<Date>

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

Dear Healthcare professional,

The Marketing Authorisation Holders (MAHs) for dexmedetomidine-containing products in agreement with the European Medicines Agency and the *<National Competent Authority >* 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 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.**

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 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)	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.

Call for reporting

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 *[include the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system*

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

TO BE COMPLETED LOCALLY

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.

Annex

Dexmedetomidine product list *<to be completed at national level>*

Product name	**Company**	**Company contact point**

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	dexmedetomidine hydrochloride, dexmedetomidine
Marketing authorisation holder(s)	*All concerned marketing authorisation holders for dexmedetomidine-containing products.* *It is expected that a single consistent message is sent to healthcare professionals in each EU Member State.* *All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The letter circulated in each Member State should cover all active substance-containing products authorised in that Member State.* *It is encouraged that the originator marketing authorisation holder (where available) in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State. If no originator product is marketed in the Member State, it is encouraged that one of the concerned generic companies acts as contact point for the competent authority.*
Safety concern and purpose of the communication	Evidence for increased risk of mortality in intensive care unit (ICU) patients ≤65 years when dexmedetomidine is used to provide sedation. To inform prescribers about the finding of increased risk of mortality in the age group ≤65 years in the academia- sponsored SPICE III study.
DHPC recipients	*Intensive care specialists, anaesthesiologists, and national professionals societies/associations within intensive care / anaesthesiology.* *The target group should be further defined at national level, in agreement with the respective national competent authority.*
Member States where the DHPC will be distributed	In all EU/EEA Member States where dexmedetomidine-containing products are marketed.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	10 March 2022
DHPC and communication plan (in English) agreed by CHMP/CMDh	19 May 2022
Submission of translated DHPCs to the national competent authorities for review	25 May 2022
Agreement of translations by national competent authorities	02 June 2022
Dissemination of DHPC	16 June 2022