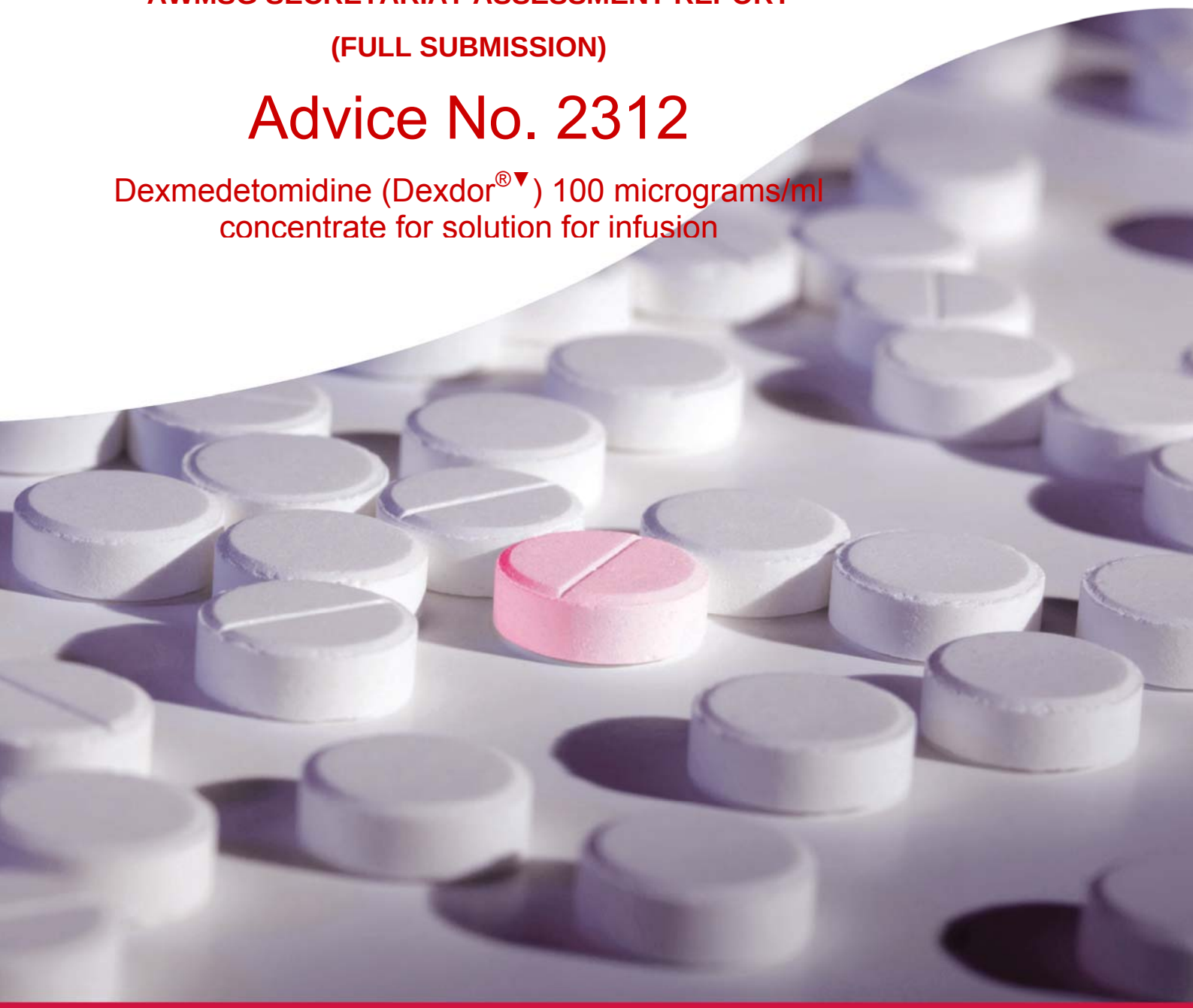
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 2312

Dexmedetomidine (Dexdor®▼) 100 micrograms/ml concentrate for solution for infusion



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 2312
Dexmedetomidine (Dexdor®▼) 100 micrograms/ml concentrate for solution for infusion

This assessment report is based on evidence submitted by Orion Pharma (UK) Ltd on 5 March 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Dexmedetomidine (Dexdor®▼) is indicated for sedation of 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)[2].
Dosing	Dexmedetomidine is for hospital use only. It 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/hour which may then be adjusted stepwise within the dose range 0.2 to 1.4 micrograms/kg/hour in order to achieve the desired level of sedation depending on the patient's response. The maximum dose of 1.4 micrograms/kg/hour should not be exceeded. Refer to the Summary of Product Characteristics (SPC) for further information regarding dosing[2].
Marketing authorisation date	16 September 2011[2].

2.0 DECISION CONTEXT

2.1 Background

The UK Intensive Care National Audit and Research Centre (ICNARC)[3] and Audit of Critical Care in Scotland 2010[4] reports that approximately 106,570 patients were admitted to NHS adult critical care units (intensive care and combined intensive care/high dependency units) in the UK between April 2009 and March 2010. Data reported in the company submission states that in 2010, approximately 80% of ICU patients required invasive mechanical ventilation[1], the vast majority of which would have been sedated[1]. In the ICU setting, sedation has several objectives such as relief of pain and anxiety, treating agitation, decreasing stress responses, facilitating uncomfortable short-term procedures and optimising mechanical ventilation conditions[5].

