Report on the Deliberation Results

February 6, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Precedex Intravenous Solution 200 μg "Pfizer," Precedex Intravenous Solution 200 μg/50 mL Syringe "Pfizer"
Non-proprietary Name	Dexmedetomidine Hydrochloride (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	March 30, 2022

Results of Deliberation

In the meeting held on October 28, 2022, the First Committee on New Drugs presented findings shown in the attachment and concluded that the deliberation should be continued.

In the subsequent meeting held on January 27, 2023, the First Committee on New Drugs had discussion based on the attachment, and concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 5 years and 10 months.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Attachment

Findings on Precedex Intravenous Solution presented at the First Committee on New Drugs and measures taken

January 20, 2023

1. Product outline

Brand Name	Precedex Intravenous Solution 200 μg "Pfizer," Precedex Intravenous Solution 200 μg/50 mL Syringe "Pfizer"
Non-proprietary Name	Dexmedetomidine Hydrochloride
Applicant	Pfizer Japan Inc.
Date of Application	March 30, 2022
Indication	Sedation of non-intubated pediatric patients during non-invasive procedures or examinations

2. Remarks made at the previous meeting of the First Committee on New Drugs

In the meeting held on October 28, 2022, the First Committee on New Drug raised mainly the following points and concluded that the deliberation should be continued at subsequent meetings of the First Committee on New Drug:

- In the clinical study conducted in Japan, propofol was the only rescue drug allowed for use in subjects who had an inadequate response to Precedex Intravenous Solution (hereinafter referred to as Precedex). However, in clinical practice in Japan, Precedex is expected to be used mainly by general pediatricians, and, therefore, propofol is very unlikely to be used as rescue drug for poorly responding patients. Information, including that pertaining to safety in co-administration with sedatives other than propofol, needs to be gathered in an organized manner.
- The investigators in the Japanese clinical study were pediatric or general anesthesiologists. Whether the safe use of Precedex can be assured in clinical practice in Japan, despite the environmental gap between medical settings in Japan and the clinical study, should be discussed with related academic societies, based on which the validity of the safety measures need to be explained.
- Serious respiratory depression was reported from 2 children in a study administering Precedex 4.0 μg/kg over 10 minutes and, based on this information, the applicant had discussion with the US Food and Drug Administration (FDA) about the administration time (administration rate) at the planning phase of clinical study. The applicant should provide clinical settings with data that support the administration time (administration rate) determined for Precedex in the clinical study.

3. Measures

In response to the remarks made at the previous meeting of the First Committee on New Drug as mentioned in 2 above, the following explains (1) safety in the co-administration of Precedex with

sedatives other than propofol and (2) safety measures to be taken in view of the environmental gap between the clinical study and medical settings in Japan. Also described are (3) outcomes of the discussion between the applicant and the related academic societies, and information to be released from the academic societies, and (4) discussion between the applicant and the US FDA about the selection of administration time (administration rate) at the planning of the clinical study and necessary measures to be taken.

(1) Safety in the co-administration of Precedex with sedatives other than propofol

1) Concomitant sedatives used in the clinical study and that expected to be used in clinical practice in Japan

In the global phase III/IV study (Study C0801039) in pediatric patients undergoing magnetic resonance imaging (MRI), the use of propofol was allowed as concomitant sedative. In Japan, there are no intravenous sedatives indicated for children undergoing examinations. When Precedex alone fails to achieve sedation adequate to complete a procedure or examination, intravenous sedatives other than propofol (barbiturates, midazolam, etc.) are likely to be used in combination.

2) Safety in co-administration with intravenous sedatives other than propofol

The following are available safety information about intravenous sedatives (barbiturates, midazolam, etc.) expected to be used in combination with Precedex in clinical practice in Japan. The attached sheets provide a summary.

- Three reports from articles on Precedex administered to children for the proposed indication at doses similar to the proposed dosage regimen in combination with midazolam, fentanyl, or barbiturate
- Safety data of Precedex administered in combination with midazolam or fentanyl in the group undergoing noninvasive procedures or examinations in the foreign phase IV study (Study DEX-10-16) of Precedex
- Safety data of Precedex administered in combination with midazolam or fentanyl in the Japanese phase III study in children in intensive care settings
- Safety data from the specified use-results survey on Precedex administered in combination with midazolam in children in intensive care settings

These safety data did not suggest serious safety concerns in the co-administration of Precedex with barbiturates, midazolam, etc., although some data were based on different indication or dosage regimen.

However, as with concomitant propofol administered with Precedex in the Study, intravenous sedatives other than propofol will increase the risk of sedation complications, i.e., adverse events related to circulatory dynamics and respiratory status, when concomitantly used with Precedex. Safety measures described in (2) and later must be taken.

As described in (3), the related academic societies will caution that, in the use of Precedex for the proposed indication, supplementary administration of propofol is not recommended except by specialists such as anesthesiologists.

(2) Safety measures to be taken in view of the environmental gap between the clinical study and medical settings in Japan

1) The environmental gap between Study C0801039 and medical settings in Japan

At the study sites of Study C0801039 in Japan, pediatric or general anesthesiologists played the role of investigator. In Japanese clinical practice, however, sedation using Precedex is expected to be performed by general pediatricians.

To provide standards for safer sedation in pediatric patients undergoing MRI, Japan Pediatric Society, the Japanese Society of Pediatric Anesthesiology, and Japanese Society of Pediatric Radiology have compiled "Joint proposal for sedation in MRI scan [in Japanese]" (*The Journal of the Japan Pediatric Society.* 2020;124:771-805) (hereinafter referred to as "the Joint Proposal"). In the clinical study, the study sites using Precedex had a set of necessary goods ready for resuscitation as per the recommendation in the Joint Proposal, and a physician or nurse was present specially for close vigilance of sedated patients, by whom heart rate, respiratory rate, peripheral oxygen saturation (SpO_2), blood pressure, end-tidal carbon dioxide ($EtCO_2$), and electrocardiogram (ECG) were carefully monitored. On the other hand, some clinical settings in Japan where Precedex will be used for the proposed indication may not necessarily have a person stationed to engage solely in vital sign monitoring or patient monitoring, or have emergency equipment or a well-maintained backup system for emergencies, etc. as recommended in the Joint Proposal (*The Journal of the Japan Pediatric Society.* 2017;121:1920-9).

As described in the above (1)1), propofol was the only sedative used in the study when Precedex did not provide adequate sedation. In Japanese clinical practice, Precedex is expected to be co-administered with sedatives other than propofol (barbiturates, midazolam, etc.).

2) Concrete safety measures

Safety measures will be taken for prompt and appropriate actions for emergencies such as adverse events related to circulatory dynamics and respiratory status, including those associated with the co-administration of other intravenous sedatives with Precedex.

The following describes details.

i) Cautionary advice in the package insert (Attached document 1)

The section "1. Warning" will include the following advice: Precedex should only be used by physicians with a good understanding of the pharmacological action of Precedex who are proficient in performing pediatric sedation under intensive care or non-intubated condition, and at facilities adequately equipped for careful and constant monitoring for systemic condition, including respiratory status and circulatory dynamics, and for emergency response.

The sections "7. Precautions Concerning Dosage and Administration" and "8. Important Precautions" will include the following advice in accordance with the Joint Proposal: The facilities should be

prepared for respiratory and circulatory controls and have healthcare professionals to be engaged solely in patient management through the monitoring for SpO_2, respiratory rate, heart rate (pulse rate), blood pressure, ECG, $EtCO_2$, etc. Additional use of other sedatives in patients with inadequate response to Precedex may enhance the sedative effect and effects on circulatory dynamics and respiratory status, possibly leading to increased risk of adverse drug reactions. Physicians should be advised to use these sedatives carefully while patient's systemic condition is closely monitored.

The section "17. Clinical Studies" section will include the following precaution: Propofol is not indicated for sedation of non-intubated children undergoing non-invasive procedures or examinations.

ii) Information provision via materials for healthcare professionals (proper use guide for Precedex) (Attached document 2)

Healthcare professionals will be provided with information through written materials (proper use guide for Precedex). Serving to supplement the package insert, the materials will provide points for sedation management in non-intubated children undergoing non-invasive procedures or examinations (relevant procedures or examinations, necessity of judgment on the use of sedatives, medical system including facilities and personnel, sedation level, assessment method, etc.), and cautions required before, during, and after Precedex administration (recommended monitoring items, etc.). The guide will cover the recommendations of the Joint Proposal and the guidelines published by related academic societies such as "Practical guide for safe sedation (revised version, June 2022)" (Japanese Society of Anesthesiologists; 2022). The proper use guide will caution that low-age patients are anatomically and physiologically immature and that the percentages of respiration-related complications are high in newborns and suckling infants. Measures to be taken against inadequate sedation achieved by Precedex alone and precautions on the concomitant use of other sedatives will also be included, by referring to the document mentioned in (3) below, which will be released by the related academic societies.

The Joint Proposal states that the physician who requests MRI examination should explain the risk of adverse drug reactions of the sedative to the patient's guardian and obtain consent, and the proper use guide will also give this advice. The patient's guardian should closely consult with the physician requesting MRI, i.e., the attending physician, about the use of the sedative to clear doubts or anxieties, if any.

iii) Implementation of proper use promotion program (Attached document 3)

The proper use promotion program will be implemented to facilitate the proper use of Precedex. Aiming to minimize the environmental gap between the clinical study and medical settings in Japan mentioned earlier in (2)1), the program will provide a commentary video (e-learning) based on the proper use guide. In the program, the requirements for facilities, physicians who administer sedation, and healthcare professionals to be engaged solely in patient monitoring (see descriptions below) will be specified by reference to the recommendation in the Joint Proposal and after discussion with the related academic societies (Japan Pediatric Society and the Japanese Society of Pediatric Anesthesiology), and all facilities supplied with Precedex will be advised to use the product appropriately for the proposed indication only when these requirements are met. At the same time, a

member of the marketing authorization holder will be assigned to assure the fulfillment of the requirements at the facilities intending to use Precedex for the proposed indication. In parallel with these activities, the marketing authorization holder will conduct a fact-finding survey on proper use. When the member of the marketing authorization holder identifies any non-compliance with the requirements in the use of Precedex through the survey, the non-compliant facilities will be persistently asked to use Precedex in a compliant manner.

Requirements for facilities

The following requirements should be all met:

(a) Every examination room, treatment room, etc. used for Precedex administration for the proposed indication has equipment/devices to monitor for the following items (MRI-compatible equipment/device for sedation for MRI scan):
- Essential: SpO_2, respiratory rate, heart rate, blood pressure, and ECG
- Recommended: $EtCO_2$

(b) Every examination room, treatment room, etc. (except ICU, CCU, NICU, etc.) used for Precedex administration for the proposed indication is properly equipped to accommodate the use of syringe pumps.
- For MRI examination, an MRI-compatible device should be used. Non-MRI-compatible devices must be installed outside the MRI room from a safety point of view.

(c) A system for emergencies ready for cardiopulmonary resuscitation, which provides:
- Equipment/devices for emergencies and/or resuscitation ready for use at any time
- A backup system for the formation of a rapid response team, etc. for emergencies

(d) A system to allocate “a physician performing sedation” and “a healthcare professional to be engaged solely in patient monitoring” qualified for the use of Precedex according the following:

Requirements for physicians who perform sedation

(a) Proficiency in the administration of Precedex

(b) No experience in sedation with Precedex but meeting all of the following requirements:
- Attendance at a course of emergency medical care for children,* familiarity with the emergency medical care and ability to perform it to deal with adverse events
- Accessibility to support from another physician who is proficient in the administration of Precedex, such as in witnessing at advance consultations or during the performance of sedation.
- Attendance at the proper use promotion program provided by Pfizer, Inc., and adequate understanding of the safety profile of Precedex based on its pharmacological characteristics, necessary preparation, and points to be checked before Precedex administration

Requirements for healthcare professionals to be engaged solely in patient monitoring
- Attendance at a course of emergency medical care for children,* familiarity with the emergency medical care and ability to perform it to deal with adverse events

* Course of emergency medical care (examples):
- PALS (Pediatric Advanced Life Support) courses co-sponsored by the Japanese Society of Pediatric Intensive and Clinical Care and by Japan ACLS Association

- JPLS (Japan Pediatric Life Support) course sponsored by the Japan Pediatric Society

(3) Outcomes of the discussion between the applicant and the related academic societies, and information to be released from the academic societies (Attached document 4)

As described in the above (2)2)iii), the applicant had discussion with related academic societies (Japan Pediatric Society and the Japanese Society of Pediatric Anesthesiology) about the requirements for facilities which will be using Precedex for the proposed indication, physicians performing sedation, and healthcare professionals to be engaged solely in patient monitoring. The related societies will call for cooperation on the proper use promotion, together with the announcement of these requirements and the proper use promotion program, as promptly as possible after the approval of Precedex for the proposed indication. In the call, the following measures will be advised to be taken when Precedex alone fails to achieve a sedation level adequate to complete a procedure or examination or when Precedex's sedative effect has decreased:

- When Precedex alone fails to achieve a sedation level to complete a procedure or examination, additional administration of other intravenous sedatives, during the use of Precedex or after Precedex is discontinued, may be a possible option. However, currently in Japan, there are no intravenous sedatives indicated for "sedation of non-intubated children undergoing non-invasive procedures or examinations" other than Precedex.
- For some patients, discontinuation or postponement of the procedure or examination should be considered instead of the use of other sedatives.
- In the case where the target sedation level is not achieved with Precedex or is achieved but waning, the administration of other intravenous sedatives may enhance the sedative effect and effects on circulatory dynamics and respiratory status, leading to increased risk of adverse drug reactions. Cautious actions must be taken while the patient is carefully monitored for systemic condition.
- In order to avoid rapid infusion of Precedex, additional sedatives should be administered through a separate intravenous line by any means possible (the same applies to the administration of other intravenous sedatives following Precedex discontinued).
- The intravenous sedative should be administered through the bypass closest possible to the patient for accurate dose adjustment.
- With the use of other intravenous sedatives or emergency drugs in mind, preferably ≥2 intravenous lines should be secured before using Precedex. When ≥2 intravenous lines cannot be secured, the concomitant drug should be administered through the bypass closest possible to the patient to avoid rapid infusion of Precedex within the line.
- Immediately after administration, monitor the patient most carefully for any change in condition.
- The concomitant use of propofol was allowed in the clinical study. However, the supplementary use of propofol is not recommended in the use of Precedex for the proposed indication, except by anesthesiologists or other specialists.

