Date: 30-08-2022

Direct Healthcare Professional Communication

Dexmedetomidine (Sedalert): Increased risk of mortality in intensive care unit (ICU) patients ≤65 years.

Dear Healthcare professional,

Tabuk Pharmaceuticals in agreement with the Saudi Food and Drug Authority (SFDA), would like to inform you about the risk of mortality in intensive care unit (ICU) patients ≤65 associated with the use of Dexmedetomidine.

Summary:

- In 3904 ventilated critically ill adult intensive care unit (ICU) patients, the SPICE III trial compared the effect of Dexmedetomidine sedation on all-cause mortality to the effect of "usual standard of care".
- When compared to other alternative sedatives, Dexmedetomidine was associated with an increased risk of mortality in the age group ≤65 years (odds ratio 1.26; 95% credibility interval 1.02 to 1.56).
- The effect of age on mortality was most noticeable in patients hospitalized for reasons other than post-operative care, and it increased as APACHE II scores increased and age decreased. The mechanism is unknown.
- 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.

Background on the safety concern:

Dexmedetomidine containing products are indicated for:

- 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).

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 randomization.[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. 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)	(29.1) 1956/569
Subgroup per age		
≤ median age 63.7 years	219/976 (22.4)	(18.1) 176/975
> 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.

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.

Call for reporting for adverse reactions:

Reporting suspected adverse reactions 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.

Saudi Food and Drug Authority, National Pharmacovigilance Center:
Unified Contact Center: 19999
Toll Free Number: 80024900000
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

Pharmacovigilance department in Tabuk Pharmaceuticals:
Email: pv.info@tabukpharmaceuticals.com
Tel: +966114774946
Fax: +966114782686

Saad Alharthi

Qualified Person Responsible for Pharmacovigilance