Many treatments are currently used in ICU for sedation, including propofol, benzodiazepines, such as midazolam, and opiates[5]; clonidine is also used for sedation, although it is unlicensed for this indication[6]. Many of these sedative agents may have an unpredictable and prolonged duration of action in critically ill patients, due to the accumulation of active metabolites. Long-term sedation is often associated with serious adverse effects, such as prolonged mechanical ventilation, coma, delusional

memories, post-traumatic stress disorder (PTSD), impaired cognitive function, prolonged hospitalisation, increased costs and mortality. Therefore, incorporating daily sedation stops, sedation protocols, spontaneous breathing trials and early mobilisation or primary use of opiates without other sedation may help to reduce these complications. Benzodiazepines and propofol have also been reportedly associated with increased risk of delirium[7]. Delirium is common during prolonged intensive care and sedation may be an independent risk factor[8].

Dexmedetomidine is an alpha 2-adrenergic receptor agonist, which creates a sedative effect via the decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem[2]. In contrast to some other sedative agents, dexmedetomidine also has a potential analgesic effect and may induce a sedative state similar to physiologic sleep without respiratory depression[7]. It has also been shown to have some analgesic and anaesthetic/analgesic sparing properties[5].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Propofol
- Midazolam
- Clonidine

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE). Clinical Guidance 83: Rehabilitation after critical illness (2009)[9].
- NICE. Clinical Guidance 50: Acutely ill patients in hospital (2007)[10].
- Intensive Care Society. Sedation Guideline (2007)[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission[1] includes details of two pivotal phase III studies, PRODEX and MIDEX, which evaluate the efficacy and safety of dexmedetomidine in adult ICU patients receiving mechanical ventilation in comparison with propofol and midazolam, respectively[12]. Several supportive active comparator-controlled studies were provided by the applicant company to demonstrate the effects of dexmedetomidine on delirium, facilitating ventilatory weaning, analgesia and cognitive function. The submission also includes single-arm observational studies and placebo-controlled trials; these are not discussed further in the report as they do not add anything to the evidence of effectiveness which cannot be derived from included studies[1].

3.1 PRODEX and MIDEX studies

The phase III, randomised, multicentre, double-blind studies, PRODEX and MIDEX, compared the use of dexmedetomidine with propofol (PRODEX) and midazolam (MIDEX) in ICU patients ≥ 18 years receiving mechanical ventilation requiring light to moderate sedation for more than 24 hours[12]. Sedation was monitored using a sedation scoring tool, Richmond Agitation-Sedation Scale (RASS). Patients in the PRODEX study (n = 500) were randomised 1:1 to receive either dexmedetomidine (0.2–1.4 micrograms/kg per hour) or propofol (0.3–4.0 mg/kg per hour). In the MIDEX study, patients (n = 501) were randomised to receive either dexmedetomidine (0.2–1.4 micrograms/kg per hour) or midazolam (0.03–0.2 mg/kg per hour). Main exclusion criteria were acute severe intracranial or spinal neurological disorder, uncompensated acute circulatory failure at time of randomisation, severe bradycardia, atrioventricular (AV) conduction block II-III (unless pacemaker installed), severe hepatic impairment,

need for muscle relaxation at the time of randomisation and any condition that would significantly interfere with data collection[13,14].

The primary endpoint of proportion of time at target depth of sedation (RASS score -3 to 0) for the per protocol (PP) population was 64.6% in the dexmedetomidine arm versus 64.7% in the propofol treatment group (PRODEX study) and 60.7% in dexmedetomidine-treated patients versus 56.6% in the midazolam group (MIDEX study). Non-inferiority was confirmed in both studies, as the lower 95% confidence interval (CI) of the estimated ratio between treatments was above the pre-defined limit of 0.85 (see Table 1)[12]. The co-primary endpoint was the duration of mechanical ventilation in the intention to treat population (ITT). This was found to be 96.5 hours for dexmedetomidine versus 117.5 hours for propofol in the PRODEX study (p = 0.24); a statistically significant reduction in duration was demonstrated in the MIDEX study (123 hours for dexmedetomidine versus 164 hours for midazolam [p = 0.033])[5,12]. This was supported by analysis of secondary and ancillary data.

Study discontinuation due to lack of efficacy accounted for 54.5% and 39.7% of study discontinuation within dexmedetomidine-treated patients in the PRODEX and MIDEX studies, respectively. These values are approximately two-fold higher than the comparator treatments (20.4% and 22.4% for midazolam and propofol, respectively). Lack of efficacy in the dexmedetomidine group was frequently associated with an increased use of rescue medicine[5].

Table 1. Overview of endpoint data from PRODEX and MIDEX studies[5,12].