(4) Discussion between the applicant and the US FDA about the selection of administration time (administration rate) at the planning of the clinical study, and necessary measures to be taken

In the discussion with the US FDA at the planning of the clinical study, the applicant proposed the initial loading dose of "Precedex 2.0 μg/kg over 5 minutes" for subjects aged ≥2 and <17 years in the

high-dose group. However, in light of serious bradycardia reported from 2 subjects in a study administering Precedex 4.0 μg/kg over 10 minutes to children aged 6 to 60 months, the US FDA expressed their view that the initial loading dose should be modified to "Precedex 2.0 μg/kg over 10 minutes." As a result of discussion with the US FDA, the initial loading dose was modified to "Precedex 2.0 μg/kg over 10 minutes."

The above-mentioned point raised by the US FDA was based on cases reported in a published article (*Br J Anaesth.* 2014;112:892-7). In the deliberation material (Common Technical Document [CTD] 2.5 p.6) in the previous meeting of the First Committee on New Drugs, these events were described as "serious respiratory depression were reported from 2 subjects." However, the published article described it as "Bradycardia (HR <60 beats min^{-1}) was seen in two children," and the description "respiratory depression" was proven to be a clerical error for "bradycardia." In the present deliberation material (CTD 2.5 p.8), the description has been corrected to "serious bradycardia was reported from 2 subjects."

The published article reports the results of a clinical study (academia-sponsored) comparing the safety and efficacy of total intravenous anesthesia using Precedex plus concomitant propofol with total intravenous anesthesia using remifentanil plus concomitant propofol in spontaneously breathing pediatric patients aged 6 to 60 months requiring airway foreign body removal. The study stipulated that, during the induction period, Precedex 4 μg/kg be administered over 10 minutes under co-administration with propofol. Bradycardia (<60 beats per min) was observed in 2 of 39 subjects receiving Precedex during the induction period, to whom atropine was administered.

The above-mentioned published article and the discussion between the applicant and the US FDA about the selection of administration time (administration rate) in the course of study planning have provided important safety information in cases of deviation from the recommended dosage regimen. The information will be disseminated through the materials for healthcare professionals (the proper use guide).

Attached documents

1. Package insert (draft)
2. Materials for healthcare professionals (proper use guide) (draft)
3. Implementation plan of the proper use promotion program (draft)
4. Document to be published by the related academic societies (draft)

(Attached sheets) Safety data in co-administration with intravenous sedatives other than propofol

Type of study	Patients studied	Dosage regimen of Precedex and rescue administration	Number of subjects	Summary of safety results
Retrospective study report (*Int J Pediatr.* 2015;2015:397372)	Pediatric patients (53.6-55.7 months of age) undergoing MRI	Dosage regimen of Precedex • Initial loading dose of 2 μg/kg over 10 minutes, followed by maintenance dose of 1 μg/kg/h • If the initial loading dose does not achieve sedation, an additional loading dose of 2 μg/kg over 10 minutes Rescue administration • Midazolam (0.05-0.1 mg/kg, 2 mg at the maximum) or fentanyl (0.5-1 μg/kg, 50 μg at the maximum)	A total of 544 subjects (including 117 with concomitant midazolam or fentanyl)	• Among 382 subjects receiving a single initial loading dose of Precedex, 162 subjects receiving 2 initial loading doses of Precedex, and 117 subjects receiving concomitant midazolam or fentanyl, statistically significant differences were observed in oxygen administration (high in the co-administration group), maximum diastolic blood pressure (high in the co-administration group), maximum respiratory rate (high in the co-administration group), and initial SpO_2 (low in the co-administration group), but the differences were not clinically significant. • The incidence of hypotension did not differ statistically significantly among 3 groups. No intervention-requiring hypotension was observed in any group. • The incidence of bradycardia was 25.4% in the group receiving a single initial loading dose of Precedex, 19.1% in the group receiving 2 initial loading doses of Precedex, and 31.6% in the group receiving concomitant midazolam or fentanyl. No treatment-requiring bradycardia was observed in any of the groups.
Retrospective study report (*Paediatr Anaesth.* 2011;21:153-8)	Pediatric patients (1-20 years of age) undergoing MRI	Dosage regimen of Precedex • Initial loading dose of 2 μg/kg over 10 minutes, followed by maintenance dose of 1 μg/kg/h • If the initial loading dose does not achieve sedation, an additional loading dose of 2 μg/kg over 10 minutes Rescue administration • Midazolam or fentanyl, etc.	A total of 77 subjects (including 22 with concomitant midazolam, fentanyl, etc.)	• No statistically significant differences were observed in the lowest values of systolic blood pressure, diastolic blood pressure, or heart rate among 36 subjects receiving a single initial loading dose (without concomitant of midazolam or fentanyl), 18 subjects receiving 2 initial loading doses (without concomitant midazolam or fentanyl), 12 subjects receiving a single initial loading dose (with concomitant midazolam, fentanyl, etc.), and 10 subjects receiving 2 initial loading doses (with concomitant midazolam, fentanyl, etc.). • Neither apnoea nor respiratory depression was observed in any of the subjects.

Type of study	Patients studied	Dosage regimen of Precedex and rescue administration	Number of subjects	Summary of safety results
Retrospective study report (*Paediatr Anaesth.* 2008;18:403-11)	Pediatric patients (0.1-19.9 years of age) undergoing MRI	Dosage regimen of Precedex • Dosage 1: Initial loading dose of 2 µg/kg over 10 minutes, followed by maintenance dose of 1 µg/kg/h • Dosage 2: Initial loading dose of 3 µg/kg over 10 minutes, followed by maintenance dose of 1.5 µg/kg/h • Dosage 3: Initial loading dose of 3 µg/kg over 10 minutes, followed by maintenance dose of 2.0 µg/kg/h • If the initial loading dose does not achieve sedation, the same additional loading dose given over 10 minutes Rescue administration • Pentobarbital (2 mg/kg)	A total of 747 subjects (including 55 with concomitant pentobarbital)	• The incidence of bradycardia was 13% (7 of 55 subjects) in the group with concomitant pentobarbital and 16% (113 of 692 subjects) in the group without concomitant pentobarbital, showing that concomitant pentobarbital did not increase the risk of bradycardia.

<table>
<tr><th>Type of study</th><th>Patients studied</th><th>Dosage regimen of Precedex and rescue administration</th><th>Number of subjects</th><th>Summary of safety results</th></tr>
<tr>
<td>Foreign phase IV study
(Study DEX-10-16)</td>
<td>Pediatric patients (≥28 weeks of corrected gestational age to <17 years postpartum) undergoing procedures or examinations requiring sedation</td>
<td>Dosage regimen of Precedex
• ≥28 weeks of corrected gestational age to <1 month postpartum: Initial loading dose of 0.1 μg/kg over 10 minutes, followed by maintenance dose started at 0.1 μg/kg/h and adjusted within the range between 0.05 and 0.2 μg/kg/h as appropriate
• ≥1 month to <17 years of age: Initial loading dose of 1 μg/kg over 10 minutes, followed by maintenance dose started at 0.6 μg/kg/h and adjusted within the range between 0.2 and 2.0 μg/kg/h as appropriate

Rescue administration
• Midazolam as rescue sedative
• Fentanyl as rescue sedative</td>
<td>A total of 46 subjects receiving non-invasive procedures or examinations, including 31 subjects with concomitant midazolam and 7 subjects with concomitant fentanyl</td>
<td>• Incidences of main adverse events by use/non-use of midazolam or fentanyl
<table>
<tr><th rowspan="2">Concomitant drug</th><th colspan="2">Midazolam</th><th colspan="2">Fentanyl</th></tr>
<tr><th>Used</th><th>Not used</th><th>Used</th><th>Not used</th></tr>
<tr><td>Number of subjects evaluated</td><td>31</td><td>15</td><td>7</td><td>39</td></tr>
<tr><td>Adverse events</td><td>19 (61.3)</td><td>13 (86.7)</td><td>5 (71.4)</td><td>27 (69.2)</td></tr>
<tr><td>Serious adverse events</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Severe adverse events</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Adverse events leading to treatment discontinuation</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Adverse events requiring intervention</td><td>0</td><td>2 (13.3)</td><td>0</td><td>2 (5.1)</td></tr>
<tr><td colspan="5">Major adverse events</td></tr>
<tr><td>Respiratory depression</td><td>16 (51.6)</td><td>10 (66.7)</td><td>4 (57.1)</td><td>22 (56.4)</td></tr>
<tr><td>Hypotension</td><td>11 (35.5)</td><td>3 (20.0)</td><td>2 (28.6)</td><td>12 (30.8)</td></tr>
<tr><td>Hypertension</td><td>2 (6.5)</td><td>0</td><td>0</td><td>2 (5.1)</td></tr>
<tr><td>Bradycardia</td><td>1 (3.2)</td><td>2 (13.3)</td><td>0</td><td>3 (7.7)</td></tr>
<tr><td>Blood pressure systolic decreased</td><td>1 (3.2)</td><td>2 (13.3)</td><td>0</td><td>3 (7.7)</td></tr>
<tr><td>Hypoxia</td><td>1 (3.2)</td><td>0</td><td>0</td><td>1 (2.6)</td></tr>
</table>
Number of subjects with events (incidence [%])</td>
</tr>
</table>

<table>
<tr><th>Type of study</th><th>Patients studied</th><th>Dosage regimen of Precedex and rescue administration</th><th>Number of subjects</th><th>Summary of safety results</th></tr>
<tr>
<td>Japanese phase III study
(sedation in ICU)</td>
<td>Japanese pediatric patients (≥45 weeks of corrected gestational age to <17 years postpartum) in an intensive care setting</td>
<td>Dosage regimen of Precedex
• ≥45 weeks of corrected gestational age to <6 years postpartum: Started at 0.2 μg/kg/h and adjusted within the range between 0.2 and 1.4 μg/kg/h as appropriate
• ≥6 to <17 years of age: Started at 0.2 μg/kg/h and adjusted within the range between 0.2 and 1.0 μg/kg/h as appropriate

Rescue administration
• Midazolam as rescue sedative
• Fentanyl as rescue sedative</td>
<td>A total of 63 subjects in the safety analysis population, including 22 subjects with concomitant midazolam or fentanyl</td>
<td>• Incidences of adverse events in the respiratory and cardiovascular systems by use/non-use of midazolam or fentanyl
<table>
<tr><th rowspan="2">Concomitant drug</th><th colspan="2">Midazolam or fentanyl</th></tr>
<tr><th>Used</th><th>Not used</th></tr>
<tr><td>Number of subjects evaluated</td><td>22</td><td>41</td></tr>
<tr><td>Hypotension</td><td>9 (40.9)</td><td>22 (53.7)</td></tr>
<tr><td>Bradycardia</td><td>6 (27.3)</td><td>12 (29.3)</td></tr>
<tr><td>Respiratory depression</td><td>6 (27.3)</td><td>11 (26.8)</td></tr>
<tr><td>Respiratory tract oedema</td><td>2 (9.1)</td><td>0</td></tr>
<tr><td>Hypoxia</td><td>1 (4.5)</td><td>0</td></tr>
<tr><td>Laryngeal oedema</td><td>1 (4.5)</td><td>0</td></tr>
<tr><td>Atelectasis</td><td>0</td><td>1 (2.4)</td></tr>
<tr><td>Pleural effusion</td><td>0</td><td>1 (2.4)</td></tr>
<tr><td>Respiratory disorder</td><td>0</td><td>1 (2.4)</td></tr>
<tr><td>Cardiac tamponade</td><td>0</td><td>1 (2.4)</td></tr>
<tr><td>Hypertension</td><td>0</td><td>1 (2.4)</td></tr>
</table>
Number of subjects with events (incidence [%])</td>
</tr>
<tr>
<td>Specified use-results survey
(ICU sedation)</td>
<td>Japanese pediatric patients in an intensive care setting</td>
<td>Dosage regimen of Precedex, Rescue administration
• Not specified in advance (actual dosage regimen in clinical settings)</td>
<td>A total of 100 subjects in the safety analysis population including 62 subjects with concomitant midazolam</td>
<td>• The incidence of adverse drug reactions was 10.5% (4 of 38 subjects) in the group without concomitant midazolam and 8.1% (5 of 62 subjects) in the group with concomitant midazolam.
• No serious bradypnoea (respiratory depression), hypoxia, hypertension, or hypotension was observed.</td>
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Review Report

October 17, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Precedex Intravenous Solution 200 μg "Pfizer," Precedex Intravenous Solution 200 μg/50 mL Syringe "Pfizer"
Non-proprietary Name	Dexmedetomidine Hydrochloride
Applicant	Pfizer Japan Inc.
Date of Application	March 30, 2022
Dosage Form/Strength	Injection in vials or in syringes: Each vial (2 mL) or syringe (50 mL) contains 236 μg of dexmedetomidine hydrochloride (200 μg of dexmedetomidine).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Specific use drug (Designation No. 1 of 2022 [*R4 tokuteiyaku*], PSEHB/PED Notification 0323-5, dated March 23, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in sedation of non-intubated children undergoing non-invasive procedures or examinations, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition.

Indications

Sedation during and after mechanical ventilation in an intensive care setting

Sedation of non-intubated adult patients during surgical and other procedures under local anesthesia

Sedation of non-intubated pediatric patients during non-invasive procedures or examinations

(Underlines denote addition.)

Dosage and Administration

1. Sedation during and after mechanical ventilation in an intensive care setting

Adults: Usually, dexmedetomidine is infused intravenously at 6 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 0.2 to 0.7 μg/kg/h as maintenance dose to achieve the optimal sedation level depending on the patient's condition (maintenance administration). The administration may be started with the maintenance dose.

Children aged ≥6 years: Usually, dexmedetomidine is infused intravenously at 0.2 μg/kg/h continuously, followed by a continuous infusion at 0.2 to 1.0 μg/kg/h to achieve the optimal sedation level depending on the patient's condition.

Children with corrected gestational age (gestational age + postnatal age) of ≥45 weeks to <6 years postpartum: Usually, dexmedetomidine is infused intravenously at 0.2 μg/kg/h continuously, followed by a continuous infusion at 0.2 to 1.4 μg/kg/h to achieve the optimal sedation level depending on the patient's condition.

The infusion rate should be decreased depending on the patient's condition.

2. Sedation of non-intubated adult patients during surgical and other procedures under local anesthesia

Adults: Usually, dexmedetomidine is infused intravenously at 6 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 0.2 to 0.7 μg/kg/h as maintenance dose to achieve the optimal sedation level (maintenance administration). The infusion rate should be decreased depending on the patient's condition.

3. Sedation of non-intubated pediatric patients during non-invasive procedures or examinations

Children aged ≥2 years: Usually, dexmedetomidine is infused intravenously at 12 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 1.5 μg/kg/h as maintenance dose (maintenance administration).

