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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Dexdor

dexmedetomidine

Procedure no: EMEA/H/C/002268/P46/015

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On December 2018, the MAH submitted 2 completed paediatric studies for Dexdor (ZIN-DEX-1506 and 3005031- Pedrux), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH states that studies ZIN-DEX-1506 and 3005031- Pedrux are stand-alone studies.

Study ZIN-DEX-1506 was a phase 3, multi-centre, single-arm, open-label study evaluating the efficacy, safety, and pharmacokinetics (PK) of dexmedetomidine in paediatric patients in the intensive care unit. The study was conducted at 12 centres in Japan.

Study 3005031- Pedrux was a phase 3, multi-centre, single arm, open-label clinical study to evaluate safety, tolerability, and efficacy of dexmedetomidine for sedation in paediatric patients in intensive care settings. Multi-centre trial conducted in Russia for marketing registration of Dexdor.

2.2. Information on the pharmaceutical formulation used in studies

In the study ZIN-DEX-1506, a single vial containing an injection solution of 2 mL of dexmedetomidine hydrochloride solution (100 µg/mL as dexmedetomidine) dissolved in physiological saline, was provided by the sponsor. Study drug was prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician or pharmacist) as allowed by local, state, and institutional guidance.

Table 1 Study drug description

Study Drug Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
Dexmedetomidine hydrochloride 200 µg intravenous injection 2 mL vial in 5 × pack	54354DK	16-000867	200 µg	Commercial product

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final reports for:

- **ZIN-DEX-1506** (Protocol C0801017) study. Phase 3, multi-centre, single-arm, open-label study evaluating the efficacy, safety, and pharmacokinetics of DA-9501 (dexmedetomidine hydrochloride) in paediatric subjects in the intensive care unit.

- **3005031- Pedrux** study. Open clinical trial to evaluate safety, tolerability, and efficacy of Dexdor for sedation in paediatric patients in intensive care settings. Multi-centre trial in Russia for marketing registration of Dexdor.

2.3.2. Clinical studies

Clinical study ZIN-DEX-1506

Description

Methods

Objectives

To evaluate the efficacy, safety, and pharmacokinetics (PK) of DA-9501 (dexmedetomidine hydrochloride) administered as continuous IV infusion in paediatric subjects who require sedation in the intensive care unit.

Study design

This study was a phase 3, multi-centre, single-arm, open-label study evaluating the efficacy, safety, and pharmacokinetics (PK) of dexmedetomidine administered as continuous IV infusion in paediatric subjects aged ≥45 weeks CGA to <17 years old. Study was conducted at 12 study centres in Japan.

Study population /Sample size

The target study population was ”paediatric subjects undergoing mechanical ventilation management under intensive care and requiring sedation (age ≥45 weeks CGA to <17 years old)”

Main Exclusion Criteria: Subjects who were judged by investigator or sub-investigator to have a neurological disease that made sedation assessment difficult. At the screening period, subjects with second- or third- degree heart block in the tests at the screening period (excluding subjects using a pacemaker); with low blood pressure (BP) levels in the tests; with bradycardia; with alanine aminotransferase ≥100 U/L in the laboratory tests; with acute febrile illness. Subjects in whom dexmedetomidine or other α2 receptor agonists, α2 receptor antagonists and drug that could be used in this study were contraindicated.

The full analysis set (FAS) was composed of all subjects who had received at least 1 dose of the study drug. The primary analysis population for efficacy evaluation was FAS. The efficacy evaluation analysis set (EE) was a subset of the FAS dataset and included subjects who did not receive any prohibited concomitant drug and received continuous IV infusion of the study drug over at least 6 hours. The secondary analysis population for efficacy evaluation was EE.

Treatments

No initial loading dose was given. Baseline body weight was used to determine the dose of the study drug.

- ≥45 Weeks CGA to <6 Years Old: Maintenance infusion was started at 0.2 μg/kg/h. The infusion rate was adjusted within a range of 0.2 μg/kg/h to 1.4 μg/kg/h according to the paediatric subject’s sedative state.