	PRODEX		MIDEX	
	Dexmedetomidine	**Propofol**	**Dexmedetomidine**	**Midazolam**
ITT population	251	247	249	252
PP population	223	214	227	233
Primary endpoints				
Proportion of time in target sedation range (%)*	64.6	64.7	60.7	56.6
Estimated ratio*	1.00 (95% CI 0.92, 1.08; p = 0.97)		1.07 (95% CI 0.97, 1.18; p = 0.15)	
Duration of mechanical ventilation (hours)	96.5	117.5	123†	164
P value	0.24		0.033†	
Secondary and ancillary analyses				
Median time to extubation (hours)	69†	93	101†	147
Length of ICU stay (days)	6.8	7.7	8.8	10.1
Discontinuation of study treatment due to lack of efficacy	36/66 (54.5%)	13/58 (22.4%)	23/58 (39.7%)	10/49 (20.4%)

* PP population analysis
† statistically significant difference between treatment arms

3.2 Supportive studies

The company submission also detailed several supportive studies relating to dexmedetomidine for the sedation of mechanically ventilated patients in ICU. A pilot phase III study demonstrated that dexmedetomidine was as effective as standard care (midazolam/propofol) at inducing light to moderate sedation in ICU patients, but was

less suitable for deep sedation[8]. Additionally, three studies demonstrated that use of dexmedetomidine in ICU patients was associated with reduced incidence of delirium compared with midazolam, lorazepam and propofol[15–17]. Dexmedetomidine also shortened time to extubation in ICU patients when compared to haloperidol[18] and reduced the need for use of analgesics in comparison to propofol[19]. Another study found that dexmedetomidine-treated patients did not display the same cognitive impairment seen in patients treated with propofol[20]; however, due to the small population group, further studies are necessary[1]. See Appendix 1 for further details of these studies.

In addition, the company submission includes a pre-specified pooled analysis, a pre-planned meta-analysis and an independent meta-analysis, which demonstrated a shortening of the duration of mechanical ventilation, time to extubation and ICU stay with dexmedetomidine[1].

3.3 Evidence of comparative safety[1,12]

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) considered the dexmedetomidine safety database, which included data from 106 clinical studies (some dosing regimens different to the currently licensed dose). The incidence of adverse events (AEs) was 1447/1879 (77.0%) for dexmedetomidine-treated patients compared with 374/463 (80.8%) and 377/401 (94.0%) for patients receiving propofol and midazolam, respectively. Serious AEs were observed in 25.5% of dexmedetomidine-treated patients compared with 32.6% and 43.9% for patients receiving propofol and midazolam, respectively. In both the PRODEX and MIDEX studies, the most common drug-related AEs in dexmedetomidine-treated patients were hypotension (13% versus 13.4% of propofol-treated patients and 20.6% versus 11.6% of midazolam-treated patients) and bradycardia (13% versus 10.1% and 14.2% versus 5.2%, respectively); these differences were statistically significant in the MIDEX study only (hypotension $p = 0.007$; bradycardia $p < 0.001$). The incidence of discontinuations due to AEs in dexmedetomidine-treated patients was 29 (11.6%) in the PRODEX study (versus 28 [11.3%] propofol-treated patients) and 23 (9.2%) in the MIDEX study (versus 19 [7.6%] midazolam-treated patients)[12]. In the PRODEX study, 17.1% of dexmedetomidine-treated patients and 19.4% of propofol-treated patients died between randomisation and follow-up at day 45; the incidence of fatalities was 27.3% and 21.1% in patients receiving dexmedetomidine and midazolam respectively in the MIDEX study. These deaths were thought to be unrelated to the study treatments[1,12].

3.4 AWTTC critique

- AWTTC requested clonidine as a comparator; however, evidence related to this treatment has not been included by the company in their submission. The company stated that there are no useful published trials demonstrating either efficacy or safety of clonidine in this population[1]. In addition, clonidine is currently unlicensed for this indication[1,21].
- Lack of efficacy accounted for 54.5% and 39.7% of study discontinuation within dexmedetomidine-treated patients in the PRODEX and MIDEX studies, respectively. These values are approximately two-fold higher than the comparator treatments[5]. However, study discontinuation rates were similar in dexmedetomidine and standard care treatment[12].
- The clinical trials were undertaken in centres across Europe, including the UK, and so the data are representative of patients in Wales. Although the trials MIDEX and PRODEX used fentanyl in combination with the treatments under investigation, the company suggest that alfentanil is the most commonly used opioid for sedation in Wales[1].

- CHMP noted that neither of the pivotal studies investigated dexmedetomidine as an 'induction agent' for the initiation of sedation, as all of the patients were already sedated and ventilated at the time of randomisation[5]. This suggests that another agent would be required to initially 'induce' sedation, as reflected in the SPC. In addition, it was thought that patients who were being switched from standard care treatments to dexmedetomidine could enter a period of "instability", potentially demonstrating bias towards standard care. However, most patients successfully treated with dexmedetomidine did not require more rescue medicine than those patients receiving propofol[1,5].
- There was no long-term follow-up of patients treated with dexmedetomidine in the clinical studies and so analysis of the effects of dexmedetomidine on prolonged cognitive dysfunction or conditions such as PTSD could not be undertaken.
- Excessive dosing of dexmedetomidine in patients with severe hepatic impairment may lead to over sedation and increase AE risk. This observation has been included in the SPC[5].
- The standard sedation preceding randomisation may have masked the benefits of dexmedetomidine during shorter exposure[12].
- The change of treatment being used for sedation may have increased the lack of efficacy in the early stages of dexmedetomidine infusion which was observed in the PRODEX study[12].
- Weaning from mechanical ventilation and criteria for extubation were not standardised across trials[12].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes cost utility analyses (CUA) of dexmedetomidine in its licensed indication for the sedation of adult ICU patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to RASS 0 to -3)[2]. Patients are assumed to be effectively sedated and ventilated prior to initiation of dexmedetomidine. The comparators used are propofol and midazolam, which are currently used in clinical practice in Wales.