Children aged ≥1 month to <2 years: Usually, dexmedetomidine is infused intravenously at 9 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 1.5 μg/kg/h as maintenance dose (maintenance administration).

The infusion rate should be decreased depending on the patient's condition.

(Underlines denote addition.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

August 16, 2022

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Precedex Intravenous Solution 200 μg "Pfizer," Precedex Intravenous Solution 200 μg/50 mL Syringe "Pfizer"
Non-proprietary Name	Dexmedetomidine Hydrochloride
Applicant	Pfizer Japan Inc.
Date of Application	March 30, 2022
Dosage Form/Strength	Injection in vials or in syringes: Each vial (2 mL) or syringe (50 mL) contains 236 μg of dexmedetomidine hydrochloride (200 μg of dexmedetomidine).
Proposed Indications	Sedation during and after mechanical ventilation in an intensive care setting Sedation of non-intubated <u>adult</u> patients during surgical and other procedures under local anesthesia <u>Sedation of non-intubated pediatric patients during non-invasive procedures or examinations</u> (Underline denotes addition.)

Proposed Dosage and Administration

1. Sedation during and after mechanical ventilation in an intensive care setting

   Adults: Usually, dexmedetomidine is infused intravenously at 6 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 0.2 to 0.7 μg/kg/h as maintenance dose to achieve the optimal sedation level depending on the patient's condition (maintenance administration). The administration may be started with the maintenance dose.

   Children aged ≥6 years: Usually, dexmedetomidine is infused intravenously at 0.2 μg/kg/h continuously, followed by a continuous infusion at 0.2 to 1.0 μg/kg/h to achieve the optimal sedation level depending on the patient's condition.

   Children with corrected gestational age (gestational age + postnatal age) of ≥45 weeks to <6 years postpartum: Usually,

dexmedetomidine is infused intravenously at 0.2 μg/kg/h continuously, followed by a continuous infusion at 0.2 to 1.4 μg/kg/h to achieve the optimal sedation level depending on the patient's condition.
The infusion rate should be decreased depending on the patient's condition.

2. Sedation of non-intubated adult patients during surgical and other procedures under local anesthesia
Adults: Usually, dexmedetomidine is infused intravenously at 6 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 0.2 to 0.7 μg/kg/h as maintenance dose to achieve the optimal sedation level (maintenance administration). The infusion rate should be decreased depending on the patient's condition.

3. Sedation of non-intubated pediatric patients during non-invasive procedures or examinations
Children aged ≥2 years: Usually, dexmedetomidine is infused intravenously at 12 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 1.5 μg/kg/h as maintenance dose (maintenance administration).
Children aged ≥1 month to <2 years: Usually, dexmedetomidine is infused intravenously at 9 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 1.5 μg/kg/h as maintenance dose (maintenance administration).
The infusion rate should be decreased depending on the patient's condition.

(Underlines denote addition.)

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Children undergoing procedures or examinations, unlike adults, have difficulty with self-restraint and thus it is hard for them to keep themselves still, needing to be put under sedation to do so. In Japan, major sedatives used for children include triclofos sodium, chloral hydrate, barbiturates, and midazolam. Among them, only triclofos sodium and chloral hydrate are indicated for sedation of children undergoing examinations.

Dexmedetomidine hydrochloride (hereinafter referred to as dexmedetomidine), a selective α2 adrenergic agonist, is considered to exhibit its sedative effect by acting mainly on α2 adrenergic receptors in the locus ceruleus. In Japan, dexmedetomidine was approved in January 2004 for the indication of "sedation during mechanical ventilation and after extubation in patients who are placed under intensive care management and are eligible for early extubation," in August 2010 for the indication of "sedation during and after mechanical ventilation in an intensive care setting" after the deletion of the restriction on its use for >24 hours, in June 2013 for the indication of "sedation of non-intubated patients during surgical and other procedures under local anesthesia," and in November 2018 for the pediatric dose for "sedation during and after mechanical ventilation in an intensive care setting."

Reports from foreign countries have demonstrated the benefits of dexmedetomidine as sedative for children undergoing examinations, especially magnetic resonance imaging (MRI) scan,[1)] suggesting that dexmedetomidine is a potential new option of sedatives in Japan for children undergoing examinations. Accordingly, a clinical study began in February 2020 involving pediatric patients undergoing MRI. Recently, the applicant has submitted a partial change application, concluding that the efficacy and safety of dexmedetomidine had been demonstrated in sedation of non-intubated children during non-invasive procedures or examinations .

As of [redacted] 20[redacted], dexmedetomidine has not been approved in any country or region outside Japan for the proposed indication. In the US, an application was submitted in [redacted] 20[redacted] and is currently under review.

Dexmedetomidine was designated as a specific use drug with the intended indication of "sedation of non-intubated children undergoing non-invasive procedures or examinations" (Designation No. 1 of 2022 [*R4 tokuteiyaku*]), dated March 23, 2022.

2. Quality and Outline of the Review Conducted by PMDA

The present application relates to a new indication and a new dosage, and no data relating to quality have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application relates to a new indication and a new dosage, the data relating to non-clinical pharmacology had been evaluated during the review process for the initial approval of dexmedetomidine, and thus, no new data have been submitted.

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1) *Paediatr Anaesth.* 2008;18:403-11, *Anesth Analg.* 2006;103:63-7, *Hosp Pediatr.* 2016;6:536-44, *Paediatr Anaesth.* 2017;27:52-9

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application relates to a new indication and a new dosage, the data relating to non-clinical pharmacokinetics had been evaluated during the review process for the initial approval of dexmedetomidine, and thus, no new data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application relates to a new indication and a new dosage. The data relating to toxicity had been evaluated during the review process for the initial approval of dexmedetomidine, and thus, no new data have been submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

No data relating to biopharmaceutic studies have been submitted.

6.2 Clinical pharmacology

Although the present application relates to a new indication and a new dosage, no new data on clinical pharmacology have been submitted [see Section 6.R].

6.R Pharmacokinetics in children undergoing procedures or examinations

The applicant's explanation about the pharmacokinetics of dexmedetomidine in children undergoing procedures or examinations:

In the global phase III/IV study (CTD 5.3.5.1, Study C0801039) targeting pediatric patients undergoing MRI, blood sampling might have some impact on the assessment of the sedative effect of dexmedetomidine, and blood sampling during MRI is practically infeasible. Therefore, obtaining pharmacokinetic data from children undergoing procedures or examinations was considered difficult in the study.

Pharmacokinetic parameter values of individual Japanese pediatric patients were estimated using a population pharmacokinetic (PPK) model constructed from the plasma drug concentration data obtained from foreign clinical studies (CHOP Study,[2)] Studies DEX-08-01,[3)] DEX-11-01,[4)] DEX-09-08[5)]), (Summary of the product application for "Precedex Intravenous Solution 200 μg 'Pfizer,' etc." [addition of pediatric dose to (Sedation during and after mechanical ventilation in an intensive care setting)]). These pharmacokinetic parameters and data on characteristics of these Japanese pediatric patients were used to simulate changes in plasma dexmedetomidine concentration in Japanese pediatric patients receiving dexmedetomidine according to the dosage regimen in the high-dose group of Study C0801039

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2) Foreign phase I study in intubated pediatric patients aged ≥1 to ≤24 months receiving mechanical ventilation after a cardiac surgery. Dexmedetomidine was administered at the initial loading dose of 0.35, 0.7, or 1 μg/kg, followed by the maintenance dose of 0.25, 0.5 or 0.75 μg/kg/h.

3) Foreign phase II study in intubated pediatric patients aged ≥2 to <17 years receiving mechanical ventilation in an intensive care setting. Dexmedetomidine was administered at the initial loading dose of 0.25, 0.5, 1.00, or 1.00 μg/kg, followed by the maintenance dose of 0.2, 0.4, 0.7, or 2.0 μg/kg/h.

4) Foreign phase II study in intubated pediatric patients aged ≥12 to <24 months receiving mechanical ventilation in an intensive care setting. Dexmedetomidine was administered at the initial loading dose of 0.7 or 1 μg/kg, followed by the maintenance dose of 0.5 or 0.75 μg/kg/h.

5) Foreign phase II/III study in intubated neonates ≥28 to ≤44 weeks of corrected gestational age receiving mechanical ventilation in an intensive care setting. Dexmedetomidine was administered at the initial loading dose of 0.05, 0.1, or 0.2 μg/kg, followed by the maintenance dose of 0.05, 0.1, or 0.2 μg/kg/h.

(initial loading dose, 1.5 μg/kg over 10 minutes in patients aged ≥1 month to <2 years and 2.0 μg/kg over 10 minutes in patients aged ≥2 to <17 years; maintenance dose, 1.5 μg/kg/h).[6)] The estimated C_{max} (geometric mean [coefficient of variance (%)]) was 1.02 ng/mL (15.6%) and 1.71 ng/mL (23.8%), respectively, in Japanese pediatric patients aged ≥1 month to <2 years and those aged ≥2 to <17 years. These estimated C_{max} values were not significantly different from the C_{max} (approximately 2 ng/mL) reported in a study (*Eur J Drug Metab Pharmacokinet.* 2017;42:201-11) in which blood pressure and the heart rate remained relatively stable in Chinese pediatric patients aged 1 to 9 years receiving intravenous dexmedetomidine 1 to 2 μg/kg over 10 minutes during surgical procedures. These findings indicate that dexmedetomidine to Japanese children with the same dosage regimen as in the high-dose group in Study C0801039 is unlikely to pose a significant safety problem.

Meanwhile, the Japanese Study C0801017[7)] and the foreign clinical studies (CHOP Study, Studies DEX-08-01, DEX-11-01, and DEX-09-08) in pediatric patients requiring sedation in an intensive care setting (Review Report of Precedex Intravenous Solution 200 μg "Pfizer," etc., dated October 19, 2018) revealed no significant difference in the pharmacokinetics of dexmedetomidine between Japanese and non-Japanese pediatric patients. Thus, the difference in the pharmacokinetics of dexmedetomidine between Japanese and non-Japanese children undergoing procedures or examinations is also considered insignificant.

PMDA's view:
The applicant had difficulty obtaining pharmacokinetic data from children undergoing procedures or examinations in the clinical studies of dexmedetomidine, which is understandable. There is no particular problem in the approach for estimating the pharmacokinetics of dexmedetomidine in children receiving dexmedetomidine as per the proposed dosage regimen, based on the PPK model constructed from the pharmacokinetic data of the clinical study in pediatric patients (≥28 weeks of corrected gestational age to <17 years postpartum) requiring sedation in an intensive care setting. However, the data used for the model construction do not include pharmacokinetic data of dexmedetomidine administered as per a regimen equivalent to the initial loading dose in the proposed regimen, limiting the estimation of pharmacokinetics and discussion on safety based on the model. The appropriateness of the proposed dosage regimen is reviewed further in Section 7.R.5, taking account of the safety data in Study C0801039.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety data from clinical studies as shown in Table 1. The dose is expressed as doses of dexmedetomidine.

6) Because the duration of sedation required for MRI is within 1 hour in most cases, pharmacokinetic parameter values were estimated based on the maintenance dose duration of 1 hour.

7) Japanese phase III study in intubated pediatric patients ≥45 weeks of corrected gestational age to <17 years of age receiving mechanical ventilation in an intensive care setting. Dexmedetomidine was administered at the loading dose of 0.2 μg/kg, followed by the maintenance dose of 0.2 to 1.4 μg/kg/h in patients ≥45 weeks of corrected gestational age to <6 years postpartum and 0.2 to 1.0 μg/kg/h in patients aged ≥6 to <17 years.

Table 1. List of clinical studies on efficacy and safety

Data category	Region	Study code CTD	Phase	Subjects	Number of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Global	C0801039 5.3.5.1	III/IV	Pediatric patients undergoing MRI (≥1 month to <17 years of age)	128	[≥1 month to <2 years of age] Continuous intravenous administration of dexmedetomidine 0.5, 1.0, or 1.5 μg/kg over 10 minutes (initial loading administration), followed by continuous intravenous administration at 0.5, 1.0, or 1.5 μg/kg/h (maintenance administration) [≥2 to <17 years of age] Continuous intravenous administration of dexmedetomidine 0.5, 1.2, or 2.0 μg/kg over 10 minutes (initial loading administration), followed by continuous intravenous administration at 0.5, 1.0, or 1.5 μg/kg/h (maintenance administration)	Efficacy Safety
Reference	Foreign	DEX-10-16 5.3.5.2	IV	Pediatric patients undergoing procedures or examinations requiring sedation (≥28 weeks of corrected gestational age to <17 years postpartum)	91	[≥28 weeks of corrected gestational age to <1 month postpartum] Continuous intravenous administration of dexmedetomidine 0.1 μg/kg over 10 minutes (initial loading administration), followed by continuous intravenous administration started at 0.1 μg/kg/h (maintenance administration), and adjusted within the range between 0.05 and 0.2 μg/kg/h, as appropriate [≥1 month to <17 years of age] Continuous intravenous administration of dexmedetomidine 1.0 μg/kg over 10 minutes (initial loading administration), followed by continuous intravenous administration started at 0.6 μg/kg/h (maintenance administration), and adjusted within the range between 0.2 and 2.0 μg/kg/h, as appropriate	Safety

7.1 Global phase III/IV study (CTD 5.3.5.1, Study C0801039 [February 2020 to November 2021])

A randomized, double-blind, dose-range finding study was conducted in Japan and the US to investigate the efficacy and safety of dexmedetomidine in pediatric patients aged ≥1 month to <17 years undergoing MRI[8)] (target sample size 120,[9)] 20 per dose group in each age group).

Subjects in each age group (low-age group [≥1 month to <2 years] and high-age group [≥2 to <17 years]) were randomized to the high-dose group, the medium-dose group, or the low-dose group at a ratio of 1:1:1,

8) The following patients were enrolled in the study: Patients with American Society of Anesthesiologists (ASA) grade of I to III who required moderate to deep sedation under non-intubated, spontaneous respiration for MRI in the presence of an intensive care specialist, an anesthesiologist, or another physician. Patients scheduled for clinical procedures during MRI or during the recovery period after MRI were excluded from the study.

9) By assuming the percentage of subjects not requiring propofol to complete MRI, the primary endpoint, to be 15% in the low-dose group and 60% in the high-dose group, and the number of subjects in each dose group to be 40, the statistical power of 99% is obtained at the significance level (α) of 0.05 in the two-sided test of the comparison between the high-dose group and the low-dose group.

and dexmedetomidine was infused intravenously over 10 minutes continuously from immediately before MRI, at the initial loading dose shown in Table 2 for each age group and dose group under double-blind condition, followed by the maintenance dose shown in Table 2 until the end of MRI. When the investigator judged that adequate sedation was not reached within 5 minutes after the start of dexmedetomidine at the maintenance dose (when the subject moved, etc.), open-label propofol was co-administered[10] to complete MRI. The target sedation level was Pediatric Sedation State Scale (PSSS)[11] score 2.