- ≥6 Years to <17 Years Old: Maintenance infusion was started at 0.2 µg/kg/h. The infusion rate was adjusted within a range of 0.2 µg/kg/h to 1.0 µg/kg/h according to the paediatric subject's sedative state.
- Dosing Duration: Dosing of dexmedetomidine was started after the subject was admitted to the ICU. Dosing of dexmedetomidine could be continued after extubation as needed. The dosing duration was at least 6 hours in elective surgical subjects and at least 24 hours in medical ICU subjects for up to 28 days.
- Target Sedation Depth: The target sedation depths during mechanical ventilation and after extubation were shown below.
    - During mechanical ventilation: SBS -2 to 0;
    - After extubation: SBS -1 to 0.

Outcomes/endpoints

Primary Endpoint(s)

Percentage of subjects who did not use a rescue sedative (midazolam) during mechanical ventilation to achieve/maintain adequate sedation (efficacy percentage) from the start of dexmedetomidine administration to 24 hours after the initial administration or conclusion of mechanical ventilation. If the mechanical ventilation is concluded within 24 hours of dexmedetomidine administration, the record at conclusion of mechanical ventilation will be used for the primary endpoint.

Secondary Endpoint(s)

i. From the start of dexmedetomidine administration to 24 hours after the initial administration or conclusion of mechanical ventilation when mechanical ventilation is concluded within 24 hours of dexmedetomidine administration,

1. Percentage of subjects who did not require administration of a rescue analgesic (fentanyl) during mechanical ventilation in addition to administration of the investigational product.

2. Dose level corrected for total dose of rescue sedative/analgesic during mechanical ventilation and for body weight.

3. Duration and percentage of maintenance of target sedation level during mechanical ventilation.

ii. From 24 hours of dexmedetomidine administration to conclusion of mechanical ventilation when dexmedetomidine administration exceeds 24 hours,

4. Percentage of subjects who did not use a rescue sedative(midazolam) during mechanical ventilation to maintain/achieve adequate sedation.

5. Percentage of subjects who did not require dosing of a rescue analgesic(fentanyl) during mechanical ventilation in addition to dosing of the investigational product.

Statistical Methods

The set of statistics included in, geometric mean, arithmetic mean, median, standard deviation, cv, geometric cv, minimum, maximum and the number of concentrations above the lower limit of quantification.

Scatter plot of dexmedetomidine concentration versus vital signs at the end of infusion was generated. In addition, the linear regression analysis was performed for investigating the relationship (Independent variable: dexmedetomidine concentration, Dependent variable: each vital sign). The

analyses were performed using the REG procedure in SAS. Table of parameters for the linear regression including the correlation coefficient were presented.

Results

Recruitment/ Number analysed

A total of 70 subjects were screened, of which 63 subjects were assigned and received study treatment. Two (2) male subjects discontinued from the study in the ≥2 years to <6 years age group. Subject 10081002 was withdrawn due to SAE of cardiac tamponade which was not related to study treatment. Subject 10021004 was withdrawn due to investigator's judgment.

Baseline data

Subjects in full analysis set (FAS) across the age groups were similar in their demographic characteristics, with all of the subjects being Asian (Japanese).