The CUA are based on a Markov state transition model consisting of five health states. Patients enter the model already sedated and ventilated before moving to: ICU extubated, hospital ward, hospital discharge (home) and/or death. Transition among the health states and resource use estimates are derived from the PRODEX and MIDEX randomised controlled trials, with additional assumptions made in relation to the management of AEs. The model has a daily cycle length and assumes a 45-day time horizon in the base case analysis. See Appendix 2 for further details.

4.1.2 Results

Table 2. Company reported results of the base case CUA[1].

	PRODEX Model			MIDEX Model		
	Dexmedetomidine	Propofol	Difference	Dexmedetomidine	Midazolam	Difference
Drug costs	£323	£234	£89	£245	£54	£192
Treatment administration	£13	£15	-£2	£10	£14	-£4
First-line rescue strategy	£3	£2	£1	£3	£3	£0
Mechanical ventilation	£14,838	£17,329	-£2,491	£17,920	£20,685	-£2,765
ICU (off mechanical ventilation)	£3,054	£2,653	£401	£2,517	£2,663	-£146
Hospital ward	£3,664	£3,580	£84	£3,276	£3,182	£93
AEs	£2	£2	£0	£2	£1	£1
Total cost	£21,897	£23,815	-£1,918	£23,973	£26,602	-£2,629
Total QALYs	0.058	0.057	0.001	0.055	0.052	0.002
ICER (£/QALY gained)	Dexmedetomidine dominant*			Dexmedetomidine dominant*		

QALY: quality adjusted life-year; ICER: incremental cost-effectiveness ratio.
*Dexmedetomidine is estimated to be both less costly and more effective than the comparator.

A wide range of one way sensitivity analyses, exploring parameter values in the range ± 50% indicate that the key drivers for the PRODEX model results, comparing dexmedetomidine to propofol, are the cost per level-3 bed day and the length of stay within each department, especially during invasive mechanical ventilation. For the MIDEX model, comparing dexmedetomidine to midazolam, the results are most sensitive to changes in time to extubation.

Probabilistic sensitivity analyses suggest that the probability that dexmedetomidine is cost-effective, compared to propofol, is 93.1%, and compared to midazolam is 85.5%, based on a cost-effectiveness threshold of £25,000 per QALY gained. Scenario analyses, using a life time horizon to capture QALYs lost due to premature death, indicate that dexmedetomidine remained the dominant strategy in both comparisons. The company also submitted the results of cost minimisation analyses (CMA) for both comparisons, which suggest that dexmedetomidine is a cost saving strategy compared with propofol and midazolam.

4.1.3 AWTTC critique

The headline results of the base case analyses and probabilistic sensitivity analyses should be interpreted with some caution, as the modelled differences in QALYs between dexmedetomidine and the comparators are very small. It would seem plausible that dexmedetomidine could reduce time to extubation, and may reduce the overall costs of ICU stay, for patients such as those in the PRODEX and MIDEX trials.

Strengths of the economic evidence include:

- The modelled patient pathway seems appropriately simplified.
- The company has provided a number of sensitivity analyses conducted using a large range for the input parameter values (± 50%).
- Both models are based on direct evidence from head-to-head randomised controlled trials (RCTs) for the two comparators.

Limitations of the economic evidence:

- The company[1] has used propofol and midazolam only as the comparators. Although acknowledging clonidine is used, the company has not considered it as a comparator in its submission, based on the fact it is not licensed for this use and there are no direct comparative studies of dexmedetomidine versus clonidine.
- Key parameter values relating to mean time to extubation, length of stay in ICU or medical wards are based on company data on file and have not been verified.
- It is not clear that all costs have been adequately incorporated in the model: time for administration are based on assumptions, and no administration costs are included for the administration of rescue therapy which was required more frequently by dexmedetomidine recipients than propofol recipients. However, the model was relatively insensitive to all costs but those associated with mechanical ventilation.
- The company notes that collection of preference-based utility values is difficult in the ICU setting and has relied on utility values from a single published study, the source of which is also unclear.
- Probabilistic sensitivity analysis around the base case comparison of dexmedetomidine versus propofol appears to be unstable, possibly reflecting the very small differences in modelled QALYs between the two treatments, and the uncertainty around mean parameter values that have been assumed.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified two relevant economic evaluations of dexmedetomidine within its current licensed indication. The first is a manufacturer-supported CMA comparing dexmedetomidine against midazolam in intubated ICU patients, conducted from a US health care provider's perspective[22]. It concluded that continuous sedation with dexmedetomidine results in significantly lower total ICU costs. The primary cost drivers were reduced costs of intensive care unit stay and of mechanical ventilation. The second study is a cost-consequences analysis (CCA) comparing dexmedetomidine against midazolam conducted from the Canadian healthcare system perspective[23]. It concluded that dexmedetomidine was associated with lower costs, lower duration of delirium and lower duration of mechanical ventilation[24]. Both studies were conducted in health care settings outside of the UK, which limits their generalisability to the NHS in Wales.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The budget impact analysis in the company submission[1] draws on national ICU admissions data. It reports that approximately 106,570 ICU admissions have been recorded in the UK in 2009-10, based on the Intensive Care National Audit and Research Centre (ICNARC) data[3] and Audit of Critical Care in Scotland 2010[4]. Extrapolating to the Welsh population, this would equate to 5,145 admissions in Wales. The company assumes that 50% of admissions require mechanical ventilation and of these, 85% of patients are sedated. This results in an anticipated 2,187 eligible patients each year in Wales. The company assumes this number will remain constant over the five years. Given the short treatment duration, mortality is not considered in the budget impact calculations. The analysis assumes that switching from each of