Table 2. Dosage regimen (Study C0801039)

	High-dose		Medium-dose		Low-dose	
	Initial loading dose	Maintenance dose	Initial loading dose	Maintenance dose	Initial loading dose	Maintenance dose
Low age (≥1 month to <2 years)	1.5 μg/kg	1.5 μg/kg/h	1 μg/kg	1 μg/kg/h	0.5 μg/kg	0.5 μg/kg/h
High age (≥2 to <17 years)	2 μg/kg	1.5 μg/kg/h	1.2 μg/kg	1 μg/kg/h	0.5 μg/kg	0.5 μg/kg/h

Of 128 randomized subjects (41 in the high-dose group, 43 in the medium-dose group, 44 in the low-dose group), 122 subjects (38, 42, 42) excluding 6 subjects received dexmedetomidine and were included in the safety analysis population and the full analysis set (FAS). FAS was regarded as the primary analysis population. A total of 5 subjects (3, 1, 1) discontinued dexmedetomidine. The reasons for discontinuation were adverse events in 3 subjects, protocol deviation in 1 subject, and administration error in 1 subject.

Table 3 shows the total dose of dexmedetomidine and the total duration of administration.

10) Propofol 0.5 mg/kg was administered intravenously by bolus over approximately 1 minute, followed by continuous intravenous infusion at 50 μg/kg/min (maintenance administration). If the subject moved or remained awake after the maintenance dose, an additional dose of propofol 0.5 mg/kg was administered intravenously by bolus while the rate of the maintenance administration was increased by 25 or 50 μg/kg/min. It was also allowed to increase maintenance administration rate by 25 or 50 μg/kg/min instead of additional bolus intravenous dose. In order to maintain the appropriate level of sedation, the maintenance administration was slowed by 25 or 50 μg/kg/min or discontinued as appropriate.

11) PSSS is a scale for evaluating the efficiency and quality of sedation in children undergoing procedure (*Pediatrics.* 2017;139: e20162897), and rated according to the following 6 grades by the investigator, etc. PSSS assessment was conducted immediately before the start of the initial loading dose, immediately after the end of the initial loading dose, and every 5 minutes during the maintenance administration and during MRI.

Score	Behavior
5	Patient is moving (purposefully or non-purposefully) in a manner that impedes the proceduralist and requires forceful immobilization. This includes crying or shouting during the procedure, but vocalization is not included. Score is based on movement.
4	Moving during the procedure (awake or sedated) that requires gentle immobilization for positioning. May verbalize some discomfort or stress, but there is no crying or shouting that expresses stress or objection.
3	Expression of pain or anxiety on face (may verbalize discomfort), but not moving or impeding completion of the procedure. May require help positioning (as with a lumbar puncture) but does not require restraint to stop movement during the procedure.
2	Quiet (asleep or awake), not moving during procedure, and no frown (or brow furrow) indicating pain or anxiety. No verbalization of any complaint.
1	Deeply asleep with normal vital signs, but requiring airway intervention and/or assistance (e.g., central or obstructive apnea, etc.).
0	Sedation associated with abnormal physiologic parameters that require acute intervention (i.e., oxygen saturation <90%, blood pressure is 30% lower than baseline, bradycardia receiving therapy).

Table 3. Total dose of dexmedetomidine and total duration of administration (Study C0801039, safety analysis population)

		High-dose	Medium-dose	Low-dose	All groups combined
Low age (≥1 month to <2 years)	Number of subjects evaluated	18	21	20	59
	Total dose (μg [range])	26.36 ± 7.939 [18.6, 45.1]	18.88 ± 5.433 [9.3, 27.3]	8.12 ± 1.770 [4.5, 10.8]	17.51 ± 9.223 [4.5, 45.1]
	Total duration of administration (min [range])	59.89 ± 25.914 [12.0, 114.0]	71.48 ± 16.540 [51.0, 102.0]	60.15 ± 20.304 [26.0, 113.0]	64.10 ± 21.372 [12.0, 114.0]
High age (≥2 to <17 years)	Number of subjects evaluated	20	21	22	63
	Total dose (μg [range])	86.55 ± 45.580 [35.4, 219.2]	57.66 ± 32.128 [18.9, 122.7]	24.48 ± 16.164 [5.0, 78.8]	55.24 ± 41.378 [5.0, 219.2]
	Total duration of administration (min [range])	64.40 ± 27.942 [29.0, 130.0]	63.38 ± 26.630 [3.0, 123.0]	64.41 ± 21.025 [44.0, 122.0]	64.06 ± 24.860 [3.0, 130.0]

Mean ± standard deviation (SD)

Table 4 shows the percentages of subjects not requiring co-administration of propofol to complete MRI, the primary endpoint, which was statistically significantly high in the high-dose group as compared with the low-dose group ($P < 0.001$, Mantel-Haenszel test).

Table 4. Percentages of subjects not requiring co-administration of propofol to complete MRI (Study C0801039, FAS)

	High-dose	Medium-dose	Low-dose
Number of subjects evaluated	38	42	42
Number of subjects not requiring propofol co-administration	24	15	6
Percentage of subjects not requiring propofol co-administration [95% CI[a)]]	63.2 [46.0, 78.2]	35.7 [21.6, 52.0]	14.3 [5.4, 28.5]
Odds ratio[b)] [95% CI]	0.10 [0.03, 0.29]	- [c)]	
P value[b)]	<0.001	- [c)]	

Subjects who did not complete MRI were counted as non-responders.
a) Exact two-sided 95% confidence interval (CI)
b) Comparison between high-dose group and low-dose group, two-sided significance level of 5%, Mantel-Haenszel test
c) In the primary analysis of the primary endpoint, between-group comparison with the medium dose group was not conducted.

Adverse events[12] were observed in 94.7% (36 of 38) of subjects in the high-dose group, 92.9% (39 of 42) of subjects in the medium-dose group, and 90.5% (38 of 42) of subjects in the low-dose group, none resulting in death. Adverse events leading to dexmedetomidine discontinuation were observed in 1 subject (hypertension) in the high-dose group, 1 subject (bradycardia) in the medium-dose group, and 1 subject (bradypnoea) in the low-dose group. All events were considered related to the study drug. Serious adverse events other than death were observed in 1 subject (hypertension) in the high-dose group and 1 subject (seizure) in the low-dose group,[13] and the event in the subject of the high-dose group was considered related to the study drug.

Adverse events considered related to the study drug were observed in 76.3% (29 of 38) of subjects in the high-dose group, 88.1% (37 of 42) of subjects in the medium-dose group, and 76.2% (32 of 42) of subjects in the low-dose group. Adverse events observed in ≥2 subjects in any dose group were bradycardia (25 in the high-dose group, 24 in the medium-dose group, 21 in the low-dose group), bradypnoea (17, 21, 15), hypotension (5, 8, 11), hypertension (6, 8, 2), hypoxia (1, 1, 3), diastolic hypertension (3, 1, 0), and systolic hypertension (2, 3, 0).

[12] Adverse events were reported during the period from the informed consent to 28 days after the end of dexmedetomidine administration. In Study C0801039, adverse events that occurred from the start of dexmedetomidine to 26 hours after the end of dexmedetomidine administration were analyzed. In this report, adverse events used for this analysis are described, unless stated otherwise. Bradycardia, hypotension, hypertension, bradypnoea, hypoxia, and apnoea were reported as adverse events if they fulfilled any of the following criteria:

Bradycardia: The heart rate meets the following criteria or decreased by ≥30% from baseline (value immediately before dexmedetomidine administration)

Age	Heart rate (beats/min)
≥1 to <3 months	<107
≥3 to <6 months	<104
≥6 to <9 months	<98
≥9 to <12 months	<93
≥12 to <18 months	<88
≥18 to <24 months	<82
≥2 to <3 years	<76
≥3 to <4 years	<70
≥4 to <6 years	<65
≥6 to <8 years	<59
≥8 to <12 years	<52
≥12 to <15 years	<47
≥15 to <17 years	<43

Hypotension: Systolic blood pressure decreased by ≥30% from baseline

Hypertension: Subjects aged ≥1 month to <1 year: Systolic blood pressure was ≥104 mmHg or diastolic blood pressure was ≥56 mmHg, when measured in the supine position twice or more sequentially at intervals of 5 minutes, or intervention is required.
Subjects aged ≥1 to <17 years: Systolic or diastolic blood pressure measured in the supine position twice or more sequentially at intervals of 5 minutes was ≥95 percentile of the value with gender, age, and height taken into account, or intervention is required.

Bradypnoea: The respiratory rate measured twice or more sequentially at an interval of ≥1 minute meets the following criteria, or intervention is required.

Age	Respiratory rate (breaths/min)
≥1 to <3 months	<25
≥3 to <6 months	<24
≥6 to <9 months	<23
≥9 to <12 months	<22
≥12 to <18 months	<21
≥18 to <24 months	<19
≥2 to <3 years	<18
≥3 to <4 years	<17
≥4 to <6 years	<17
≥6 to <8 years	<16
≥8 to <12 years	<14
≥12 to <15 years	<12
≥15 to <17 years	<11

Hypoxia: SpO_2 is <90% regardless of the duration

Apnoea: $EtCO_2$ is 0 for ≥30 seconds by capnography

[13] Serious adverse events (acute respiratory failure/sepsis) were reported in 1 subject in the low-dose group 29 days after the end of dexmedetomidine administration (considered unrelated to the study drug).

7.2 Foreign phase IV study (Reference CTD 5.3.5.2, Study DEX-10-16 [October 2012 to January 2014])

An open-label, uncontrolled study was conducted in the US to investigate the safety of dexmedetomidine in pediatric patients[14] ≥28 weeks of corrected gestational age to <17 years postpartum (target sample size, 90 subjects[15]) undergoing procedures or examinations requiring sedation.

In subjects ≥28 weeks of corrected gestational age to <1 month postpartum, dexmedetomidine was infused intravenously at the initial loading dose of 0.1 μg/kg continuously over 10 minutes, followed by a maintenance dose of 0.1 μg/kg/h. Then, the dose was adjusted to between 0.05 and 0.2 μg/kg/h.[16] In subjects aged ≥1 to <17 years, dexmedetomidine was infused intravenously at the initial loading dose of 1.0 μg/kg continuously over 10 minutes, followed by a maintenance dose of 0.6 μg/kg/h, after which the dose was adjusted to between 0.2 and 2.0 μg/kg/h.[16] Co-administration of rescue drugs (midazolam,[17] fentanyl[18]) was allowed when needed.

Of the total of 91 subjects enrolled in the study (1 subject ≥28 weeks of corrected gestational age to <1 month postpartum, 90 subjects aged ≥1 month to <17 years), 90 subjects (1, 89), excluding 1 subject, received dexmedetomidine and were included in the safety analysis population. A total of 6 subjects (0, 6) discontinued the study. The main reasons were discretion of the investigator in 2 subjects, adverse event in 1 subject, and lost to follow-up in 1 subject.

Table 5 shows the total dose of dexmedetomidine and the total duration of administration.

Table 5. Total dose of dexmedetomidine and total duration of administration (Study DEX-10-16, safety analysis population)

	Number of subjects evaluated	Total dose (μg [range])	Total duration of administration (min [range])
≥28 weeks of corrected gestational age to <1 month postpartum	1	1.200[a]	76.0[a]
≥1 month to <17 years	89	85.369 ± 74.364 [10.37, 480.00]	65.1 ± 33.3 [4, 228]

Mean ± SD, a) Individual value

[14] The study targeted non-intubated, spontaneously breathing patients with ASA grade I to III who required medium to deep sedation for procedures or examinations lasting ≥30 minutes in the presence of an intensive care specialist, an anesthesiologist, or a dental anesthesiologist.

[15] A total target sample size of 90 was determined to allow the enrollment of ≥25 subjects in each of 3 age groups ([a] ≥28 weeks of corrected gestational age to <3 years postpartum, [b] ≥3 to <12 years, and [c] ≥12 to <17 years) and ≥25 subjects in each of the following 3 procedure/examination groups:
(a) Non-invasive procedure/examination group: Ultrasonography, computed tomography (CT), MRI, cardiac catheterization, transthoracic echocardiogram (TTE), etc.
(b) Low-invasive procedure/examination group: Low-invasive procedure/examination conducted under ultrasonography or CT guide (biopsy of parenchymal organ under the guidance of ultrasonography or CT, etc.), myocardial biopsy usually performed on patients after heart transplantation, etc.
(c) Surgical procedure group: Small-scale surgical procedures (excision, biopsy, etc.), dental procedures (dental extraction, pulp extirpation, pediatric rehabilitation dental practice, tooth polishing, tooth crowning, etc.)

[16] From 15 minutes after the start of dexmedetomidine, the administration rate was adjusted to achieve and maintain the target sedation level, with the adjustment interval of ≥5 minutes. The target sedation level was Neonatal Pain, Agitation and Sedation Scale (N-PASS) of −2 to −5 in subjects ≥28 weeks of corrected gestational age to <1 month postpartum, and University of Michigan Sedation Scale (UMSS) of 1 to 3 in subjects aged ≥1 month to <17 years.

[17] If the target sedation level was not reached at the maximum the dexmedetomidine administration rate (0.2 μg/kg/h in subjects ≥28 weeks of corrected gestational age to <1 month postpartum, 2.0 μg/kg/h in subjects aged ≥1 month to <17 years), midazolam was administered intravenously at the age-appropriate dose.

[18] From 15 minutes after the start of dexmedetomidine, fentanyl was administered intravenously at the age-appropriate dose when the subject (a) had pain or (b) was scheduled to undergo painful stimuli in 5 minutes.

Adverse events[19] were observed in 74.4% (67 of 90) of subjects. There were no adverse events resulting in death. Adverse events leading to dexmedetomidine discontinuation were observed in 1 subject (vomiting, rash), and they were considered related to the study drug. A serious adverse event other than death was observed in 1 subject (syncope), and the event was considered related to the study drug.

Adverse events considered related to the study drug occurred in 54.4% (48 of 90) of subjects. Events observed in ≥2 subjects were hypotension in 30 subjects, respiratory depression in 19 subjects, bradycardia in 3 subjects, vomiting, blood pressure systolic decreased, headache, and hypoxia in 2 subjects each.

