

dexmedetomidine 100 micrograms/mL concentrate for solution for infusion (Dexdor®) SMC No. (784/12)

Orion Pharma UK

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

dexmedetomidine (Dexdor®) is accepted for use within NHS Scotland.

Indication under review: for sedation in adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale [RASS] 0 to -3).

Dexmedetomidine was as effective as propofol and midazolam in maintaining the target depth of sedation in ICU patients. The median duration of mechanical ventilation was numerically shorter with dexmedetomidine than with propofol and significantly shorter than with midazolam.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

For sedation in adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale [RASS] 0 to -3).

Dosing Information

Dexmedetomidine is for hospital use only and should be administered by healthcare professionals skilled in the management of patients requiring intensive care.

For patients already intubated and sedated switching to dexmedetomidine at an initial infusion rate of 0.7 micrograms/kg/h then adjusted stepwise within the dose range 0.2 to 1.4 micrograms/kg/h to achieve the desired level of sedation, depending on the patient's response. The maximum dose of 1.4 micrograms/kg/h should not be exceeded and patients failing to achieve an adequate level of sedation with the maximum dose should be switched to an alternative sedative agent.

Use of a loading dose of dexmedetomidine 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.

There is no experience in the use of dexmedetomidine for more than 14 days. The use for longer periods should be regularly reassessed.

Product availability date

October 2011

Summary of evidence on comparative efficacy

Patients in intensive care units (ICU) often require sedation to improve comfort, provide relief from pain and anxiety, treat agitation, optimise mechanical ventilation and decrease the response to stress. Currently available therapeutic options include benzodiazepines, propofol, general anaesthetics and opioids. Dexmedetomidine is a selective alpha-2 receptor agonist with sedative, analgesic and anaesthetic/analgesic sparing effects.

Two similar, phase III studies are pivotal in supporting the use of dexmedetomidine in ICU patients requiring light to moderate sedation: one versus propofol (PRODEX) and one versus midazolam (MIDEX).^{1,2} These studies were preceded by a phase III, pilot study in 85 ICU patients.³

The pivotal studies were of multi-centre, randomised and double-blind design. They were designed first to determine non-inferiority (using a margin of 15%) of dexmedetomidine versus either propofol or midazolam in terms of maintaining a target depth of sedation, and then superiority in terms of reduced duration of mechanical ventilation. They were performed in Europe, Estonia and Russia. Eligible patients were aged ≥ 18 years and had a clinical need for sedation and mechanical ventilation. They were already prescribed light to moderate sedation (target RASS 0 to -3, where 0=alert and calm, and -3=responds to verbal stimulation by movement or eye opening to voice but no eye contact), and were initially intubated (or

tracheotomised) and ventilated (with inspiratory assistance). They were expected to stay in ICU for ≥ 48 hours from admission and require sedation for ≥ 24 hours from randomisation. They were randomised (within 72 hours of ICU admission and within 48 hours of beginning sedation in ICU) to receive dexmedetomidine ($n=251$) or propofol ($n=247$) in the PRODEX study or dexmedetomidine ($n=249$) or midazolam ($n=251$) in the MIDEX study. Dexmedetomidine, propofol and midazolam were administered at an initial infusion rate which best matched the pre-randomisation dose of sedative (not exceeding 0.7micrograms/kg/h, 1.6mg/kg/h and 0.09mg/kg/h respectively) for one hour with no dose adjustments but rescue medication if necessary. The infusion rates were then adjusted in incremental steps within licensed doses to maintain a target RASS score of 0 to -3. At the start of randomised study drug, previous sedative therapy was stopped. Study treatment was continued for at least 24 hours up to a maximum of 14 days. Patients were followed-up for 48 hours after stopping study medication and contacted by telephone 31 to 45 days after randomisation. First-line rescue medication (midazolam in the PRODEX study and propofol in the MIDEX study) and second-line rescue medication were permitted during the study periods.^{1,2}