propofol and midazolam to dexmedetomidine will occur at a rate of 10% in year 1, rising to 20% in years 4 and 5.

5.1.2 Company-reported results of budget impact analysis

Total cost estimates from the economic model suggest cost savings with the use of dexmedetomidine, of £1,918 versus propofol and £2,629 versus midazolam per patient treated. Assuming an equal proportion of patients switch from propofol and midazolam, the company estimates cost savings[1] as detailed in Table 3.

Table 3. Budget impact analysis results.

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of eligible patients	2,187	2,187	2,187	2,187	2,187
Uptake (%)	20%	30%	30%	40%	40%
Treated patients	437	656	656	875	875
Net costs					
Drug treatment	£61,279	£91,918	£91,918	£122,558	£122,558
Treatment administration	-£1,336	-£2,004	-£2,004	-£2,673	-£2,673
First-line rescue strategy	£346	£519	£519	£692	£692
Mechanical ventilation (bed days)	-£1,149,588	-£1,724,383	-£1,724,383	-£2,299,177	-£2,299,177
ICU off mechanical ventilation (bed days)	£55,814	£83,721	£83,721	£111,628	£111,628
Hospital ward (bed days)	£38,840	£58,260	£58,260	£77,680	£77,680
AEs	£229	£344	£344	£459	£459
Overall net cost for whole population	-£994,417	-£1,491,625	-£1,491,625	-£1,988,833	-£1,988,833

5.1.3 AWTTC critique of the budget impact analysis

- The annual number of ICU admissions estimated for Wales was calculated on a percentage basis from the overall ICU admissions reported for adults in the UK. The basis of the assumptions regarding the proportion of patients requiring ventilation and sedation is not stated. There would, therefore, appear to be uncertainty in these estimates.
- There is uncertainty in the company estimates of market uptake, and the anticipated number of patients expected to switch to dexmedetomidine.
- Since the budget impact analysis is based on the economic evaluation results, all limitations relating to the calculation of costs in the economic evaluation will apply equally to the budget impact estimations.

5.2 Comparative unit costs

Propofol and midazolam can be administered for induction as well as maintenance of sedation, therefore, average doses in Table 4 refer only to the use of these agents for maintenance of sedation as quoted in the BNF 62[25]. Clonidine is not licensed for use as a sedative, but is used off-label in practice[26]. Sedatives administered in ICU require titration to maintain a target level of sedation; hence, the cumulative dose will vary from

one patient to another. The example acquisition costs of dexmedetomidine and comparators in Table 4 are therefore indicative only.

Table 4. Examples of acquisition costs of sedative agents used for maintenance of sedation in ventilated patients.

Regimen	Example dose[25]	Approximate cost per patient per day*
Dexmedetomidine (Dexdor®▼) 100 microgram/ml (2 ml amp, 4 ml vial, 10 ml vial)	0.2–1.4 microgram/kg/hour	£26.11–£182.77**
Propofol (Non-proprietary) 1% injection, i.e. 10 mg/ml (20 ml amp, 50 ml amp, 100 ml bottle) 2% injection, i.e. 20 mg/ml (50 ml vial)	0.3–4 mg/kg/hour	£9.78– £143.14
Midazolam (Hypnovel®) 1 mg/ml (2 ml amp, 5ml amp, 10ml vial) 2 mg/ml (5 ml amp) 5 mg/ml (10 ml amp)	30–200 microgram/kg/hour	£2.52– £84
Clonidine (Catapres®)† 150 microgram/ml (1 ml amp)	100 microgram/hour	£4.42

*Costs based an adult with an average body weight of 70 kg and calculated using BNF 62 list prices (which exclude VAT)[25] or MIMS list prices as of 1 May 2012[27].
**The cost of dexmedetomidine includes the cost of 0.9% sodium chloride injection solution required for the dilution.
†Clonidine is not licensed for use as a sedative in ICU. Dose based on published review of its use in ICU[26].
Note: See all relevant SPCs for full dosing details[1,28,29].
This table does not imply therapeutic equivalence of the stated medicines and doses.