Table 2 Full analysis set

	Full Analysis Set				
	≥45 W CGA to <12 M	**≥12 M to <24 M**	**≥2 Y to <6 Y**	**≥6 Y to <17 Y**	**Total**
Number (%) of Subjects	**14**	**18**	**19**	**12**	**63**
Gender					
Male	6 (42.9)	11 (61.1)	12 (63.2)	7 (58.3)	36 (57.1)
Female	8 (57.1)	7 (38.9)	7 (36.8)	5 (41.7)	27 (42.9)
Age:					
≥45 W CGA to <12 M	14 (100.0)	0	0	0	14 (22.2)
≥12 M to <24 M	0	18 (100.0)	0	0	18 (28.6)
≥2 Y to <6 Y	0	0	19 (100.0)	0	19 (30.2)
≥6 Y to <17 Y	0	0	0	12 (100.0)	12 (19.0)
Mean (SD) (M)	6.1 (2.1)	16.9 (3.6)	45.7 (14.6)	112.1 (37.9)	41.3 (41.8)
Range (M)	1-9	12-23	24-69	73-175	1-175
Race:					
Asian	14 (100.0)	18 (100.0)	19 (100.0)	12 (100.0)	63 (100.0)
Weight (kg):					
Mean (SD)	6.3 (1.1)	9.3 (1.5)	15.2 (3.0)	29.2 (14.5)	14.2 (10.3)
Range	4.5-8.3	6.4-12.0	10.1-20.2	16.1-70.8	4.5-70.8
Height (cm):					
Mean (SD)	65.3 (5.2)	77.4 (5.9)	98.7 (11.3)	129.6 (18.6)	91.1 (24.9)
Range	55.0-72.8	66.8-93.7	82.1-117.0	111.0-167.2	55.0-167.2

Table 3

Table S3. Summary of Patient Types

Number (%) of Subjects	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months	≥12 Months to <24 Months	≥2 Years to <6 Years	≥6 Years to <17 Years	Total
Full Analysis Set					
Evaluable subjects	14	18	19	12	63
Elective surgery	13 (92.9)	18 (100.0)	18 (94.7)	12 (100.0)	61 (96.8)
Medical ICU	1 (7.1)	0	1 (5.3)	0	2 (3.2)
Efficacy Evaluation Analysis Set					
Evaluable subjects	13	17	18	11	59
Elective surgery	12 (92.3)	17 (100.0)	17 (94.4)	11 (100.0)	57 (96.6)
Medical ICU	1 (7.7)	0	1 (5.6)	0	2 (3.4)

Abbreviations: CGA=corrected gestation age; ICU=intensive care unit.

Pharmacokinetic results

The PK analysis population was defined as subjects treated with dexmedetomidine over at least 6 hours, and with at least 1 plasma concentration measured. The set of statistics included number, geometric mean, arithmetic mean, median, SD, coefficient of variation (CV), geometric CV, minimum, maximum and the number of concentrations above the lower limit of quantification.

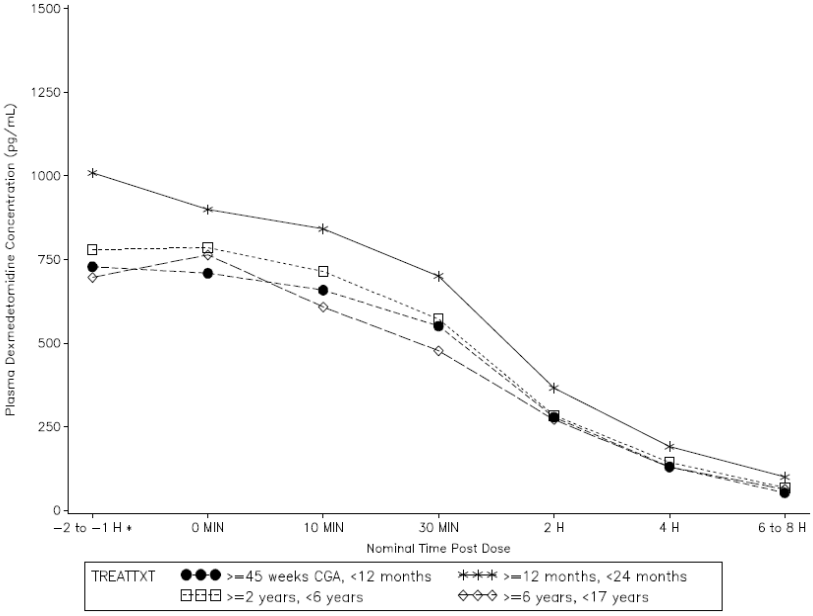
Number of subjects included in the PK analysis per each age group was the following:

- ≥45 week CGA , <12 months (N=11)
- ≥12 months, <24 months (N=16)
- ≥2 years, <6 years (N=11)
- ≥6 years, <17 years (N=8)

For all patients, maintenance infusion was started at 0.2 µg/kg/h. The infusion rate was adjusted within a range of 0.2 µg/kg/h to 1.4 µg/kg/h for ≥45 weeks CGA to <6 years old patients, and 0.2 µg/kg/h to 1.0 µg/kg/h for ≥6 years to <17 years old patients according to the paediatric patient's sedative state.

