dexmedetomidine and so should be treated with care.

Transient hypertension has been observed primarily during the loading dose in association with the peripheral vasoconstrictive effects of dexmedetomidine and a loading dose is not recommended. 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.

Patients with hepatic impairment

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

Patients with neurological disorders

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

Other

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

It is not known whether dexmedetomidine is safe to use in malignant hyperthermia-sensitive individuals therefore it is not recommended. Dexdor treatment should be discontinued in the event of a sustained unexplained fever.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, including sedative, anaesthetic and cardiorespiratory effects. Specific studies have confirmed enhanced effects with isoflurane, propofol, alfentanil, and midazolam.

No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with dexmedetomidine, a reduction in dosage of dexmedetomidine or the concomitant anaesthetic, sedative, hypnotic or opioid may be required.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Studies in animals have shown reproductive toxicity (see section 5.3). Dexdor 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

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The adverse reactions listed in Table 1 have been accumulated from pooled data of clinical trials in intensive care.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 1. Adverse reactions

Metabolism and nutrition disorders
Common: Hyperglycaemia, hypoglycaemia
Uncommon: Metabolic acidosis, hypoalbuminaemia

Psychiatric disorders
Common: Agitation
Uncommon: Hallucination

Cardiac disorders
Very common: Bradycardia*
Common: Myocardial ischaemia or infarction, tachycardia
Uncommon: Atrioventricular block first degree, cardiac output decreased

Vascular disorders:
Very common: Hypotension*, hypertension*

Respiratory, thoracic and mediastinal disorders
Common: Respiratory depression
Uncommon: Dyspnoea, apnoea

Gastrointestinal disorders
Common: Nausea, vomiting, dry mouth
Uncommon: Abdominal distension

Renal and urinary disorders
Not known: Polyuria

General disorders and administration site conditions
Common: Withdrawal syndrome, hyperthermia
Uncommon: Drug ineffective, thirst

* See section on Description of selected adverse reactions

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 and this reaction can be reduced by avoiding such a loading dose or reducing the infusion rate or size of the loading dose.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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

Dexmedetomidine is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstricting effects prevail leading to an increase in systemic vascular resistance and blood pressure, while the bradycardic effect is further emphasised. Dexmedetomidine is relatively free from respiratory depressive effects when given as monotherapy to healthy subjects.

In placebo controlled trials in a post-operative ICU population previously intubated and sedated with midazolam or propofol, Dexdor 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 Dexdor infusion. Studies from outside the ICU have confirmed that Dexdor can be administered safely to patients without endotracheal intubation provided adequate monitoring is in place.

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

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

5.2 Pharmacokinetic properties

The pharmacokinetics of dexmedetomidine has been assessed following short term IV administration in healthy volunteers and long term infusion in ICU population.

Distribution

Dexmedetomidine exhibits a two-compartment disposition model. In healthy volunteers it exhibits a rapid distribution phase with a central estimate of the distribution half-life ($t_{1/2\alpha}$) 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.

Biotransformation and Elimination

Dexmedetomidine is eliminated by extensive metabolism in the liver. There are three types of initial metabolic reactions; direct N-glucuronidation, direct N-methylation and cytochrome P450 catalysed oxidation. The most abundant circulating dexmedetomidine metabolites are two isomeric N-glucuronides. Metabolite H-1, N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide, is also a major circulating product of dexmedetomidine biotransformation. Cytochrome P-450 catalyses the formation of two minor circulating metabolites, 3-hydroxymethyl dexmedetomidine produced by hydroxylation at the 3-methyl group of dexmedetomidine and H-3 produced by oxidation in the imidazole ring. Available data suggest that the formation of the oxidised metabolites is mediated by several CYP forms (CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19). These metabolites have negligible pharmacological activity.

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

Special Populations

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

Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment compared with healthy subjects. The mean percentage of unbound dexmedetomidine in plasma ranged from 8.5% in healthy subjects to 17.9% in subjects with severe hepatic impairment. Subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C) had decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. The mean plasma clearance values of unbound dexmedetomidine for subjects with mild, moderate, and severe hepatic impairment were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively. The mean $t_{1/2}$ for the subjects with mild, moderate or severe hepatic impairment was prolonged to 3.9, 5.4, and 7.4 hours, respectively. Although dexmedetomidine is administered to effect, it may be necessary to consider initial/maintenance dose reduction in patients with hepatic impairment depending on the degree of impairment and the response.

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

Data in new-born infants (28 - 44 weeks gestation) to children 17 years of age are limited. Dexmedetomidine half life in children (1 months 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 months 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;

		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)

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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

6.3 Shelf life

3 years

After dilution
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°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 glass ampoules
2, 5 or 10 ml Type I glass vials (with filling volumes of 2, 4 and 10 ml), grey bromobutyl rubber closure with fluoropolymer coating

Pack sizes
5 x 2 ml ampoules
25 x 2 ml ampoules
5 x 2 ml vials
4 x 4 ml vials
4 x 10 ml vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ampoules and vials are intended for single patient use only.

Preparation of solution

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

In case the required concentration is 8 micrograms/ml:

Volume of Dexdor 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.