The first co-primary endpoint was the maintenance of target depth of sedation (defined as the proportion of time during sedation infusion with a RASS score within the individually prescribed target range [0 to -3] without first line rescue medication) measured in the per-protocol population. In the PRODEX study, this was reported as 65% in the dexmedetomidine group ($n=223$) and 65% in the propofol group ($n=214$) corresponding to a hazard ratio (HR) of 1.0 (95% confidence interval [CI]: 0.92 to 1.07). Since the lower limit of the 95% CI was above the predefined limit (>0.85) according to the margin of 15%, non-inferiority was considered to be demonstrated. This was confirmed in the intention to treat (ITT) population (63% versus 66% respectively: HR 0.97 [95% CI: 0.89 to 1.04]). In the PRODEX study, 14% (36/251) dexmedetomidine patients and 5.3% (13/247) propofol patients discontinued because of lack of efficacy ($p<0.001$), and use of first-line rescue medication with midazolam was reported in 73% and 64% of patients respectively ($p=0.054$). In the MIDEX study, the first co-primary endpoint was reported as 61% in the dexmedetomidine group ($n=227$) and 57% in the midazolam group ($n=233$), corresponding to a HR of 1.07 (95% CI: 0.97 to 1.18), demonstrating non-inferiority. This was confirmed in the ITT population (60% versus 55% respectively: HR 1.09 [95% CI: 0.99 to 1.19]). In this study, discontinuation because of lack of efficacy was reported in 9.2% (23/249) and 4.0% (10/250) dexmedetomidine and midazolam patients respectively ($p=0.02$), and use of first-line rescue medication with propofol was reported in 44% and 45% respectively ($p=0.72$).

The second co-primary endpoint was the duration of mechanical ventilation (defined as the time from randomisation to being free from any kind of mechanical ventilation provided that it was not re-instituted within 48 hours) in the ITT population. In the PRODEX study, this was not significantly different: a median of 96.5 hours in the dexmedetomidine group ($n=251$) compared with 117.5 hours in the propofol group ($n=247$). In the MIDEX study, it was significantly different: a median of 123.0 hours in the dexmedetomidine group ($n=249$) compared with 164.0 hours in the midazolam group ($n=251$) (Gehan-Wilcoxon test: $p=0.033$).^{1,2}

Various secondary endpoints were reported. Nurse assessment of subject communication, presented as total visual analogue scale scores, was significantly better for dexmedetomidine versus propofol and midazolam in each study. ICU length of stay (defined as the time from randomisation to 'medically fit for discharge' according to the treating clinician) was numerically but not significantly shorter for dexmedetomidine versus comparator (6.8 days versus 7.7 days in the propofol group; 8.8 days versus 10.1 days in the midazolam group). There were no significant differences in median length of hospital stay between dexmedetomidine and propofol patients (33.0 versus 38.0 days respectively), or between dexmedetomidine and midazolam

patients (42.0 versus 38.0 days respectively). The median time to extubation from randomisation was significantly shorter in the dexmedetomidine groups of both studies (69 versus 93 hours in the dexmedetomidine and propofol groups respectively, and 101 versus 147 hours in the dexmedetomidine and midazolam groups respectively). The median times to extubation from end of infusion were numerically but not significantly shorter in the dexmedetomidine groups of both studies (4.0 versus 7.0 hours in the dexmedetomidine and propofol groups respectively, and 35.0 versus 53.5 hours in the dexmedetomidine and midazolam groups respectively).^{1,2}

Another randomised, double-blind, phase IV study (SEDCOM) compared the efficacy and safety of dexmedetomidine with midazolam in 366 mechanically ventilated ICU patients requiring light sedation (RASS score -2 to 1) for an expected duration of >24 hours. The primary endpoint of time within the target sedation range (RASS score -2 to 1) was not significantly different between the two treatments and there was no significant difference in the median lengths of ICU stay. The time to extubation was significantly shorter in the dexmedetomidine group and the incidence of delirium was reported to be significantly lower in dexmedetomidine treated patients: 54% (132/244) versus 77% (93/122) ($p < 0.001$) using the confusion assessment method adapted for ICU (CAM-ICU).⁴ These results were confirmed in the subgroup of patients who actually received study drug for >24 hours.¹