7.R Outline of the review conducted by PMDA

7.R.1 Plan of global phase III/IV study (Study C0801039)

The applicant's explanation about the justification for the plan of the global phase III/IV study (Study C0801039) and the grounds for the feasibility of the study as Japan-US joint study in developing dexmedetomidine as sedative for children undergoing procedures or examinations:

Upon the approval of dexmedetomidine with the indication "sedation of non-intubated adult patients prior to and/or during surgical and other procedures" in the US, the applicant was requested to conduct a clinical study in children based on the Pediatric Research Equity Act (PREA). In response, Study DEX-10-16 was conducted, but the US Food and Drug Administration (FDA) concluded that the study was not designed appropriately for efficacy evaluation and failed to meet the criteria for PREA. After discussion with the US FDA, the applicant decided to conduct an additional study (Study C0801039) on pediatric sedation during procedures or examinations, and the applicant in Japan participated in the study.

MRI requires most careful sedation management to ensure the complete stillness of examinees under exposure to intense noise and takes longer time than other sedation-requiring procedures or examinations in children. In other words, the efficacy and safety of dexmedetomidine demonstrated with MRI would support its efficacy and safety also in non-invasive procedures or examinations other

[19] Reporting period of serious adverse events was from the informed consent to 30 days after the end of dexmedetomidine administration. Reporting period of non-serious adverse events was from the start of dexmedetomidine to 24 hours after the end of administration. In Study DEX-10-16, adverse events that occurred for the first time after the start of dexmedetomidine or worsened from before dexmedetomidine administration were subjected to analysis. In this report, adverse events subjected to said analysis are described unless specified otherwise. Bradycardia, hypotension, respiratory depression, hypoxia, and apnoea were reported as adverse events if they met any of the following criteria:
Bradycardia: The heart rate met the following criteria.
Hypotension: Systolic blood pressure met the following criteria.
Respiratory depression: The respiratory rate met the following criteria or decreased by >30% from baseline.
Hypoxia: SpO_2 was <90% or decreased by 10% from baseline.
Apnoea: $EtCO_2$ was 0 by capnography.

<table>
<tr><th>Age</th><th>Heart rate (beats/min)</th><th>Systolic blood pressure (mmHg)</th><th>Respiratory rate (breaths/min)</th></tr>
<tr><td>≥28 weeks of corrected gestational age to <1 month postpartum</td><td><120</td><td><60</td><td><40</td></tr>
<tr><td>≥1 to <3 months</td><td><100</td><td rowspan="3"><70</td><td><35</td></tr>
<tr><td>≥3 to <6 months</td><td><90</td><td><30</td></tr>
<tr><td>≥6 months to <1 year</td><td><80</td><td><25</td></tr>
<tr><td>≥1 to <2 years</td><td><70</td><td rowspan="3"><70 + (2 × age [years])</td><td rowspan="2"><20</td></tr>
<tr><td>≥2 to <6 years</td><td><60</td></tr>
<tr><td>≥6 to <10 years</td><td rowspan="2"><55</td><td rowspan="2"><14</td></tr>
<tr><td>≥10 to <12 years</td><td rowspan="2"><90</td></tr>
<tr><td>≥12 to <17 years</td><td><50</td><td><12</td></tr>
</table>

than MRI. For this reason, Study C0801039 was conducted in pediatric patients undergoing MRI. For targeting pediatric patients requiring sedation for MRI, the efficacy evaluation of dexmedetomidine was designed without a placebo group from an ethical point of view, and dexmedetomidine was administered in 3 dose groups (high-, medium-, and low-dose groups). The main analysis of the primary endpoint was designed to demonstrate the efficacy of the high dose by verifying the superiority of the high-dose group to the low-dose group.

With children, it is important that MRI is completed while examinees keep themselves completely still under sedation. It will be of high clinical significance if dexmedetomidine alone provides adequate sedation lasting throughout an examination without other concomitant sedatives. For this reason, the primary endpoint was the percentage of subjects not requiring a concomitant rescue drug to complete MRI. Propofol, the drug commonly used in the US, albeit off-label, as a sedative for children undergoing MRI, was specified as rescue drug. Propofol provides a sedative effect immediately after the start of administration and is easy to adjust the dose. Rescue propofol would allow a prompt start of MRI and its completion while appropriate sedation level is maintained even when dexmedetomidine alone does not work satisfactorily.

Before participating in Study C0801039 from Japan, the applicant conducted the following studies on differences in intrinsic and extrinsic ethnic factors that might affect the efficacy and safety of dexmedetomidine, and concluded that Study C0801039 would be feasible as a global study in Japan and the US, with necessary measures taken.

- Pharmacokinetic data from the clinical study of dexmedetomidine in pediatric patients requiring sedation in an intensive care setting did not differ significantly between Japanese and non-Japanese children, suggesting no large different in pharmacokinetics between Japanese and non-Japanese pediatric patients in sedation for procedures or examinations [see Section 6.R].
- According to a report on medical environment in Japan and the US pertaining to pediatric MRI requiring sedation, anesthesiologists were involved in 1.8% of sedation cases in Japan (*The Journal of the Japan Pediatric Society.* 2012;116:1653-65). In the US, sedation-requiring procedures or examinations outside the operating room were performed by intensive care specialists (28.4%), emergency physicians (27.9%), and anesthesiologists (19.2%) (*Pediatrics.* 2006;118:1087-96). Thus, MRI in sedation-requiring children is performed mainly by physicians other than anesthesiologists both in Japan and in the US. While, in Japan, triclofos sodium, chloral hydrate, and barbiturates are commonly used in sedation-requiring children for MRI, with only 5.3% of cases with propofol (*The Journal of the Japan Pediatric Society.* 2017;121:1920-9). In the US, in contrast, propofol was used in 57% of sedation cases for pediatric examinations (MRI accounted for 76.8%) performed outside the operating room (*J Pediatr Nurs.* 2017;35:129-33), indicating a gap between Japan and the US in the use of propofol for sedation in children undergoing MRI. Taking account of the possibility that the difference in the use experience of propofol might influence the decision making on rescue use of propofol, which affects the primary endpoint, investigators in Study C0801039 were selected from pediatric or general anesthesiologists who routinely use propofol and understand the characteristics of propofol well.
- PSSS, the sedation scale used in Study C0801039, is a relatively new scale published in 2017 (*Pediatrics.* 2017;139: e20162897). The applicant considered that PSSS, albeit uncommon in

clinical practice in Japan, would allow appropriate assessment at study sites in Japan as long as investigators are appropriately trained beforehand. Nevertheless, whether to administer rescue propofol was to be determined not by PSSS-based target sedation level but based on investigator's judgment.

PMDA's view:
For the development of dexmedetomidine as sedative for children undergoing procedures or examinations, Study C0801039, which was regarded as the phase III/IV study, targeted pediatric patients undergoing MRI. This approach is acceptable. Efficacy assessment based on the superiority of the high-dose group to the low-dose group without using placebo, and the primary endpoint of the percentage of subjects not requiring concomitant rescue drug to complete MRI are also acceptable. In terms of rescue drug, which was limited only to propofol, the study plan should preferably have included the collection of safety data, etc. with rescue drugs other than propofol, taking into account that sedatives other than propofol are more likely to be used in Japan when dexmedetomidine alone does not provide adequate sedation. Nevertheless, this is not a major problem from the standpoint of efficacy and safety assessment of dexmedetomidine alone, and Japan's participation in Study C0801039 with the study design to select investigators from pediatric or general anesthesiologists who are familiar with the characteristics of propofol, in light of the gap between Japan and the US in the use of propofol for pediatric sedation for MRI, etc.

The design of Study C0801039 including target subjects and efficacy endpoints is acceptable. There is no major problem in conducting the study as Japan-US global study from the point of efficacy and safety evaluation of dexmedetomidine alone. Efficacy and safety of dexmedetomidine are further discussed in Sections 7.R.2 and 7.R.3 based on the results of Study C0801039. The range of the procedures or examinations for which the use of dexmedetomidine is recommended and the clinical positioning of dexmedetomidine, including the measures to be taken in case of inadequate response to dexmedetomidine, are further discussed in Section 7.R.4.

7.R.2 Efficacy

The applicant's explanation about the efficacy of dexmedetomidine in procedures or examinations in children:
The following conclusions were reached from the results from the global phase III/IV study (Study C0801039), which demonstrated the efficacy of dexmedetomidine alone at the dosage regimen used in the high-dose group, and this is expected to be true in Japanese patients as well.

- Table 4 shows the percentages of subjects not requiring concomitant propofol to complete MRI, the primary endpoint. The percentages were statistically significantly higher in the high-dose group than in the low-dose group. A tendency of dexmedetomidine dose-dependent increase was observed in the percentage of these subjects including those in the medium-dose group.
- Table 6 shows the percentages of subjects not requiring concomitant propofol to complete MRI, by age group and in the Japanese subpopulation. The percentages tended to be higher in the high-dose group than in the low-dose group in all age groups. The Japanese subpopulation and the entire population showed generally similar tendencies.

Table 6. Percentages of subjects not requiring concomitant propofol to complete MRI, by age group and in the Japanese subpopulation (Study C0801039, FAS)

	High-dose		Medium-dose		Low-dose	
	Entire population	Japanese	Entire population	Japanese	Entire population	Japanese
All-age	63.2 (24/38)	71.4 (5/7)	35.7 (15/42)	50.0 (8/16)	14.3 (6/42)	0 (0/11)
Low age (≥1 month to <2 years)	50.0 (9/18)	50.0 (2/4)	9.5 (2/21)	25.0 (2/8)	15.0 (3/20)	0 (0/2)
High age (≥2 to <17 years)	75.0 (15/20)	100.0 (3/3)	61.9 (13/21)	75.0 (6/8)	13.6 (3/22)	0 (0/9)

Percentages of applicable subjects (number of subjects/number of subjects evaluated)
Subjects who did not complete MRI were counted as non-responders.

- Table 7 shows the percentages of duration achieving the target sedation level (PSSS score 2) during the maintenance dose of dexmedetomidine and the total dose of the rescue propofol, the secondary endpoints. The percentage of duration achieving the target sedation level (PSSS score 2) during the maintenance dose of dexmedetomidine tended to increase with dose in the all-age population and in each age group. The total dose of rescue propofol in subjects requiring concomitant propofol generally tended to decrease in a dexmedetomidine dose-dependent manner in the all-age population and in each age group. These findings corroborate the results of the primary endpoint.

Table 7. Percentages of duration achieving the target sedation level (PSSS score 2) during the maintenance dose of dexmedetomidine and total dose of propofol (Study C0801039, FAS)

		High-dose	Medium-dose	Low-dose
Percentages of duration achieving the target sedation level (PSSS score 2) during the maintenance administration	All-age	91.1 ± 18.71 (38)	87.2 ± 11.88 (41)	77.2 ± 17.04 (42)
	Low age (≥1 month to <2 years)	87.8 ± 23.93 (18)	82.5 ± 12.04 (21)	77.5 ± 15.94 (20)
	High age (≥2 to <17 years)	94.1 ± 12.22 (20)	92.2 ± 9.72 (20)	76.8 ± 18.36 (22)
Total propofol dose (μg/kg)	All-age	3426.4 ± 2973.00 (14)	4810.7 ± 3538.71 (27)	4828.6 ± 3390.42 (36)
	Low age (≥1 month to <2 years)	2822.8 ± 1593.84 (9)	4730.3 ± 3398.21 (19)	4012.1 ± 2334.66 (17)
	High age (≥2 to <17 years)	4513.0 ± 4620.56 (5)	5001.9 ± 4093.70 (8)	5559.2 ± 4038.95 (19)

Mean ± SD (number of subjects evaluated)

PMDA asked the applicant to explain the clinical significance of efficacy in the high-dose group in view of the fact that 36.8% (14 of 38) of subjects in the high-dose group of Study C0801039 required rescue drug (propofol) to complete MRI, failing to obtain adequate sedation with dexmedetomidine alone.

The applicant's explanation:
In the high-dose group of Study C0801039, the percentage of subjects not requiring concomitant propofol to complete MRI was 50.0% (9 of 18 subjects) in the age group ≥1 month to <2 years and 75.0% (15 of 20 subjects) in the age group ≥2 to <17 years (Table 6), showing the tendency of lower percentage in the age group ≥1 month to <2 years. This was inferred to be due to the difficulty in verbal communication in lower-age children, being more likely to feel scared and anxious before examination than older children. Despite the tendency of inferior efficacy of dexmedetomidine in the low-age group in the study, in clinical practice, dexmedetomidine may possibly bring greater efficacy in lower-age children than in Study C0801039, when administered following non-medication treatment that helps them calm down with the least possible anxiety.

In Japan, triclofos sodium is commonly used for sedating children undergoing sedation-requiring examinations and is indicated for pediatric sedation during examinations. When triclofos sodium alone was orally administered to children undergoing MRI, the sedation success rate was 25% (7 of 28) (≥6 months to <6 years of age) and 68.2% (152 of 223) (≥1 month to <7 years of age) (*The Journal of the Japan Pediatric Society.* 2016;120:869-75, *The St. Marianna Medical Journal.* 2019;46:231-7). Barbiturates and midazolam are also used, albeit off-label in Japan, in clinical practice for children undergoing sedation-requiring procedures or examinations. The sedation success rate in intravenous monotherapy in children undergoing MRI was 100% (300 of 300 subjects) (0.1-17 years of age) with thiopental, 96.6% (114 of 118 subjects) (≥1 month to <8 years of age) with thiamylal, 91% (32 of 35 subjects) (2-12 years of age) with pentobarbital, and 20% (8 of 40 subjects) (1-7 years of age) with midazolam.[20)] According to the reports on thiopental and thiamylal, additional dosing with respective sedative followed their initial dose depending on the sedation level reached, in contrast to the fixed-dose administration in Study C0801039.

As mentioned, the efficacy of dexmedetomidine particularly in the low-age group tended to be inadequate in Study C0801039 but may be greater in clinical settings than in the study. Despite the difficulty in strict efficacy comparison with other studies, the efficacy of dexmedetomidine alone at the high-dose group dosage regimen is not necessarily inferior to that of triclofos sodium, barbiturates, and midazolam used in Japan. Given the efficacy observed in the high-dose group, dexmedetomidine will provide a novel option for sedation of children undergoing procedures or examinations.

PMDA's view:

Based on the results in Study C0801039 as summarized below, dexmedetomidine has shown a certain level of efficacy in pediatric patients undergoing MRI, when administered alone according to the dosage regimen of the high-dose group. At the same time, dexmedetomidine alone will not provide adequate sedation in a certain percentage of patients. Countermeasures for such cases are further discussed in Section 7.R.4.