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

Dexdor 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

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/718/001-002, EU/1/11/718/004, EU/1/11/718/006-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 September 2011
Date of latest renewal: 26 May 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dexdor 100 micrograms/ml concentrate for solution for infusion
dexmedetomidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains sodium chloride,water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

5 x 2 ml ampoules
25 x 2 ml ampoules
5 x 2 ml vials
4 x 4 ml vials
4 x 10 ml vials

200 micrograms/2 ml
400 micrograms/4 ml
1000 micrograms/10 ml

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use
Dexdor should be used immediately after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the ampoules/vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/718/001
EU/1/11/718/002
EU/1/11/718/004
EU/1/11/718/006
EU/1/11/718/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULES OR VIALS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Dexdor 100 micrograms/ml sterile concentrate
dexmedetomidine
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mcg/ 2 ml
400 mcg/ 4 ml
1000 mcg/ 10 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Dexdor 100 micrograms/ml concentrate for solution for infusion
Dexmedetomidine

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Dexdor is and what it is used for

Dexdor contains an active substance called dexmedetomidine which belongs to a medicine group called sedatives. It is used to provide sedation (a state of calm, drowsiness or sleep) for adult patients in hospital intensive care settings.

2. What you need to know before you are given Dexdor

You must not be given Dexdor

- if you are allergic to dexmedetomidine or any of the other ingredients of this medicine (listed in section 6).
- if you have some disorders of heart rhythm (heart block grade 2 or 3).
- if you have very low blood pressure which does not respond to treatment.
- if you have recently had a stroke or other serious condition affecting blood supply to the brain.

Warnings and precautions

Before you have this medicine, tell your doctor or nurse if any of the following apply as Dexdor should be used cautiously:

- if you have an abnormally slow heart rate (either due to illness or high levels of physical fitness)
- if you have low blood pressure
- if you have low blood volume, for example after bleeding
- if you have certain heart disorders
- if you are elderly
- if you have a neurological disorder (for instance head or spinal cord injury or stroke)
- if you have severe liver problems
- if you have ever developed a serious fever after some medicines, especially anaesthetics

Other medicines and Dexdor

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

The following medicines may enhance the effect of Dexdor:
- medicines that help you sleep or cause sedation (e.g. midazolam, propofol)
- strong pain medicines (e.g. opioids such as morphine, codeine)
- anaesthetic medicines (e.g. sevoflurane, isoflurane)

If you are using medicines which lower your blood pressure and heart rate, co-administration with Dexdor may enhance this effect. Dexdor should not be used with medicines that cause temporary paralysis.

Pregnancy and breast-feeding

Dexdor should not be used during pregnancy or breast-feeding unless clearly necessary.
Ask your doctor for advice before having this medicine

3. How to use Dexdor

Dexdor is administered to you by a doctor or nurse in hospital intensive care.

Your doctor will decide on a suitable dose for you. The amount of Dexdor depends on your age, size, general condition of health, the level of sedation needed and how you respond to the medicine. Your doctor may change your dose if needed and will monitor your heart and blood pressure during the treatment.

Dexdor is diluted and it is given to you as an infusion (drip) into your veins.

If you have been given more Dexdor than you should

If you are given too much Dexdor, your blood pressure may drop, your heartbeat may slow down and you may feel more drowsy. Your doctor will know how to treat you based on your condition.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (*affects more than 1 user in 10*)
- slow heart rate
- low or high blood pressure.

Common (*affects 1 to 10 users in 100*)
- chest pain or heart attack
- fast heart rate
- low or high blood sugar
- change in breathing pattern or stopping breathing
- nausea, vomiting or dry mouth
- restlessness
- high temperature
- symptoms after stopping the medicine

Uncommon (*affects 1 to 10 users in 1,000*)
- reduced heart function
- swelling of the stomach
- thirst

- a condition where there is too much acid in the body
- low albumin level in blood
- shortness of breath
- hallucinations
- the medicine is not effective enough.

Not known (frequency cannot be estimated from the available data)
- increased need to pass urine

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dexdor

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP.

This medicine does not require any special temperature storage conditions. Keep the ampoules or vials in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Dexdor contains

- The active substance is dexmedetomidine. Each ml of concentrate contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine.
- The other ingredients are sodium chloride and water for injections.

Each 2 ml ampoule contains 200 micrograms of dexmedetomidine (as hydrochloride).
Each 2 ml vial contains 200 micrograms of dexmedetomidine (as hydrochloride).
Each 4 ml vial contains 400 micrograms of dexmedetomidine (as hydrochloride).
Each 10 ml vial contains 1000 micrograms of dexmedetomidine (as hydrochloride).

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

What Dexdor looks like and contents of the pack

Concentrate for solution for infusion (sterile concentrate).
The concentrate is a clear, colourless solution.

Containers
2 ml glass ampoules
2, 5 or 10 ml glass vials

Pack sizes
5 x 2 ml ampoules
25 x 2 ml ampoules
5 x 2 ml vials
4 x 4 ml vials

4 x 10 ml vials

Not all pack sizes may be marketed.

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Manufacturer
Orion Corporation
Orion Pharma
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Dexdor 100 micrograms/ml concentrate for solution for infusion

Method of administration

Dexdor should be administered by healthcare professionals skilled in the management of patients requiring intensive care. It must be administered only as a diluted intravenous infusion using a controlled infusion device

Preparation of solution

Dexdor 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 the case the required concentration is 4 micrograms/ml:

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

In the case the required concentration is 8 micrograms/ml:

Volume of Dexdor 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.

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

Dexdor 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.

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.

Shelf life

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

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for dexmedetomidine, the scientific conclusions of the CHMP are as follows:

The MAH undertook a full cumulative review of case reports of polyuria, identified by the search of polyuria and related PTs, taking into consideration temporal relationship, dose, age, and use.

Based on the association of polyuria with induction of dexmedetomidine infusion, and reports of recovery after discontinuation of dexmedetomidine representing positive dechallenge, the data are supportive of a causal association.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing dexmedetomidine were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for dexmedetomidine the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing dexmedetomidine is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.