The submitting company presented results of an unpublished meta-analysis of the PRODEX, MIDEX and pilot studies which reported a significantly shorter median duration of mechanical ventilation with dexmedetomidine versus standard care (109 hours versus 140 hours, $p = 0.017$ using the Gehan-Wilcoxon test). A separate, unpublished, meta-analysis of the PRODEX, MIDEX and SEDCOM studies on the endpoint of time to extubation estimated an HR of 0.84 (95% CI: 0.75 to 0.95) for dexmedetomidine versus comparator using a fixed effect model and of 0.84 (95% CI: 0.74 to 0.96) using a random effects model.⁵

Summary of evidence on comparative safety

The most common adverse events with dexmedetomidine were hypotension, hypertension and bradycardia which are reported in the Summary of Product Characteristics (SPC) to occur in approximately 25%, 15% and 13% of patients respectively. The SPC notes that patients should have continuous cardiac monitoring during treatment.

In the PRODEX study period to day 45, the most frequently reported adverse events in the dexmedetomidine and propofol groups respectively were hypertension (21% versus 15%), sinus tachycardia (20% versus 11%), hypotension (13% in both), bradycardia (13% versus 10%), atrial fibrillation (12% versus 14%), respiratory failure (12% versus 14%), pleural effusion (7.3% versus 14%), agitation (7.7% versus 12%) and anxiety (8.5% versus 10%). Significantly more dexmedetomidine than propofol patients had sinus tachycardia, first degree AV block and drug ineffective events. Significantly more propofol than dexmedetomidine patients had pleural effusion and critical illness polyneuropathy. Neurocognitive adverse events, including agitation, anxiety and delirium, were reported in significantly less dexmedetomidine than propofol patients up to the 48 hours post-treatment follow-up (18% versus 29% respectively).²

In the MIDEX study period to day 45, the most frequently reported adverse events in the dexmedetomidine and midazolam groups respectively were hypertension (22% versus 21%), hypotension (21% versus 12%), agitation (16% in both), bradycardia (14% versus 5.2%), sinus

tachycardia (14% versus 22%), atrial fibrillation (13% versus 17%) and delirium (7.7% versus 10%). Significantly more dexmedetomidine than midazolam patients had hypotension, bradycardia, sepsis, hypoglycaemia and haemorrhagic shock events. Significantly more midazolam than dexmedetomidine patients had sinus tachycardia and increased gamma glutamyl transpeptidase. Neurocognitive adverse events reported up to the 48 hours post-treatment follow-up were similar in the dexmedetomidine and midazolam groups (29% and 27% respectively).²

Summary of clinical effectiveness issues

The two pivotal studies described provide data versus relevant comparators (propofol and midazolam) using co-primary endpoints of direct health outcomes. In both studies, dexmedetomidine was found to be as effective as (non-inferior to) the active comparator (propofol or midazolam) in terms of time in the target sedation range. The sedation range chosen was broad and although the proportions of patients achieving this were similar, patients treated with propofol and midazolam had a significantly higher level of sedation during treatment (RASS -1.7 and -1.5 respectively) compared with dexmedetomidine (-1.0 and -0.9 respectively). There was no statistically significant difference between dexmedetomidine and propofol groups in the duration of mechanical ventilation, although the duration was numerically shorter in the dexmedetomidine group. The duration of mechanical ventilation was significantly shorter in the dexmedetomidine compared with the midazolam group.

There was a higher discontinuation rate in the dexmedetomidine arm of each study and the differences due to lack of efficacy were significant. The use of first-line rescue medication for sedation was higher in the dexmedetomidine than the propofol arm of the PRODEX study. However, a post hoc analysis of the PRODEX study, which removed patients who had discontinued due to a lack of efficacy, found that the use of first-line rescue medication was similar in both groups.

The non-inferiority margin in the pivotal studies (15%) was larger than the 10% margin selected for the pilot study. However, in the primary analysis of both studies, the lower limit of the 95% CI was well above this limit (0.92 in the PRODEX study and 0.97 in the MDEX study).

In both pivotal studies, the duration of study drug infusion was limited to a maximum of 14 days and this is noted in the SPC. The duration of follow-up was limited to 45 days which is insufficient to allow longer term effects of use in ICU (e.g. post traumatic stress disorder) to be assessed.