- In Study C0801039, the percentage of subjects not requiring concomitant propofol to complete MRI increased with the dose of dexmedetomidine. The percentage was statistically significantly higher in the high-dose group than in the low-dose group. The results of this primary endpoint are supported by the results of the secondary endpoints. In addition, the tendencies in the Japanese subpopulation are generally similar to those in the entire population.
- In their remarks on the clinical significance of the efficacy of dexmedetomidine in the high-dose group, the applicant mentioned that dexmedetomidine may show greater efficacy in its clinical use than in the clinical study despite lower efficacy particularly in the low-age group in the study. However, this is a matter of speculation, and it is not necessarily true that the clinical use of dexmedetomidine can exhibit greater efficacy than in the study. In terms of the efficacy of drugs used for sedation of children undergoing examinations in Japan, drawing conclusions about differences between dexmedetomidine and other drugs is difficult because the published literature presented by the applicant did not directly compare the efficacy of other drugs with dexmedetomidine administered by the dosage regimen of the high-dose group. However, given the percentage of subjects adequately sedated by dexmedetomidine alone in the high-dose group of Study C0801039, dexmedetomidine is

[20)] *Saudi J Anaesth.* 2017;11:185-9, *Brain Dev.* 2020;42:477-83, *Paediatr Anaesth.* 2004;14:589-95, *Br J Anaesth.* 2005;94:821-4

expected to be beneficial in the clinical setting in Japan where there are only limited choices of sedatives indicated for children undergoing procedures or examinations.

PMDA will finalize the appropriateness of the above conclusion, taking account of comments raised in the Expert Discussion.

7.R.3 Safety

Based on the review of the submitted clinical study results and on the discussions in Sections 7.R.3.1 to 7.R.3.3, PMDA concluded that dexmedetomidine must be used with attention to its impact on circulatory dynamics and respiratory status. Nevertheless, safety management with dexmedetomidine is possible in its use for sedation of non-intubated children undergoing procedures or examinations under a system that allows for constant monitoring for such impact, and as long as appropriate cautionary advice is given, i.e., the use of dexmedetomidine is restricted only by physicians who are proficient in the management of non-intubated children undergoing sedation, etc.

PMDA will finalize the appropriateness of the above conclusion, taking account of comments raised in the Expert Discussion.

Measures to promote the proper use of dexmedetomidine under an appropriate medical system mentioned above is further discussed in Section 7.R.6.1.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of dexmedetomidine used in non-intubated children undergoing procedures or examinations, based on the incidences of adverse events in the global phase III/IV study (Study C0801039) in pediatric patients undergoing MRI and in the foreign phase IV study (Study DEX-10-16) in pediatric patients undergoing procedures or examinations:

Table 8 shows the incidences of adverse events by dose group and age group in Study C0801039 and those of adverse events in the group undergoing non-invasive procedures or examinations in Study DEX-10-16. In Study C0801039, no significant difference was observed in the incidences of adverse events among dose groups or age groups. The majority of adverse events were mild in severity. Moderate events were observed in 2 subjects (bradycardia, bradycardia/tachycardia/hypertension) in the high-dose group and in 2 subjects (hypoxia, hypotension) in the low-dose group. No severe event was observed. Serious adverse events were observed in 1 subject (hypertension) in the high-dose group. Adverse events requiring intervention were observed in 2 subjects (bradycardia, bradycardia/hypertension) in the high-dose group, in 2 subjects (diastolic hypotension, bradypnoea) in the medium-dose group, and in 3 subjects (hypotension, hypoxia, bradypnoea/hypoxia) in the low-dose group. Adverse events leading to treatment discontinuation were observed in 1 subject each in the high-dose group (hypertension), the medium-dose group (bradycardia), and the low-dose group (bradypnoea). In the group undergoing non-invasive procedures or examinations in Study DEX-10-16, there were no severe or serious adverse events, while adverse events requiring intervention were observed in 1 subject (bradycardia/hypotension). The incidences of bradycardia and hypertension, etc. tended to be lower in Study DEX-10-16 than in Study C0801039, presumably due to the lower dose of

dexmedetomidine in Study DEX-10-16 than in Study C0801039 and the different definitions[21] of adverse events of bradycardia and hypertension between the 2 studies.

Table 8. Incidences of adverse events (Studies C0801039 and DEX-10-16, safety analysis population)

	Study C0801039									Study DEX-10-16
	High-dose			Medium-dose			Low-dose			Non-invasive procedure/ examination
	All ages	1 month to 2 years	2-17 years	All ages	1 month to 2 years	2-17 years	All ages	1 month to 2 years	2-17 years	
Number of subjects evaluated	38	18	20	42	21	21	42	20	22	46
All adverse events	36 (94.7)	17 (94.4)	19 (95.0)	39 (92.9)	20 (95.2)	19 (90.5)	38 (90.5)	19 (95.0)	19 (86.4)	32 (69.6)
Serious adverse events	1 (2.6)	0	1 (5.0)	0	0	0	1 (2.4)	0	1 (4.5)	0
Adverse events leading to treatment discontinuation	1 (2.6)	0	1 (5.0)	1 (2.4)	0	1 (4.8)	1 (2.4)	1 (5.0)	0	0
Adverse events requiring intervention	2 (5.3)	0	2 (10.0)	2 (4.8)	1 (4.8)	1 (4.8)	3 (7.1)	0	3 (13.6)	2 (4.3)
Adverse events considered related to the study drug	29 (76.3)	13 (72.2)	16 (80.0)	37 (88.1)	19 (90.5)	18 (85.7)	32 (76.2)	17 (85.0)	15 (68.2)	23 (50.0)
Main adverse events (events observed in ≥2 subjects of any group in Study C0801039)										
Bradycardia	27 (71.1)	13 (72.2)	14 (70.0)	24 (57.1)	12 (57.1)	12 (57.1)	24 (57.1)	9 (45.0)	15 (68.2)	3 (6.5)
Bradypnoea or respiratory depression[a)]	22 (57.9)	12 (66.7)	10 (50.0)	27 (64.3)	16 (76.2)	11 (52.4)	33 (78.6)	19 (95.0)	14 (63.6)	26 (56.5)
Hypertension	18 (47.4)	9 (50.0)	9 (45.0)	17 (40.5)	12 (57.1)	5 (23.8)	11 (26.2)	9 (45.0)	2 (9.1)	2 (4.3)
Hypotension	6 (15.8)	3 (16.7)	3 (15.0)	11 (26.2)	6 (28.6)	5 (23.8)	13 (31.0)	9 (45.0)	4 (18.2)	14 (30.4)
Diastolic hypertension	4 (10.5)	3 (16.7)	1 (5.0)	3 (7.1)	3 (14.3)	0	3 (7.1)	1 (5.0)	2 (9.1)	0
Systolic hypertension	3 (7.9)	1 (5.6)	2 (10.0)	5 (11.9)	3 (14.3)	2 (9.5)	1 (2.4)	0	1 (4.5)	0
Hypoxia	1 (2.6)	0	1 (5.0)	3 (7.1)	3 (14.3)	0	6 (14.3)	3 (15.0)	3 (13.6)	1 (2.2)
Tachycardia	1 (2.6)	0	1 (5.0)	1 (2.4)	1 (4.8)	0	3 (7.1)	2 (10.0)	1 (4.5)	0
Nasopharyngitis	0	0	0	0	0	0	2 (4.8)	1 (5.0)	1 (4.5)	0

Number of subjects with events (incidence [%])

a) Collected as bradypnoea in Study C0801039 and as respiratory depression in Study DEX-10-16.

Table 9 shows the incidences of adverse events in Study C0801017 in pediatric patients requiring sedation in an intensive care setting (Japanese clinical study on approved indication) and in Study DEX-301 in non-intubated adult patients undergoing surgery and procedures. Although different duration of administration and definition of adverse events among the studies precluded precise comparison, the incidences of bradycardia and hypertension (including diastolic hypertension and systolic hypertension) tended to be higher in the high-dose group of Study C0801039 than in other studies. All these events were mild or moderate, and the incidences of serious adverse events and adverse events leading to treatment discontinuation did not tend to be higher than in other studies.

[21] In Study C0801039, the heart rate defined as bradycardia in each age group was high as compared with Study DEX-10-16. Adverse events of hypertension were defined in Study C0801039 but not in Study DEX-10-16.

Table 9. Incidences of adverse events in clinical studies on dexmedetomidine in children and adults (Studies C0801039, C0801017, and DEX-301, safety analysis population)

	Children		Adults
	Study C0801039[a)]	Study C0801017[b)]	Study DEX-30[c)]
Subjects	Patients undergoing MRI	Patients requiring sedation in an intensive care setting	Non-intubated patients undergoing surgery and procedures
Age	≥1 month to <17 years of age	≥45 weeks of corrected gestational age to <17 years postpartum	≥20 years of age
Number of subjects evaluated	38	63	56
All adverse events	36 (94.7)	55 (87.3)	50 (89.3)
Serious adverse events	1 (2.6)	4 (6.3)	0
Adverse events leading to treatment discontinuation	1 (2.6)	1 (1.6)	1 (1.8)
Main adverse events (events observed in ≥2 subjects of the high-dose group in Study C0801039)			
Bradycardia	27 (71.1)	20 (31.7)	17 (30.4)
Bradypnoea or respiratory depression[d)]	22 (57.9)	17 (27.0)	26 (46.4)
Hypertension	18 (47.4)	1 (1.6)	15 (26.8)
Hypotension	6 (15.8)	31 (49.2)	35 (62.5)
Diastolic hypertension	4 (10.5)	0	0
Systolic hypertension	3 (7.9)	0	0

Number of subjects with events (incidence [%])

a) Results in the high-dose group

b) Continuous intravenous infusion of dexmedetomidine was started at 0.2 μg/kg/h, followed by the maintenance dose at 0.2 to 1.4 μg/kg/h in subjects ≥45 weeks of corrected gestational age to <6 years postpartum and at 0.2 to 1.0 μg/kg/h in subjects aged ≥6 to <17 years.

c) Results in the dexmedetomidine 1.0 μg/kg group (dexmedetomidine 1.0 μg/kg was administered intravenously over 10 minutes continuously, followed by the maintenance dose started at 0.4 μg/kg/h, then adjusted within the range of 0.2-0.7 μg/kg/h)

d) Counted as bradypnoea in Study C0801039 and as respiratory depression in Studies C0801017 and DEX-301.

In the Japanese population of Study C0801039, the incidence of adverse events was 85.7% (6 of 7 subjects) in the high-dose group, 93.8% (15 of 16 subjects) in the medium-dose group, and 90.9% (10 of 11 subjects) in the low-dose group, showing no significant difference from the incidence in the entire population (Table 8). Adverse events with an incidence of ≥20% in any dose group of the Japanese population were bradycardia (71.4% in the high-dose group, 62.5% in the medium-dose group, 72.7% in the low-dose group), bradypnoea (42.9%, 68.8%, 72.7%), diastolic hypertension (28.6%, 18.8%, 18.2%), hypertension (28.6%, 37.5%, 9.1%), hypotension (0%, 25.0%, 36.4%) and systolic hypertension (28.6%, 18.8%, 9.1%). The occurrence of each event tended to be generally similar to that in the entire population (Table 8).

In view of the safety of dexmedetomidine in non-intubated children undergoing procedures or examinations, major adverse events observed in Studies C0801039 and DEX-10-16 are related to circulatory dynamics and respiratory status, which were predictable from the pharmacological action of dexmedetomidine. Also, the safety profiles in the Japanese population were shown to be similar to those in the entire population.

PMDA has confirmed that, based on the occurrence of adverse events in Studies C0801039 and DEX-10-16, in non-intubated children undergoing procedures or examinations, dexmedetomidine is unlikely to cause adverse events not observed in its use for the approved indications, and that no Japanese population-specific concerns have been suggested. Details of the occurrence of adverse events related to circulatory dynamics and respiratory status and the time until awakening are further discussed in the following Sections 7.R.3.2 and 7.R.3.3.

7.R.3.2 Effect on circulatory dynamics and respiratory status

PMDA asked the applicant to explain the occurrence of adverse events related to circulatory dynamics and respiratory status observed after the administration of dexmedetomidine in pediatric patients undergoing MRI in the global phase III/IV study (Study C0801039).

The applicant's explanation:

Table 8 shows the incidences of adverse events related to circulatory dynamics (bradycardia, tachycardia, hypotension, and hypertension) and respiratory status (bradypnoea, hypoxia) in Study C0801039, indicating a tendency of increased incidences of bradycardia and hypertension with increased dose of dexmedetomidine, while the incidences of tachycardia, hypotension, bradypnoea, and hypoxia tended to decrease. Dexmedetomidine is known to decrease blood pressure and heart rate by its central α_{2A} adrenergic receptor-mediated sympathoinhibitory effect, while increasing blood pressure mediated by peripheral α_{2B} adrenergic receptor of vascular smooth muscle cells at high doses (*Anesthesiology.* 2000;93:1345-9). There is a possibility that the increased dose of dexmedetomidine caused peripheral α_{2B} receptor-mediated blood pressure-elevating effect, resulting in the increased incidence of hypertension and the decreased incidence in hypotension in the high-dose group. Table 10 shows the incidence of each event classified by use or non-use of propofol as rescue drug. The incidences of hypotension and tachycardia tended to be high in the population who used concomitant propofol, and the percentage of subjects using concomitant propofol decreased with increasing the dose of dexmedetomidine (Table 4). These results suggest that the decrease in the incidences of hypotension and tachycardia with the increase in dose of dexmedetomidine is partly due to the effect of concomitant propofol, a drug with a hypotensive effect. Also, in the population with concomitant propofol, the incidences of bradypnoea and hypoxia tended to increase with decreased dose of dexmedetomidine, and decreased dose of dexmedetomidine led to the increases in the percentage of subjects who used propofol (Table 4) and the total dose of propofol (Table 7). These results indicate that increased incidences of bradypnoea and hypoxia with decreased dose of dexmedetomidine was likely to be partly due to the concomitant propofol, a drug with a respiratory depressant effect.

Table 10. Incidences of adverse events related to circulatory dynamics and respiratory status by use/non-use of concomitant propofol (Study C0801039, safety analysis population)

	With propofol			Without propofol		
	High-dose	Medium-dose	Low-dose	High-dose	Medium-dose	Low-dose
Number of subjects evaluated	14	27	36	24	15	6
Bradycardia	7 (50.0)	18 (66.7)	22 (61.1)	20 (83.3)	6 (40.0)	2 (33.3)
Bradypnoea	6 (42.9)	17 (63.0)	29 (80.6)	16 (66.7)	10 (66.7)	4 (66.7)
Hypertension	6 (42.9)	14 (51.9)	9 (25.0)	12 (50.0)	3 (20.0)	2 (33.3)
Hypotension	5 (35.7)	9 (33.3)	13 (36.1)	1 (4.2)	2 (13.3)	0
Tachycardia	1 (7.1)	1 (3.7)	3 (8.3)	0	0	0
Hypoxia	0	3 (11.1)	6 (16.7)	1 (4.2)	0	0

Number of subjects with events (incidence [%])

In Study C0801039, circulatory dynamics or respiratory status-related adverse events which required intervention were observed in 2 subjects (bradycardia, bradycardia/hypertension) in the high-dose group, 2 subjects (diastolic hypotension, bradypnoea) in the medium-dose group, and 3 subjects (hypotension, hypoxia, bradypnoea/hypoxia) in the low-dose group. One subject (bradypnoea) in the medium-dose group belonged to the age group ≥1 month to <2 years, while other subjects belonged to

the age group ≥2 to <17 years. Dexmedetomidine was discontinued in 1 subject in the high-dose group (bradycardia/hypertension). Bradycardia and hypertension were treated with medication, hypotension with transfusion, and bradypnoea and hypoxia with oxygen, which led to recovery in all subjects.