MAH concluded that there were no obvious differences observed among age groups in plasma dexmedetomidine concentration-time profiles, and plasma dexmedetomidine concentration at 1 to 2 hours before the end of dosing or before the start of tapering. Because tapering was done for only 2 subjects, the effect of tapering on dexmedetomidine PK could not be evaluated. Similar dexmedetomidine PK profiles were observed in the presence and absence of midazolam.

Figure 1 Mean plasma dexmedetomidine concentration-time profiles on linear (upper panel) and semi-log graph (lower panel).



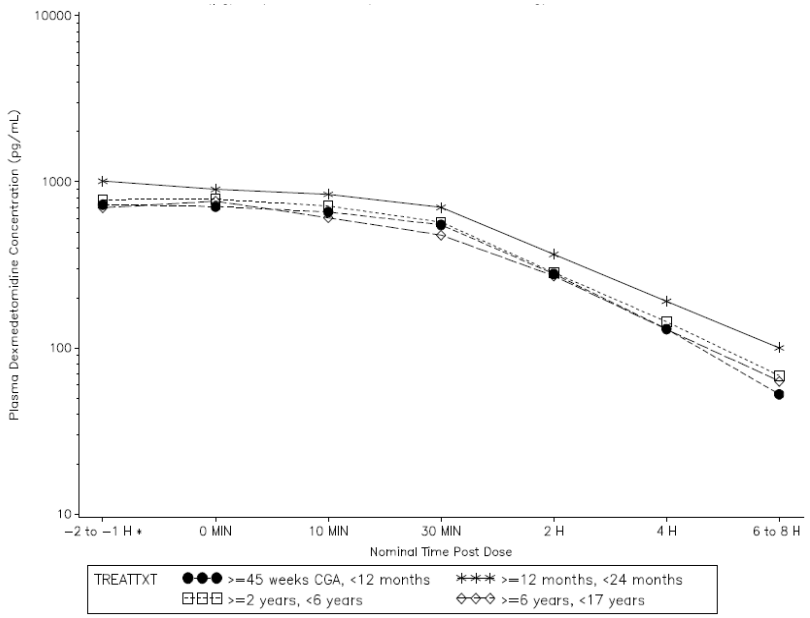
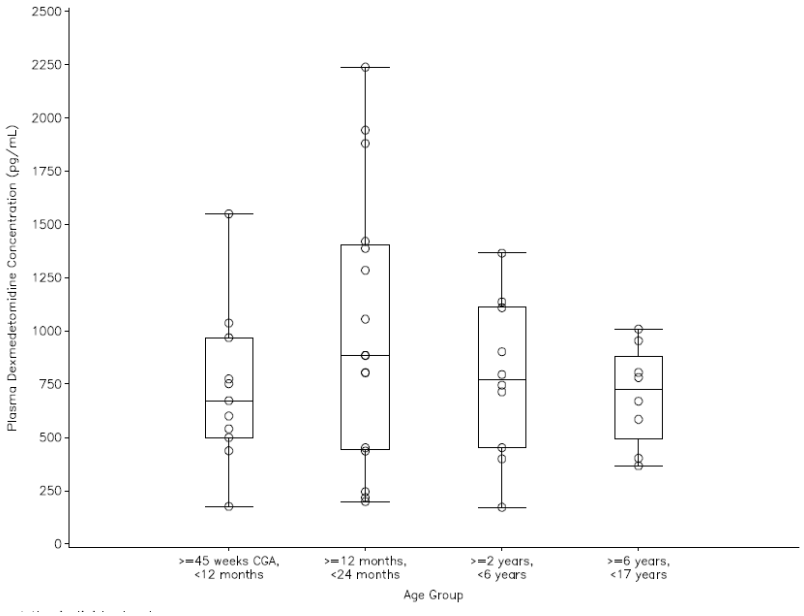
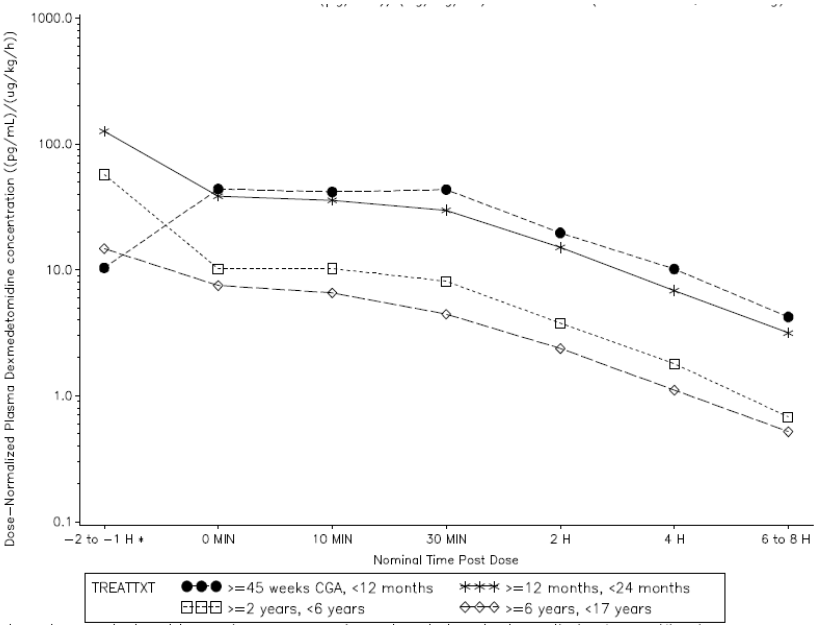