Dexmedetomidine is the first selective alpha-2 receptor agonist available in the UK and its introduction would offer an alternative sedative which may be valuable in patients requiring only light to moderate sedation level. It will not be suitable for patients requiring deep sedation. The use of a loading dose of dexmedetomidine is not recommended and it should not be used as an induction agent for intubation. Therefore, in clinical practice, patients would need to be sedated initially with another agent (usually propofol or midazolam) and then switched to dexmedetomidine for maintenance.

During the pivotal studies, dexmedetomidine was associated with numerically, but not always statistically significantly, shorter durations of mechanical ventilation, and ICU and hospital stay. It remains to be seen whether these reductions will be achievable in clinical practice.

In the submission, the submitting company suggests that dexmedetomidine may be associated with less delirium than alternatives. This was demonstrated in the phase IV SEDCOM study versus midazolam described above.⁴ However, the two pivotal studies (PRODEX and MIDEX) did not incorporate a delirium scale therefore there was no reported difference between dexmedetomidine and propofol or midazolam in the incidence of delirium as an adverse event.^{1,2}

Summary of comparative health economic evidence

The submitting company presented an economic comparison between dexmedetomidine and (i) propofol and (ii) midazolam. Each comparison used a Markov model with a similar structure and a 45-day time horizon. Rates for events were taken from the respective key clinical studies. Costs included medicines, preparation and administration, management of adverse events and co-prescribed medicines. An important driver of the results was the impact on length of stay in hospital and specifically on different types of ward (intensive care, high dependency, general ward) while in hospital. Transfers between levels of care in the economic model were based on data from the clinical studies on when intubation ceased and on observed length of stay. No differences were assumed in mortality. Utility data with and without intubation were taken from published studies.

The results were presented as a cost-minimisation analysis, assuming no differences in quality adjusted life years (QALYs), and as a cost-utility analysis. In the latter case the submitting company valued QALYs at £25k and used a net benefit analysis approach to avoid the instability in an incremental cost effectiveness ratio (ICER) produced by a very small denominator (given the short time horizon). The results were as follows:

Compared with propofol

As a cost-minimisation analysis:

Cost driver	Dexmedetomidine	Propofol	Incremental cost
Treatment (i.e. drug)	£323	£234	£89
Treatment administration	£13	£15	-£2
First-line rescue strategy	£3	£2	£1
MV (bed days)	£12,173	£14,216	-£2,044
ICU off MV (bed days)	£3,063	£2,661	£402
Hospital ward (bed days)	£3,252	£3,177	£75
Adverse events	£2	£1	£0
Total costs	£18,828	£20,307	-£1,479

An alternative approach was through cost-utility analysis and in this case, the submission estimated that patients who are admitted to the ICU and are treated with dexmedetomidine gain 0.001 QALYs over 45 days and save the healthcare provider approximately £1,479.

Compared with midazolam

As a cost-minimisation analysis:

Cost driver	Dexmedetomidine	Midazolam	Incremental cost
Treatment (i.e. drug)	£245	£54	£192
Treatment administration	£10	£14	-£4
First-line rescue strategy	£3	£3	£0
MV (bed days)	£14,701	£16,969	-£2,269
ICU off MV (bed days)	£2,525	£2,671	-£146
Hospital ward (bed days)	£2,907	£2,825	£83
Adverse events	£2	£1	£1
Total costs	£20,393	£22,536	-£2,143

The economic model estimated that patients who are admitted to the ICU and are treated with dexmedetomidine gain 0.002 QALYs over 45 days and save the healthcare provider approximately £2,143.

Sensitivity analysis showed that the assumptions about hospital stay and the type of ward were the key drivers of results.

The following table shows the main driver of the results (D=dexmedetomidine, P=propofol, M=midazolam):

State	Cost	Utility	D versus P (days)	D versus M (days)
ICU intubated	£2,044/day	0.1	6.2 vs 7.3 = -1.1	7.7 vs 9.0 = -1.3
Additional duration of MV	£702/day	0.2	1.6 vs 0.8 = +0.8	0.6 vs 0.7 = -0.1
Additional stay in ICU off MV	£702/day	0.2	3.1 vs 3.3 = -0.2	3.4 vs 3.6 = -0.2
Hospital stay	£277/day	0.5	15.2 vs 14.9 = +0.3	14 vs 14 = 0
Home	£0/day	0.8		

The main case made for the medicine is a claim of savings, especially in intensive care.

