16th June 2022

Dexmedetomidine: clinical trial finds increased risk of mortality in intensive care unit (ICU) patients aged 65 years or younger

Dear Healthcare professional,

The Marketing Authorisation Holders (MAHs) for dexmedetomidine-containing products in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- **The SPICE III study was a randomised clinical trial comparing the effect of sedation with dexmedetomidine on all-cause mortality with the effect of "usual standard of care" in 3904 ventilated critically ill adult intensive care unit (ICU) patients.**
- **Dexmedetomidine was associated with an increased risk of mortality in the age group 65 years or younger, compared with alternative sedatives (odds ratio 1.26; 95% credibility interval 1.02 to 1.56).**
- **This heterogeneity of effect on mortality from age was most prominent in patients admitted for reasons other than post-operative care, and increased with increasing APACHE II scores and with decreasing age. The mechanism is not known.**
- **These findings should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in younger patients.**
- **The product information of dexmedetomidine containing products is being updated with a warning statement describing the evidence, and risk factors, for increased risk of mortality in ICU patients 65 years of age or younger.**

Background on the safety concern

Dexmedetomidine-containing products are indicated for:

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

The academia-sponsored SPICE III trial enrolled 4000 ICU patients needing mechanical ventilation, who were randomly allocated to receive sedation with either dexmedetomidine as primary sedative or with standard of care (propofol, midazolam). Although the target sedation range was light sedation (RASS -2 to +1), deeper sedation levels (RASS -4 and -5) were also allowed. The administration of dexmedetomidine was continued as clinically required for up to 28 days after randomisation.[1]

Altogether, 3904 patients were included in an intention-to-treat analysis. Results are shown in Table 1 below. The study showed no difference in 90-day mortality overall between the dexmedetomidine and the usual care group (propofol, midazolam). The median age of patients included in the analysis was 63.7 years.[1]

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

Table 1: 90-days mortality

	Dexmedetomidine n/total (%)	Usual care n/total (%)
Total	566/1948 (29.1)	569/1956 (29.1)
Subgroup per age		
≤ median age 63.7 years	219/976 (22.4)	176/975 (18.1)
> median age 63.7 years	347/972 (35.7)	393/981 (40.1)

The product information of dexmedetomidine-containing products is being updated with a warning statement describing increased risk of mortality in ICU patients 65 years of age or younger.

Call for reporting

Reporting suspected adverse reactions is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason

- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

It is easiest and quickest to report ADRs online via the Yellow Card website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store. Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Company contact point

Product name	Company	Company contact point
Dexdor 100 micrograms/ml concentrate for solution for infusion	Orion Pharma (UK) Ltd	uk.medicalinformation@orionpharma.com +44 (0) 1635 520300
Dexmedetomidine Accord 100 micrograms/ml concentrate for solution for infusion	Accord Healthcare Limited	medinfo@accord-healthcare.com
Dexmedetomidine 100 micrograms/ml concentrate for solution for infusion	Altan Pharma Limited	anne.lloyd@ethypharm.com
Dexmedetomidine 4 micrograms/ml solution for infusion	Altan Pharma Limited	anne.lloyd@ethypharm.com
Dexmedetomidine 100 micrograms/ml concentrate for solution for infusion	Baxter Healthcare Limited Caxton Way Thetford Norfolk IP24 3SE United Kingdom	Tiina Nykänen, tiina_nykanen@baxter.com Trupti Pol trupti_pol@baxter.com> – Local Representative UK
Dexmedetomidine EVER Pharma 100 micrograms/ml concentrate for solution for infusion	EVER Valinject GmbH	barbara.koeth@everpharma.com
Dexmedetomidine 100 micrograms/ml concentrate for solution for infusion	JSC "Kalceks" 71E Krustpils street Riga, LV – 1057, Latvia Reg. No. 40003059981	1.Marika Berga marika.berga@grindeks.lv; 2. Contact point locally in UK:Rosina Zahoor rosina.zahoor@biomapas.com

Yours Sincerely

Julie Boothe
Medical Director
Orion Pharma (UK) Ltd

References

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

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