Figure 2 Plasma dexmedetomidine concentrations at 1 to 2 hours before the end of dosing or before the start of tapering.



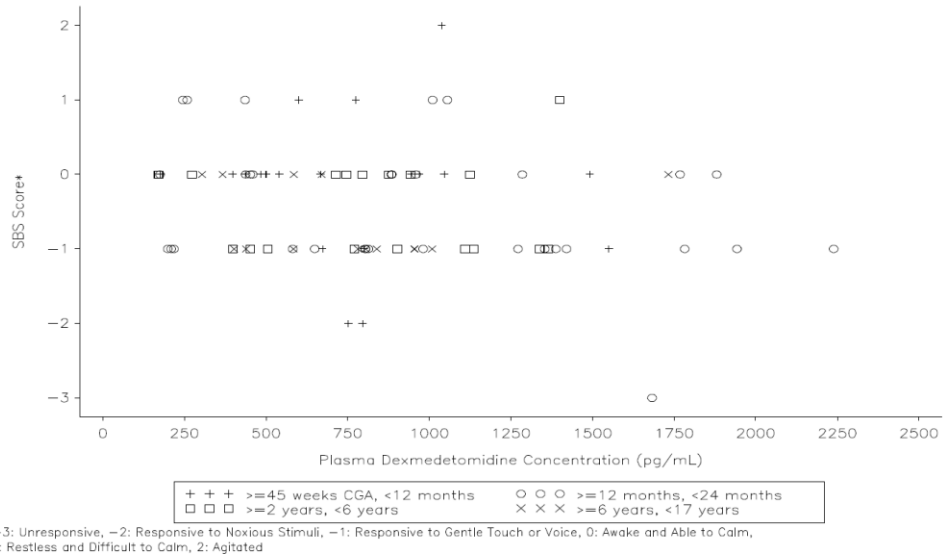
In addition, MAH also presented dose-normalised plasma concentrations of dexmedetomidine (Figure 3). Concentrations were dose normalised by the rate of administration (µg/kg/h) at the sampling time or at the end of dosing for the measurements after the end of dosing.

Figure 3 Dose normalised plasma dexmedetomidine concentration-time profiles (mean values, semi-log graph).