As mentioned, most of the circulatory dynamics- and respiratory status-related adverse events observed in Study C0801039 did not require intervention. Those that required intervention were manageable by appropriate medication and oxygen supply. Thus, the impact of dexmedetomidine on the circulatory dynamics and respiratory status of sedated non-intubated children can be controlled as long as proper advice is offered through the package insert, i.e., for dexmedetomidine administration, the settings should (a) be prepared for airway control, oxygen inhalation, mechanical ventilation, and circulatory control, and ensure that the sedation level and systemic condition are carefully and constantly managed by a physician who is proficient in sedation management in non-intubated children and have a good understanding of the pharmacological action of dexmedetomidine; (b) besides the one who performs the procedure/examination, have a healthcare professional stationed to engage solely in close observation of patient's systemic condition including conscious state, respiratory status, and circulatory dynamics throughout the procedure/examination, by whom respiratory rate, heart rate (pulse), blood pressure, electrocardiogram (ECG), saturation of peripheral oxygen (SpO_2), end-tidal carbon dioxide ($EtCO_2$), etc. will be monitored. As stated earlier, concomitant propofol may increase the incidence of adverse events, such as hypotension, bradypnoea, and hypoxia in particular, and this concern is likely to be true with concomitant use of sedatives other than propofol. The package insert will advise caution that other supplemental sedatives should be administered carefully because of possible increase in the risk of adverse drug reactions.

PMDA's view:
Given the occurrence of adverse events related to circulatory dynamics and respiratory status in Study C0801039, these events are controllable when it is ensured that dexmedetomidine is administered carefully under the supervision of a physician proficient in the management of sedated non-intubated pediatric patients, in the presence of a healthcare professional who is engaged in systemic condition monitoring, by whom circulatory dynamics and respiratory status are monitored during procedures or examinations, besides the healthcare professional who performs procedures/examinations. Co-administration of other sedatives may increase the risk of adverse events related to circulatory dynamics and respiratory status, thus supplementary use of other sedatives may enhance the risk of adverse drug reactions. The package insert should advise careful use of other sedatives.

Information collection on the risk of adverse events related to circulatory dynamics and respiratory status and safety in the co-administration of other sedatives should be continued in the post-marketing setting, and the necessity of additional safety measures should be discussed.

7.R.3.3 Time to awakening

Taking account of time to awakening in the global phase III/IV study (Study C0801039) in pediatric patients undergoing MRI, PMDA asked the applicant to explain whether time to awakening can be longer in pediatric patients receiving dexmedetomidine for procedures or examinations than in non-intubated adult patients undergoing procedures or examinations or in pediatric patients receiving other sedatives.

The applicant's explanation:

In Study C0801039, the median time [range] to awakening[22] was 35.0 [3, 80] minutes in the low-dose group, 42.5 [4, 148] minutes in the medium-dose group, and 45.5 [3, 161] minutes in the high-dose group. In the high-dose group, the median time was 38.0 [3, 161] minutes in the age group ≥1 month to <2 years and 50.0 [15, 82] minutes in the age group ≥2 to <17 years. In the Japanese clinical study of dexmedetomidine (Study DEX-301) in non-intubated adult patients undergoing surgery and procedures, the median time to awakening[23] in the dexmedetomidine 1.0 μg/kg group[24] was 15.0 minutes, suggesting possible prolonged time to awakening in children receiving dexmedetomidine for procedures or examinations as compared with adults undergoing surgery and procedures. In children receiving triclofos sodium, chloral hydrate, barbiturates, or midazolam, the main sedatives used in children undergoing sedation-requiring examinations in Japan, time to awakening is estimated to be 1 to 7 hours with triclofos sodium or chloral hydrate (*Sedation and Analgesia for Pediatric Procedures*. Chugai-Igakusha; 2013:p159-69), 8 to 10 minutes (median) with thiamylal or thiopental (*Brain Dev.* 2020;42:477-83, *Saudi J Anaesth.* 2017;11:185-9), and 25 minutes (mean) with midazolam (*Br J Anaesth.* 2005;94:821-4). Time to awakening after dexmedetomidine administration may become shorter than after the administration of triclofos sodium or chloral hydrate but may be longer than after the administration of barbiturates or midazolam. In Study C0801039, adverse events related to withdrawal symptoms of dexmedetomidine were observed, i.e., agitation in 1 subject and anaesthetic complication neurological (the term used by the attending physician, delirium on awakening) in 2 subjects.

The above findings suggest the possibility that time to awakening is prolonged in children receiving dexmedetomidine for procedures or examinations as compared with adults receiving barbiturates or midazolam or in adults for surgery or procedures. In addition, agitation and delirium on awakening were reported as adverse events related to withdrawal symptoms after dexmedetomidine administration. Along with this information, the package insert will advise that patients be placed under supervision until recovery to deal with complications that may occur before awakening after procedure or examination.

PMDA's view:

Based on the results of Study C0801039, etc. that suggest the possible prolonged time to awakening in children receiving dexmedetomidine for procedures or examinations as compared with children receiving barbiturates or midazolam or adults receiving dexmedetomidine for surgery or procedures, and given time to awakening after MRI that largely varied among patients in Study C0801039,

[22] Modified Aldrete score (table below) was evaluated every 15 minutes from the time point when the subject arrived at the post-procedure recovery area after the MRI scan until he/she was allowed to leave the area. Time to awakening was defined as the time to total Modified Aldrete score of ≥9.

	Score		
	2	1	0
Activity	Able to move 4 extremities voluntarily or by instruction	Able to move 2 extremities voluntarily or by instruction	Unable to move extremities
Respiration	Able to breathe deeply and cough freely	Dyspnea or limited breathing	Apneic
Blood pressure	Less than ±20% of pre-anesthetic level	±20%-49% of pre-anesthetic level	Greater than ±50% of pre-anesthetic level
Consciousness	Fully awake	Arousable on calling	Not responding
SpO_2	Able to maintain O_2 saturation ≥92% on room air	Needs oxygen to maintain O_2 saturation ≥90%	O_2 saturation <90% even with supplemental oxygen

[23] Defined as time from the end of the study drug administration until total Modified Aldrete score reached ≥9.

[24] Dexmedetomidine 1.0 μg/kg was continuously infused intravenously over 10 minutes, followed by the maintenance administration started at 0.4 μg/kg/h, then adjusted within the range of 0.2 to 0.7 μg/kg/h.

information provision via the package insert about the possible prolonged time to awakening and advice on the supervision of patients until recovery after procedure or examination are appropriate.

7.R.4 Clinical positioning and indication

The applicant's explanation about the clinical positioning and indication of dexmedetomidine:
Triclofos sodium, chloral hydrate, barbiturates, and midazolam are the sedatives mainly used in children undergoing sedation-requiring examinations in Japan. Triclofos sodium and chloral hydrate take longer time to exert sedative effect and have difficulty in additional administration when their effects wane during examination. Barbiturates pose concerns about respiratory or circulatory depression. Midazolam has the problem of causing not only respiratory or circulatory depression but adverse drug reactions such as hyperactivity and aggression. Only triclofos sodium and chloral hydrate are indicated for sedation of children undergoing examinations in Japan. For these reasons, there are needs for a new option of sedatives to be used in children undergoing examinations in clinical practice in Japan.

In the US, since the approval for the indication of "sedation of non-intubated adult patients prior to and/or during surgical and other procedures," dexmedetomidine has been commonly used as a sedative for children undergoing procedures or examinations. Surveillance on dexmedetomidine used for sedation outside operating room in the US and Canada showed that dexmedetomidine was administered mainly for imaging examinations such as MRI, resulting in a high sedation success rate and low incidence of serious adverse events (*Hosp Pediatr.* 2016;6:536-44). The Japanese clinical practice guidelines state that dexmedetomidine is a safe sedative for computed tomography (CT), MRI, electroencephalography, etc. with only minimal respiratory depression, albeit off-label and unestablished pharmacokinetics and safety in pediatric patients (*Guidelines for using anesthetics and anesthesia-related drugs* [in Japanese]. the fourth edition, the third revision, Japanese Society of Anesthesiologists; 2018:p414-6).

The global phase III/IV study (Study C0801039) in pediatric patients undergoing MRI demonstrated dexmedetomidine's sedative effect in children undergoing MRI only by the dosage regimen of the high-dose group without requiring rescue drugs [see Section 7.R.2] and its tolerable safety profile when used under appropriate management [see Section 7.R.3]. If dexmedetomidine alone does not provide sedative effect adequate to complete a procedure or examination, either of the following measures is recommended: (a) the administration of other sedatives in addition to dexmedetomidine; or (b) discontinuation of dexmedetomidine followed by the administration of other sedatives to obtain adequate sedation so that the planned procedure or examination is completed. Supplementary administration of other sedatives should be performed carefully because of possible increased risk of adverse drug reactions [see Section 7.R.3.2].

Based on the above, the applicant considered it of clinical significance to provide dexmedetomidine to clinical settings as a novel option of sedatives for children undergoing non-invasive procedures or examinations, with the proposed indication of "sedation of non-intubated children during non-invasive procedures or examinations."

PMDA asked the applicant to explain the types of procedures or examinations for which sedation with dexmedetomidine is recommended based on the results of Study C0801039 in pediatric patients

undergoing MRI, and the appropriateness of the definition of "non-invasive procedures or examinations" in the proposed indication.

The applicant's explanation:
Stedman's Medical Dictionary (2016) defines the term "noninvasive" as "denoting a procedure that does not require insertion of an instrument or device through the skin or a body orifice for diagnosis or treatment." By reference to this, procedures or examinations performed in non-inbubated children are classified as either non-invasive or invasive as shown in Table 11.

Table 11. Examples of non-invasive and invasive procedures or examinations

Non-invasive procedures	Non-invasive examinations
Hemodialysis procedure Radiation therapy of cancer Laser irradiation of skin Cardioversion	CT MRI Ultrasonography (TTE, etc.) Electroencephalography Radionuclide scanning Audiometry (auditory brainstem response testing, etc.)
Invasive (minimally invasive) procedures	Invasive (minimally invasive) examinations
Bronchoscopic surgery Peripherally inserted central venous catheter Lumbar puncture Joint injection Sclerotherapy Surgical procedures (excision, biopsy) Dental procedures (extraction, pulp extirpation, dental procedure in pediatric rehabilitation, polishing, tooth crown, etc.) Anal dilatation	Transesophageal echocardiogram Cardiac catheterization Upper gastrointestinal endoscopy Lower gastrointestinal endoscopy Bronchoscopy

According to the above definition, MRI, the target examination in Study C0801039, is classified as non-invasive examination. Thus, based on the results of Study C0801039, the use of dexmedetomidine is recommended when sedation is required for the above-defined non-invasive procedures or examinations. Usually MRI is physically painless and does not require pain relief or local anesthesia. Study C0801039 therefore did not investigate the efficacy of dexmedetomidine in non-invasive but physically painful procedures or examinations requiring pain relief or local anesthesia (such as laser irradiation of skin, etc. in Table 11). MRI takes longer time than other examinations, during which patients are completely physically restrained and exposed to intense noise, requiring most careful sedation management. Study C0801039 demonstrated that dexmedetomidine provides an appropriate level of sedation with the dosage regimen of the high-dose group [see Section 7.R.2]. The target sedation level in non-invasive procedures or examinations (Table 11) other than MRI is considered to be more or less equal (minimal, moderate, or deep sedation)[25] to or lower (minimal or moderate sedation) than the level required for MRI. These examinations take similar or shorter time than MRI, except hemodialysis, which requires approximately 4 hours to complete. Dexmedetomidine is thus suggested to be effective for sedation in non-invasive procedures or examinations other than MRI as well, if used at the dosage regimen which provided adequate sedation in the high-dose group for MRI. MRI needs similar or longer time than other procedures or examinations, during which access to the examinee in the MRI scanner is restricted, and only limited emergency measures are available inside the MRI room that do not allow magnetic medical devices to be brought in. MRI also covers a wide

[25] Sedation level is classified into minimal sedation, moderate sedation, deep sedation, and general anesthesia (*Sedation and Analgesia for Pediatric Procedures*. Chugai-Igakusha; 2013:p76-81).

range of diseases. Study C0801039 has demonstrated the safety of dexmedetomidine in MRI under appropriate management [see Section 7.R.3], suggesting that dexmedetomidine can also be used safely in non-invasive procedures or examinations other than MRI, under appropriate management as in MRI.

Thus, dexmedetomidine is recommended for use in non-invasive procedures or examinations in non-intubated patients who require sedation, including those other than MRI. The applicant considers it appropriate to define the indication of dexmedetomidine as "non-invasive procedures or examinations in non-intubated children." As described earlier, the efficacy of dexmedetomidine has not been established for non-invasive procedures or examinations in non-intubated children which require pain relief or local anesthesia, and this will be communicated via the package insert to raise caution.

PMDA's view:
From the discussion in Sections 7.R.2 and 7.R.3 and the applicant's explanation above, dexmedetomidine may be regarded as an option of sedatives for children undergoing non-invasive procedures or examinations, and the indication of "sedation of non-intubated children during non-invasive procedures or examinations," including MRI investigated in Study C0801039 and other than MRI, is acceptable. Study C0801039 did not investigate the efficacy of dexmedetomidine in procedures or examinations requiring pain relief or local anesthesia or its safety in the co-administration with analgesic drugs or local anesthetics. Therefore, the package insert should caution that efficacy and safety in procedures or examinations requiring pain relief or local anesthesia have not been established. Furthermore, the applicant's recommendation, i.e., the supplementary use of other sedatives to complete the intended procedure or examination when dexmedetomidine alone does not provide adequate effect, is understandable, in light of the medical system in Japan. Nevertheless, the package insert should provide precautions on such co-administration, while relevant information is also disseminated through materials for healthcare professionals [see Section 7.R.6.1].