There were some weaknesses in the economic analysis:

- It is recognized that UK clinical practice differs from that in other countries in terms of access to and use of intensive care; this raised a concern about whether savings in Level 3 would be seen in practice. SMC clinical experts have suggested that median lengths of stay for ICU patients may be shorter than that seen in the key trial and thus it was not clear if the reductions in length of stay would be achievable. The submitting company subsequently provided some threshold analysis to indicate the minimum difference in length of stay that would be necessary for dexmedetomidine to remain a cost-effective treatment option. This revised analysis showed that if a reduction of only

around 4 hours was achieved, dexmedetomidine could still be considered cost effective.

- The economics model includes 'additional duration of MV' but there was a lack of clarity around the clinical situation this relates to and why this should be costed at Level II rather than Level III. However, the submitting company subsequently provided clarification and additional sensitivity analysis to show that dexmedetomidine remained a cost-effective treatment option even it was assumed that no patients were transferred to lower levels of care after the end of MV.

Given the additional analysis provided by the company in response to these issues, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In the UK, the Intensive Care Society (ICS) published guidelines on sedation in 2007. This details the main aims of treatment (patients must be comfortable and pain free, have minimal anxiety, be calm, co-operative and able to sleep when undisturbed, be able to tolerate appropriate organ system support and must not be paralysed and awake). Guidance on the principles of management recommend that sedation is initiated with a loading dose titrated to effect and an infusion started which is increased by small increments.

Additional information: comparators

Other agents licensed for sedation in ICU include propofol and midazolam.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 24 hours (£)
Dexmedetomidine	0.2 to 1.4 micrograms/kg/h by continuous intravenous infusion	31 to 188
Propofol	0.3 to 4mg/kg/h by continuous intravenous infusion	10 to 131
Midazolam	Intravenous loading dose of 0.03 to 0.3mg/kg in increments of 1 to 2.5mg Maintenance dose of 0.03 to 0.2mg/kg/h by continuous intravenous infusion	4 to 24

Doses are for general comparison and do not imply therapeutic equivalence. Costs for dexmedetomidine from the submitting company. Costs for propofol from BNF September 2011. Costs for midazolam from eVadis on 5 March 2012. Costs are calculated for a 24 hour period based on an adult with a bodyweight of 70kg.

Additional information: budget impact

The submitting company provided two budget impact estimates, one in which dexmedetomidine displaces propofol and one which it displaces midazolam.

Displacement of propofol

The company estimated the population eligible for treatment to be 8,274 and, based on an estimated uptake of 10% in year 1 and 20% in year 5, the gross impact on the medicines budget was estimated at £138.1K in year 1 and £276.2K in year 5. Savings on the medicines budget would be in terms of propofol avoided only. The net medicines budget impact was estimated at £32.7K and £65.4K.

Displacement of midazolam

The company estimated the population eligible for treatment to be 8,274 and, based on an estimated uptake of 10% in year 1 and 20% in year 5, the gross impact on the medicines budget was estimated at £110.1K in year 1 and £220.1K in year 5. Savings on the medicines budget would be in terms of midazolam avoided only. The net medicines budget impact was estimated at £96K and £192K.

References

The undernoted references were supplied with the submission.

1. European Medicines Agency: European public assessment report (EPAR) for dexmedetomidine. Procedure no EMEA/H/C/002268, 22 September 2011.
2. Jakob SM, Ruokonen E, Grounds RM et al. Dexmedetomidine versus midazolam or propofol for sedation during prolonged mechanical ventilation. Two randomised controlled trials. JAMA 2012;307:1151-60.
3. Ruokonen E, Parviainen I, Jakob SM et al. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med 2009; 35:282-290.
4. Riker RR, Shehabi Y, Bokesch PM et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009; 301(5):489-499.
5. Orion Pharma Data on file.

This assessment is based on data submitted by the applicant company up to and including 20 April 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.