Furthermore, MAH concluded that there were no apparent direct relationships observed between SBS score and plasma dexmedetomidine concentration (Figure 4).

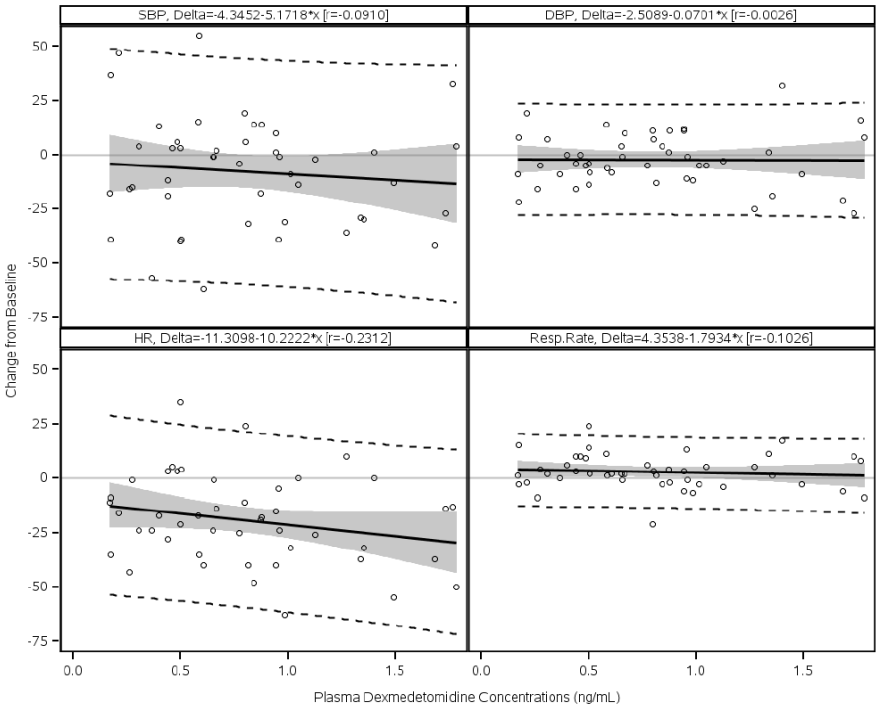
Figure 4 Individual plots for SBS score versus plasma dexmedetomidine concentration (pg/mL) before end of dosing.



* −3: Unresponsive, −2: Responsive to Noxious Stimuli, −1: Responsive to Gentle Touch or Voice, 0: Awake and Able to Calm, 1: Restless and Difficult to Calm, 2: Agitated

Moreover, the relationships between plasma dexmedetomidine concentration and change from baseline of four vital signs (systolic blood pressure SBP, diastolic blood pressure DBP, heart rate and respiratory rate) at the end of infusion were investigated) The effect of plasma concentration on DBP and respiratory rate were not observed. SBP and heart rate appeared to decrease with increasing plasma concentration, and it is expected at the median concentration of the end of infusion of 0.784 ng/mL, changes in SBP and HR would be -8.4 mmHg and -19.3 bpm, respectively.

Figure 5 Relationships between plasma dexmedetomidine concentration and change from baseline of vital signs (Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate and Respiratory Rate) at the end of infusion.



SBP: Systolic BP (mmHg), DBP: Diastolic BP (mmHg), HR: Heart Rate (BPM), Resp. Rate: Respiratory Rate (RPM)
Circle symbols represent observed data, dashed lines present 95% limit of prediction, shaded area present predicted 95% CI of regression, black solid line present regression, grey solid line present line of zero.

Efficacy results

Result of the primary endpoint: overall 77.8% of the patient did not require rescue midazolam for additional sedation.