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place of prescribing
AWTTC is of the opinion that, if given a positive recommendation, dexmedetomidine is appropriate for specialist only prescribing within NHS Wales for the stated indication.

6.2 Ongoing studies
The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review
This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search
Date of evidence search: 22 March 2012.
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1. Additional clinical information.

Study design	Treatment regimens	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
SEDCOM study (Riker et al, 2009)[15]				
A prospective, double-blind, multicentre randomised controlled trial	Dexmedetomidine 0.2–1.4 micrograms/kg per hour (n = 244) Midazolam 0.02–0.1 mg/kg per hour (n = 122)	Inclusion criteria • 18 years or older • Intubated and mechanically ventilated for less than 96 hours prior to start of study drug, with an anticipated sedation duration of at least three more days Exclusion criteria • Trauma or burns • Dialysis of all types • Pregnancy or lactation • Neuromuscular blockade other than for intubation • Epidural or spinal analgesia • General anaesthesia 24 hours before or planned after initiation of study drug • Serious central nervous system pathology • Cardiac or circulatory problems • Severe liver disease	375 mechanically ventilated medical or surgical ICU patients, of which, 366 patients received the study drug	Time within the target sedation range (RASS score −2 to +1) during the double-blind treatment period: • 77.3% for dexmedetomidine versus 75.1% for midazolam group (p = 0.18) Prevalence of delirium assessed by CAM-ICU: • 54% in dexmedetomidine treated patients versus 76.6% in midazolam-treated patients (p < 0.001) Median length of ICU stay: 5.9 days for dexmedetomidine versus. 7.6 days for midazolam (p = 0.24) Median time to extubation: • 3.7 days for dexmedetomidine versus 5.6 days for midazolam (p = 0.01)

Appendix 1. Continued.

Study design	Treatment regimens	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
Pandharipande et al (2007)[16]				
A double-blind randomised controlled trial	Dexmedetomidine maximum dose 1.5 micrograms/kg per hour (n = 52) Lorazepam maximum dose 10 mg/hour (n = 51)	Inclusion criteria • Adult medical and surgical ICU patients • Require mechanical ventilation for longer than 24 hours Exclusion criteria • Neurological disease (previous stroke, cerebral palsy, etc.) that would confound the diagnosis of delirium • Active seizures • Liver disease • Active myocardial ischemia, second- or third-degree heart block • Severe dementia • Pregnancy or lactation		Delirium and coma-free days (defined as the days alive during follow up without delirium or coma): • 7 days for dexmedetomidine versus 3 days for lorazepam (p = 0.01)
Maldonado et al (2009)[17]				
Open-label randomised controlled trial	Dexmedetomidine loading dose: 0.4 micrograms/kg, followed by a maintenance drip of 0.2–0.7 micrograms/kg/hour n = 40 Propofol drip 25–50 micrograms/kg/minute n = 38 Midazolam drip 0.5–2 mg/hour n = 40	Exclusion criteria • Pre-existing diagnosis of dementia or schizophrenia • Preoperative use of psychotropic medications • Active or recent substance abuse or dependence • Age < 18 or > 90 years • Documented stroke within the last six months • Evidence of advanced heart block • Pregnancy • Anticipated intraoperative deep hypothermic circulatory arrest	Patients undergoing cardiac-valve procedures	The incidence of delirium: • 3% for dexmedetomidine versus 50% for propofol and, 50% for midazolam

Appendix 1. Continued.

Study design	Treatment regimens	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
Reade et al (2009)[18]				
Randomised, open-label, parallel group pilot trial	Dexmedetomidine 0.2–0.7 micrograms/kg/hour (n = 10) Haloperidol 0.5–2 mg/hour (n = 10)	Exclusion criteria • Those who could not be extubated even if their agitation were corrected (e.g. those receiving high-dose opioid analgesia for pain, those with a plan to shortly return to the operating theatre, those likely to require ongoing airway protection or ventilatory support or patients that are physiologically unstable so extubation would be unsafe) • Adverse reaction to haloperidol or alpha 2-adrenergic receptor agonists	Patients undergoing mechanical ventilation where extubation was not possible solely because of agitated delirium	Time from the commencement of study drug to extubation: • 42.5 hours for for haloperidol versus 19.9 hours for dexmedetomidine (p = 0.016)
Herr et al (2003)[19]				
Randomised, controlled, open-label study	Dexmedetomidine bolus dose of 1.0 micrograms/kg over 20 minutes as loading dose and then an infusion of 0.2–0.7 micrograms/kg/hour (n = 148) Propofol No dose or rate specified in the study protocol and investigators followed usual practice (n = 147)	Exclusion criteria • Pregnant or lactating women • Patients whose neurologic condition or responses could be difficult to evaluate • Unstable or uncontrolled diabetes • Grossly obese • Ejection fraction of < 30% • Hospitalised for a drug overdose	Patients who had a coronary artery bypass graft (CABG) surgery in the ICU	Efficacy of sedation with dexmedetomidine compared to current propofol-based ICU sedation: • Mean sedation levels were within target ranges in both groups. Mean times to weaning and extubation were similar Morphine use for pain relief while ventilated: • 40/144 (28%) dexmedetomidine patients versus 91/154 (63%) for propofol (p < 0.001) • Patients treated with dexmedetomidine received a mean dose of 0.23 mg/h (n = 132) of morphine compared to 0.84 mg/h (n = 140) in those treated with propofol (p < 0.001)

Appendix 1. Continued.