Table 4

Table S5. Percentage of Subjects Who Did Not Use Rescue Midazolam Within 24 Hours or Conclusion of Mechanical Ventilation - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=14)	≥12 Months to <24 Months (N=18)	≥2 Years to <6 Years (N=19)	≥6 Years to <17 Years (N=12)	Total (N=63)
Number of subjects with no rescue midazolam	11	12	15	11	49
Percent of subjects with no rescue midazolam	78.6	66.7	78.9	91.7	77.8
95% CI[a]	51.7-93.2	43.6-83.9	56.1-92.0	62.5-100.0	66.0-86.4

Abbreviations: CGA=corrected gestation age; CI=confidence interval; FAS=full analysis set; N=number of subjects.

a. 95% CI was calculated as a 2-sided, 2.5% upper and lower intervals, based on Agresti-Coull's method.

Secondary endpoints: within 24 h after start of study treatment (or until the end of mechanical ventilation, if shorter than 24 h) 88.9% of patients did not require rescue fentanyl. There was only

minimal difference among age groups. The median weight adjusted rescue dose for midazolam was 0.18 mg/kg, for fentanyl 4.92 µg/kg. A total of 95.2% of patients were in the target sedation level in the first period (up to 24 h). Maintenance of the target sedation level was median 60.86%. Over 24 h until the end of mechanical ventilation no patient required rescue midazolam or fentanyl. Target sedation level was maintained in median 100% of time. From extubation until the end of study drug treatment a total of 96.75% of patients were in the target sedation level, the median percentage of maintenance of the target sedation level was 57.11. In this period five patients (8.2%) used rescue midazolam in median 0.093 mg/kg weight adjusted dose, and one patient received rescue fentanyl, in 3.0 µg/kg weight adjusted dose. Time from the start of the study drug treatment to conclusion of mechanical ventilation was median 6.0 hours.

Safety results

A total of 129 all-causalities treatment-emergent adverse events (TEAEs) were reported of which 25 were considered treatment-related by the investigator. Similar proportions of subjects in each age group experienced all-causalities TEAEs (78.6% to 88.9%) except for ≥6 years to <17 years age group (100.0%). A total of 25 TEAEs reported by 16 (25.4%) subjects were considered treatment-related by the investigator.

One (1) subject discontinued due to an SAE of moderate cardiac tamponade reported in ≥2 years to <6 years age group; considered not related to the treatment by the investigator. Three (3) SAEs in 3 subjects were reported post-therapy. No severe AEs were reported during the study. None of the subjects with dose reduced or temporary discontinuation due to TEAEs were reported. There were no deaths among subjects who participated in this study.

The most frequently reported all-causalities TEAEs by preferred term were hypotension, bradycardia, and respiratory depression. Of the subjects who had all-causalities events of hypotension (31 [49.2%] subjects), bradycardia (20 [31.7%] subjects) and respiratory depression (17 [27.0%] subjects), 5 (7.9%), 8 (12.7%) and 2 (3.2%) subjects were considered as treatment-related, respectively. Only 4 subjects with most common TEAEs (hypotension, bradycardia, and respiratory depression) needed interventions: 3 subjects with hypotension were given treatment and 1 subject with respiratory depression was given reduced dose of fentanyl.

Clinical study Pedrux

Description

Open clinical trial to evaluate safety, tolerability, and efficacy of Dexdor for sedation in pediatric patients in intensive care settings. Multi-centre trial in Russia for marketing registration of Dexdor.

Methods

Objective(s)

- Evaluation of efficacy of Dexdor for prolonged sedation in pediatric patients;
- Evaluation of safety and tolerability of Dexdor in pediatric population

Study design

An open-label multicentre study including pediatric patients at 12-17 years of age hospitalised in intensive care units (ICUs).

Study population /Sample size

Inclusion criteria (abbreviated):

1. Age from 12 to 17 years;
2. Clinical need for prolonged (>24 h) light to moderate sedation in ICU patients with spontaneous or artificial ventilation
3. Negative urine pregnancy test (for female patients);

Exclusion criteria:

1. Acute severe intracranial or spinal neurological disorder due to vascular causes, infection, intracranial expansion or injury; any other disorder where sedation assessment is not reliable due to any neurological conditions;
2. Uncompensated acute circulatory failure
1. Severe hypotension or hypertension
2. Severe bradycardia or tachycardia
3. A/V-conduction block II-III;
4. Severe hepatic impairment
5. Loss of hearing or vision, or any other condition which would have significantly interfered with the collection of study data;
6. Use of centrally acting alpha-2 agonists or antagonists in the period less than 5x half-life between drug discontinuation and the time of randomisation;
7. Patients who had or were expected to have treatment withdrawn or withheld due to poor prognosis
8. Patients receiving sedatives for therapeutic indications (e.g. epilepsy);
9. Patients allergic to dexmedetomidine and rescue medications
10. Haemodialysis and peritoneal dialysis;
11. Those requiring deep sedation or neuromuscular blocking agents;
12. Injuries requiring regular anaesthesia or surgery; burn injuries;
13. History / family history of malignant hyperthermia;
14. Patients unlikely to be weaned from the ventilator during the study;
15. Patients with early-onset ventilator-associated pneumonia;
16. Any investigational drug within the preceding 30 days;
17. Any other reason which in the investigator's opinion would have made it detrimental for the subject to participate in the study.

Treatments

Dexdor 100 micgrograms/ml concentrate for solution for infusion. Maximal duration of sedation with Dexdor was defined as 5 days.

Recruitment/ Number analysed

60 patients requiring prolonged sedation were enrolled in this study.

2.3.3. Discussion on clinical aspects

Pharmacokinetics

The PK analysis was performed in paediatric populations belonging to different age groups from ≥45 weeks CGA to <17 years. The PK dataset consisted of subjects treated with continuous IV infusion of dexmedetomidine over at least 6 hours, and with at least 1 plasma concentration measured. In all patients, treatment was initiated with the maintenance infusion at the rate of 0.2 µg/kg/h. The infusion rate was then adjusted according to the paediatric patient's sedative state (based on the target value on State Behavioural Scale – SBS score). MAH concluded that there were no obvious differences observed among age groups in plasma dexmedetomidine concentration-time profiles. No PK parameters were presented for any of the age groups. In addition, MAH concluded that the presence or absence of midazolam did not affect plasma exposures of dexmedetomidine. Moreover, MAH concluded that there were no apparent direct relationships observed between plasma dexmedetomidine concentration and SBS score (no direct PK-PD relationship). Finally, relationships between plasma dexmedetomidine concentration and change from baseline of four vital signs (systolic blood pressure SBP, diastolic blood pressure DBP, heart rate and respiratory rate) at the end of infusion were investigated. MAH stated that the effect of plasma concentration on DBP and respiratory rate were not observed, while SBP and heart rate appeared to decrease with increasing plasma concentrations.

Experimental design involving adjustment of infusion rates for different individuals based on their pharmacodynamic responses is challenging in terms of PK interpretations as their final concentration-time profiles are achieved by different infusion rates. Achievement of steady state plasma concentrations before the end of infusion was not discussed by MAH. Dose-normalised PK profiles (concentrations divided by the respective infusion rates) still indicated potential differences in dexmedetomidine plasma exposures between different age groups, which could also imply potential differences in PK parameters. Therefore, MAH was advised to perform estimation of relevant PK parameters (primarily CL and half-life) for each age group. MAH is also encouraged to use modelling approaches for estimation of PK parameters in order to take into account experimental design with different infusion rates administered to different individuals.

MAH has provided plausible explanations regarding previously noted differences in half-life and CL values between SmPC and ZIN-DEX-1506 study. By age-matching study groups and by excluding study subjects with insufficient PK sampling, half-life values in the SmPC were comparable with corresponding values from the ZIN-DEX-1506 study. Moreover, by re-calculating CL values of ZIN-DEX-1056 study with simplified approach (CL=R/Css) which did not require estimation of AUCs, a more comparable CL values between two studies were obtained.

Efficacy and safety

No new efficacy or safety information that justifies regulatory action has been identified. The benefit/risk relation remains unchanged and favourable.

3. CHMP overall conclusion and recommendation

The benefit/risk relation remains unchanged and favourable. It was concluded that the ZIN-DEX-1506 trial conducted in Japanese children did not reveal any unexpected PK parameter values which would trigger an update in the current SmPC.