Study design	Treatment regimens	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
ANIST study (Mirski et al 2010)[20]				
Prospective, randomised, double-blind crossover study	Dexmedetomidine 0.2–0.7 micrograms/kg/hour Propofol 20–70 micrograms/kg/hour n = 30	Inclusion criteria • Being awake, able to follow commands and displaying restlessness or agitation • Requiring new implementation of continuous intravenous sedation or an increase in opioid above analgesic dosing	18 intubated brain-injured patients and 12 non brain-injured patients	Difference in the change in cognitive function between the adaptive cognitive exam (ACE) score at relative baseline on fentanyl (baseline or washout phase) and that following sedation by propofol or dexmedetomidine: • Propofol diminished adjusted ACE scores by a mean of -12.4 points • Dexmedetomidine improved ACE scores by 6.8 points • The difference in the change of ACE scores between dexmedetomidine versus propofol was 19.2 points (95% CI 12.3, 26.1 p < 0.001) in favour of dexmedetomidine
ACE: adaptive cognitive exam, CABG: coronary artery bypass graft; CAM: confusion assessment method; CI: confidence interval; ICU: intensive care unit; RSS: Ramsay sedation scale; RASS: Richmond agitation sedation scale.				

Appendix 2. Additional health economic information.

Table 1. Health economic model detail

	Base case model	Appropriate?
Comparator(s)	Dexmedetomidine concentrate for solution for infusion is compared against propofol and midazolam.	AWTTC requested midazolam (administered with an opiate), propofol and clonidine as comparators. The company has used propofol and midazolam only as the comparators. Although acknowledging clonidine is used, the company has not considered it as a comparator in its submission, based on the fact it is not licensed for this use and there are no direct comparative studies of dexmedetomidine versus clonidine.
Population	Adult intensive care unit (ICU) patients requiring sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale [RASS] 0 to -3). Patients are assumed to require invasive mechanical ventilation.	Yes, population meets the licensed indication. The randomised patient populations in the pivotal RCTs, which provide the transition probabilities for the models, include only mechanically ventilated patients who were already intubated and effectively sedated.
Model type and description	Cost utility analysis (CUA) based on a Markov state transition model consisting of five health states. Patients enter the model in the ICU intubated state and may progress to ICU extubated, hospital ward, hospital discharge (home) and death. The time to extubation, length of stay in ICU and in hospital ward as observed in the pivotal RCTs drive patients' movements among the modelled states. A daily cycle length is assumed. Only short-term outcomes are considered in the model, which has a 45-day time horizon, in line with the pivotal trials' lengths of follow up. Two similar but separate models are provided for the analysis of dexmedetomidine versus propofol and dexmedetomidine versus midazolam. A scenario analysis, in which a life time horizon is used and incorporates death, is also provided. A separate cost minimisation analysis (CMA) is also described, in which only costs are compared between the alternative treatments.	Yes, CUA is the preferred type of analysis. The model pathway seems reasonable. The implicit assumption of a CMA would be equivalence in all health outcomes, which would not be the case given the modelled differences in time to extubation, etc.
Perspective	NHS Wales.	Yes.

Table 1. Continued.

	Base case model	Appropriate?
Time Horizon	Analytical time horizon of 45 days is used in the base-case analysis. A life time horizon is also used in a sensitivity analysis.	Yes. The time horizon used in the scenario analysis of a lifetime analytical horizon appears to be based on the proportion of patients reaching 100 years of age, and does not take into account the actual life expectancy of this group of patients who experienced an ICU admission and are likely to have shorter life expectancy compared with population norms. The source of the life tables used in the model is unclear.
Discount rate	No discount is applied in the base case analysis where a 45-day time horizon is used. In the scenario analysis, a discount rate of 3.5% is used for the outcomes.	Yes, discounting not required for the short-term base case model, and 3.5% discount rate is appropriate for longer-term scenario analysis.
Efficacy	Efficacy estimates for the two comparisons are based on the results of the PRODEX and MIDEX RCTs during the observation period. Transition probabilities used in the models are based on the hospital length of stay data from the trials. Mortality rate is assumed to be equivalent in both trial arms.	In both RCTs, the patient population included patients who were mechanically ventilated and their sedation has been successfully induced on the comparator treatment. For the co-primary endpoint (duration of mechanical ventilation [MV]), dexmedetomidine reduced the median duration of MV versus the comparator, but this only achieved statistical significance in the MIDEX trial. The model employs mean estimates of time to extubation and other length of stay estimates, which are reported to be taken from data on file and have not been verified by AWTTC. Neither trial was powered to detect differences in the length of stay in ICU or other wards.
Adverse effects	The model incorporates the incidence of the most relevant short-term adverse events (AEs) in the PRODEX and MIDEX RCTs during the observation period (45 days). These include bradycardia, hypotension and sinus tachycardia.	The AEs considered are consistent with the AEs reported in the trial; however the actual rates assumed are based on data on file (not verified). Some AEs that showed significantly different incidence between dexmedetomidine and its comparators in the PRODEX and MIDEX trials are not incorporated in the model (e.g. hypertension, hypokaleamia were significantly more common in dexmedetomidine recipients, and atrial fibrillation was more common among propofol recipients).

Table 1. Continued.

	Base case model	Appropriate?
Utility values	Utility values assumed in the model for ICU and hospital ward health states are based on those used in a published economic analysis of sedation of patients admitted to ICU with acute respiratory distress syndrome[30]. The utility weights used for the post discharge health state is taken from the UK population norms of the EQ-5D[31].	The utility weights used in the model are taken from a single study[30] and it is not clear if or how other potential sources of utility values were explored. The company highlights the difficulties in estimating utility weights using preference-based methods in this patient population, and notes that the utility values should be viewed with caution as it is not clear what preference elicitation method was used in this study. The utility value used for the post discharge health state is based on population norms despite the fact that this patient population is likely to have lower quality of life in the immediate time post discharge, where the time horizon is very short and is unlikely to allow for a return to normality following an ICU admission episode. However, sensitivity analyses exploring the assumed utility values within the range ± 50% indicate that the model is relatively insensitive to the values assumed for this parameter.
Resource use and costs	Resource use estimates are derived from the PRODEX and MIDEX RCTs, and include: mean length of stay in ICU and hospital ward, mean drug doses based on observed cumulative doses and patient body weight, time to prepare infusions of drugs, first line rescue drug doses). Resources used for the management of AEs are reported to be based on expert opinion and company assumptions. Unit costs are taken from the published sources (BNF 62, NHS Reference Costs PSSRU 2010 unit costs)[25,32]. Drug acquisition costs were based on BNF 2011 prices and calculated based on the average body weight for each trial's population, assuming an equal average body weight for both trial arms. The estimate of nurse's time spent in preparing the infusions are based on expert opinion. Standard errors around the mean cost estimates are assumed to be 10% of the mean, if not available.	There are some uncertainties and limitations associated with the assumed costs of drugs. As doses are assumed to be on a per microgram or per mg basis, drug wastage is not considered, although this is unlikely to exert a large impact. The acquisition cost of midazolam used in the model appears incorrect. The nursing time estimates assumed in the model for administration costs and AE costs are based on assumptions and hence, subject to uncertainty. Although administration costs are assumed for the primary comparators, administration costs associated with the use of rescue therapy with midazolam or propofol, which was required to a greater extent in dexmedetomidine recipients in the PRODEX trial, appears not to be considered. The company assumes that the need for analgesia is equivalent in both trial arms and has not included its cost despite the presence of a difference in the proportion of patients using fentanyl. However, with the exception of time to extubation, and the time spent in ICU and hospital wards, the model appears relatively insensitive to changes in assumed resource use and costs explored within the range ± 50%.

Table 1. Continued.

	Base case model	Appropriate?
Uncertainty	A range of one-way sensitivity and scenario analyses has been conducted. Probabilistic sensitivity analyses (PSA) results have been reported in the submission. A scenario analysis considering disutility due to premature death is also reported.	One way sensitivity analyses for the PRODEX model indicate that the key drivers are the cost per level 3 bed day and the length of stay in the different hospital departments especially during invasive mechanical ventilation. The model outputs appeared largely insensitive to changes in other parameter values in the range ± 50%. For the MIDEX model, the main driver is the time to extubation. Threshold analysis around the key parameter estimates would have been useful. The reported results of the PSAs suggest that the probability that dexmedetomidine is more cost-effective compared to propofol is 85.5% and compared with midazolam is 93.1%, assuming a cost-effectiveness threshold of £25,000 per QALY gained. AWTTC analyses using the model suggest that thresholds for cost-effectiveness in the range of £20,000–30,000 per QALY gained have little influence in these results; however, the standard errors around mean parameter values have in the main been simply assumed (as 10% of the mean). AWTTC has run the PSA several times and each run has generated widely varying results, ranging from dexmedetomidine being dominant, to having an ICER in excess of £700,000 per QALY gained, to being dominated in the modelled comparison against propofol. The PSA results therefore appear to be unstable, possibly reflective of the very small differences in modelled QALY gains between dexmedetomidine and the comparator, and the simple assumptions used to quantify uncertainty around the mean parameter values. The headline results of the PSA (and the deterministic analyses) should therefore be interpreted with caution.
Model Provided?	Yes. Three Excel models are provided, one for each of the comparisons considered (dexmedetomidine vs. propofol and vs. midazolam) and one for the budget impact analysis.	Yes

AEs: adverse events; AWTTC: All Wales Therapeutics and Toxicology Centre; BNF: British National Formulary; CMA: cost minimisation analysis; CUA: cost utility analysis; EQ-5D: EuroQoL - 5 Dimensions health outcome measure; ICER: incremental cost-effectiveness ratio; MV: mechanical ventilation; PSA: probabilistic sensitivity analysis; QALYs: quality adjusted life years; RASS: Richmond agitation-sedation scale; RCT: randomised controlled trial; SPC: Summary of Product Characteristics.