PMDA will finalize the appropriateness of the above conclusion, taking account of comments raised in the Expert Discussion.

7.R.5 Dosage and administration

PMDA asked the applicant to explain the appropriateness of the proposed dosage regimen, taking account of justification for the dosage regimen and results in each dexmedetomidine dose group of the global phase III/IV study (Study C0801039) in pediatric patients undergoing MRI.

The applicant's explanation about justification for the dosage regimen in each dexmedetomidine group in Study C0801039:
In the use of dexmedetomidine for sedation during and after mechanical ventilation in an intensive care setting, the approved indication, the initial loading dose is administered in adults. In contrast, the dosage regimen for children did not require an initial loading dose due to its possible effect on the circulatory dynamics, and because rapid increase in plasma drug level would not be essential for sedation management in an intensive care setting. However, in terms of the proposed indication in the

present application, a rapid increase in plasma drug concentration is essential to promptly bring pediatric patients to the intended sedation level, because mostly they are presumed to be anxious and agitated before procedure or examination. Also, according to a published article, the initial loading dose was administered in studies on the usefulness of dexmedetomidine in children undergoing procedures or examinations including MRI. For these reasons, the initial loading dose was administered in Study C0801039.

In Study C0801039 regarded as a dose range finding study, based on the following consideration, the high-dose group received the initial loading dose of 2.0 μg/kg (over 10 minutes) and the maintenance dose of 1.5 μg/kg/h, which are higher than the doses for the approved indication, for expected adequate efficacy. The initial loading dose in the low-age group (≥1 month to <2 years) was determined as 1.5 μg/kg (over 10 minutes) to minimize the incidence of adverse events, taking account of immature hepatic and renal functions and smaller blood volume in this population.

- Ideally in an intensive care setting, patients' level of consciousness should be observable so that they can be sedated adequately to stay free from anxiety or pain even during administration. However, the proposed indication is intended for children, who have difficulty staying still on their own will. Thus the desired level of sedation must allow patients to stay still completely throughout a certain period of time without unpleasant feeling, and therefore a deeper level of sedation must be obtained relative to that in intensive care settings.
- In the PPK model constructed from the plasma drug concentration data obtained from the foreign clinical study in pediatric patients requiring sedation in an intensive care setting, CL_w and $V_{c,w}$ in children aged <17 years except neonates were generally higher than those in adults (Summary of the product application for "Precedex Intravenous Solution 200 μg 'Pfizer,' etc." [addition of pediatric dose to (Sedation during and after mechanical ventilation in an intensive care setting)]). In order to achieve the plasma drug level with a sedative effect, children except infants require a higher dose per body weight than adults.
- The published literature on the usefulness of dexmedetomidine in MRI in children (*Paediatr Anaesth.* 2008;18:403-11, *Paediatr Anaesth.* 2011;21:153-8) reported the use of the initial loading dose of 2 to 3 μg/kg (over 10 minutes) or 2 μg/kg (over 10 minutes), and the maintenance dose of 1 to 2 μg/kg/h and 1 μg/kg/h.

In the low-dose group that regarded as the lowest effective dose group in Study C0801039, dexmedetomidine was administered at the initial loading dose of 0.5 μg/kg (over 10 minutes) and the maintenance dose of 0.5 μg/kg/h. These doses were reported to be adequate for intensive care albeit inadequate for MRI (*Pediatr Crit Care Med.* 2005;6:435-9). The dose response evaluation included the group of the medium-dose, which was regarded as the intermediate dose between the low and high doses, received the initial loading dose of 1.2 μg/kg (over 10 minutes) and the maintenance dose of 1.0 μg/kg/h. The age group of <2 years in the the medium dose group received the initial loading dose of 1.0 μg/kg (over 10 minutes).

Because Study C0801039 was regarded as a dose range finding study and according to the published article which reported the usefulness of dexmedetomidine in children undergoing MRI in a study using a fixed maintenance dose of dexmedetomidine (*Paediatr Anaesth.* 2008;18:403-11, *Paediatr Anaesth.*

2011;21:153-8, *Int J Pediatr.* 2015;2015:397372), Study C0801039 employed the fixed maintenance dose without adjustment.

The applicant's explanation about the appropriateness of the proposed dosage regimen based on the results of Study C0801039 conducted with the dosage regimen described earlier:
In Study C0801039, the percentage of subjects not requiring concomitant propofol to complete MRI was high in the high-dose group as compared with the low-dose and medium-dose groups, in both low- and high-age groups (Table 6). The percentage of subjects[26)] with sedation fell below the target level (PSSS score 2) 5 minutes after the start of maitenance administration of dexmedetomidine was higher in the high-dose group (76.3% [29 of 38 subjects] in all-age population, 72.2% [13 of 18 subjects] in the age group ≥1 month to <2 years, 80.0% [16 of 20 subjects] in the age group ≥2 to <17 years) than in the medium-dose group (70.7% [29 of 41 subjects], 52.4% [11 of 21 subjects], and 90.0% [18 of 20 subjects]) and the low-dose group (47.6% [20 of 42 subjects], 35.0% [7 of 20 subjects], and 59.1% [13 of 22 subjects]). Also, of the subjects who reached the target sedation score (PSSS score 2) within 5 minutes after the start of the maintenance dose, the percentage of subjects who did not need concomitant propofol during the subsequent maintenance administration was high in the high-dose group (72.4% [21 of 29 subjects], 61.5% [8 of 13 subjects], 81.3% [13 of 16 subjects]) as compared with the medium-dose group (48.3% [14 of 29 subjects], 9.1% [1 of 11 subjects], 72.2% [13 of 18 subjects]) and in the low-dose group (25.0% [5 of 20 subjects], 28.6% [2 of 7 subjects], 23.1% [3 of 13 subjects]). These data indicate that the dosage regimen of dexmedetomidine used in the high-dose group, with both the initial loading and maintenance doses, is expected to contribute to greater efficacy.

Table 12 shows the incidences of adverse events during the initial loading dose period in Study C0801039. During this period, the incidences of bradycardia and hypertension were higher in the high-dose group than in the medium-dose and low-dose groups, requiring intervention in 2 subjects with bradycardia in the high-dose group. The adverse events resolved by medication, and dexmedetomidine was continued. In each dose group, the incidence of hypertension tended to be higher in the age group <2 years than in the age group ≥2 years, but hypertension in the age group <2 years in the high-dose group was mild, allowing continued dexmedetomidine administration without intervention. These results suggest that, in all age groups, the initial loading dose of the high-dose group is unlikely to cause safety problems.

[26)] In subjects without PSSS score evaluated at 5 minutes after the start of the maintenance dose, PSSS score at the latest timing within 5 minutes after the start of the maintenance dose was used. In subjects with no PSSS score evaluated during 5 minutes after the start of the maintenance administration, PSSS score at the earliest time point after the start of the maintenance dose was used. Subjects who discontinued dexmedetomidine before the start of the maintenance dose were excluded from the analysis.

Table 12. Incidences of adverse events during the initial loading dose period (Study C0801039, safety analysis population)

	High-dose			Medium-dose			Low-dose		
	All ages	1 month to <2 years	2 to <17 years	All ages	1 month to <2 years	2 to <17 years	All ages	1 month to <2 years	2 to <17 years
Number of subjects evaluated	38	18	20	42	21	21	42	20	22
All adverse events	27 (71.1)	12 (66.7)	15 (75.0)	21 (50.0)	11 (52.4)	10 (47.6)	21 (50.0)	11 (55.0)	10 (45.5)
Adverse events leading to treatment discontinuation	0	0	0	1 (2.4)	0	1 (4.8)	0	0	0
Adverse events requiring intervention	2 (5.3)	0	2 (10.0)	1 (2.4)	0	1 (4.8)	0	0	0
Adverse events considered related to the study drug	22 (57.9)	8 (44.4)	14 (70.0)	17 (40.5)	7 (33.3)	10 (47.6)	12 (28.6)	8 (40.0)	4 (18.2)
Main adverse events (adverse events reported in ≥2 subjects among all subjects evaluated)									
Bradycardia	15 (39.5)	6 (33.3)	9 (45.0)	6 (14.3)	1 (4.8)	5 (23.8)	6 (14.3)	3 (15.0)	3 (13.6)
Hypertension	12 (31.6)	7 (38.9)	5 (25.0)	7 (16.7)	5 (23.8)	2 (9.5)	5 (11.9)	4 (20.0)	1 (4.5)
Bradypnoea	8 (21.1)	3 (16.7)	5 (25.0)	6 (14.3)	2 (9.5)	4 (19.0)	10 (23.8)	6 (30.0)	4 (18.2)
Systolic hypertension	3 (7.9)	1 (5.6)	2 (10.0)	3 (7.1)	2 (9.5)	1 (4.8)	1 (2.4)	0	1 (4.5)
Diastolic hypertension	2 (5.3)	1 (5.6)	1 (5.0)	2 (4.8)	2 (9.5)	0	1 (2.4)	0	1 (4.5)
Hypotension	1 (2.6)	1 (5.6)	0	3 (7.1)	1 (4.8)	2 (9.5)	2 (4.8)	2 (10.0)	0
Hypoxia	1 (2.6)	0	1 (5.0)	1 (2.4)	1 (4.8)	0	1 (2.4)	1 (5.0)	0
Tachycardia	0	0	0	1 (2.4)	1 (4.8)	0	2 (4.8)	2 (10.0)	0

Number of subjects with events (incidence [%])

Table 13 shows the incidences of adverse events during the maintenance dose period in Study C0801039. During the maintenance dose period, the incidences of bradycardia and hypertension were higher in the high-dose group than in the medium-dose and low-dose groups. Two subjects (bradycardia and hypertension/bradycardia) in the high-dose group required intervention. Dexmedetomidine was discontinued in 1 subject because of hypertension. These adverse events resolved by medication in both subjects. In all dose groups, the incidence of hypertension tended to be higher in the age group <2 years than the age group ≥2 years, as was the case during the initial loading dose period. Hypertension observed in the age group <2 years in the high-dose group was mild and did not require intervention. Hypertension considered related to the study drug was observed in 16.7% of subjects in the age group <2 years and in 15.0% of subjects in the age group ≥2 years, showing no significant difference between the age groups. Administering the maintenance dose of dexmedetomidine in the high-dose group is unlikely to pose safety problems in either of the age group.

Table 13. Incidences of adverse events during the maintenance administration period (Study C0801039, safety analysis population)

	High-dose			Medium-dose			Low-dose		
	All ages	1 month to <2 years	2 to <17 years	All ages	1 month to <2 years	2 to <17 years	All ages	1 month to <2 years	2 to <17 years
Number of subjects evaluated	38	18	20	42	21	21	42	20	22
All adverse events	36 (94.7)	17 (94.4)	19 (95.0)	38 (90.5)	20 (95.2)	18 (85.7)	38 (90.5)	19 (95.0)	19 (86.4)
Adverse events leading to treatment discontinuation	1 (2.6)	0	1 (5.0)	0	0	0	1 (2.4)	1 (5.0)	0
Adverse events requiring intervention	2 (5.3)	0	2 (10.0)	3 (7.1)	1 (4.8)	2 (9.5)	3 (7.1)	0	3 (13.6)
Adverse events considered related to the study drug	29 (76.3)	13 (72.2)	16 (80.0)	36 (85.7)	19 (90.5)	17 (81.0)	32 (76.2)	17 (85.0)	15 (68.2)
Main adverse events (adverse events reported in ≥2 subjects among all subjects evaluated)									
Bradycardia	26 (68.4)	13 (72.2)	13 (65.0)	23 (54.8)	12 (57.1)	11 (52.4)	24 (57.1)	9 (45.0)	15 (68.2)
Bradypnoea	21 (55.3)	12 (66.7)	9 (45.0)	27 (64.3)	16 (76.2)	11 (52.4)	33 (78.6)	19 (95.0)	14 (63.6)
Hypertension	18 (47.4)	9 (50.0)	9 (45.0)	16 (38.1)	12 (57.1)	4 (19.0)	10 (23.8)	9 (45.0)	1 (4.5)
Hypotension	6 (15.8)	3 (16.7)	3 (15.0)	9 (21.4)	6 (28.6)	3 (14.3)	13 (31.0)	9 (45.0)	4 (18.2)
Diastolic hypertension	4 (10.5)	3 (16.7)	1 (5.0)	3 (7.1)	3 (14.3)	0	3 (7.1)	1 (5.0)	2 (9.1)
Systolic hypertension	3 (7.9)	1 (5.6)	2 (10.0)	5 (11.9)	3 (14.3)	2 (9.5)	1 (2.4)	0	1 (4.5)
Anaesthetic complication neurological	1 (2.6)	1 (5.6)	0	1 (2.4)	0	1 (4.8)	0	0	0
Tachycardia	1 (2.6)	0	1 (5.0)	1 (2.4)	1 (4.8)	0	3 (7.1)	2 (10.0)	1 (4.5)
Nausea	1 (2.6)	0	1 (5.0)	1 (2.4)	0	1 (4.8)	0	0	0
Hypoxia	0	0	0	3 (7.1)	3 (14.3)	0	6 (14.3)	3 (15.0)	3 (13.6)
Diastolic hypotension	0	0	0	1 (2.4)	0	1 (4.8)	1 (2.4)	1 (5.0)	0
Nasopharyngitis	0	0	0	0	0	0	2 (4.8)	1 (5.0)	1 (4.5)

Number of subjects with events (incidence [%])

Based on the efficacy and safety findings in Study C0801039, the above results support the appropriateness of the dosage regimen of dexmedetomidine, i.e., the initial loading dose (1.5 μg/kg in children aged ≥1 month to <2 years, 2.0 μg/kg in children aged ≥2 years) administered over 10 minutes followed by the maintenance dose of 1.5 μg/kg/h in the high-dose group. Although not allowed in Study C0801039, dose adjustment will be allowed in case of an adverse event by adjusting the administration rate at the discretion of the physician. The dosage regimen will have a note that the administration rate should be reduced as appropriate according to patient condition, and the package insert will advise that the reduction of the loading rate, etc. should be considered in case of elevated blood pressure especially during the administration of the initial loading dose of dexmedetomidine.

In Study C0801039, the lowest age of subjects assigned to the high-dose group was 0.4 years. There is no use experience of dexmedetomidine in patients aged ≥1 month to <0.4 years by the dosage regimen of the high-dose group. PMDA asked the applicant to explain whether the proposed dosage regimen is recommended for patients of this age group.

The applicant's explanation:
Performing examinations in neonates aged <1 month is possible only after the onset of spontaneous sleep. For this reason, Study C0801039 enrolled subjects aged ≥1 month. The age (median [range]) of subjects randomized to the age group ≥1 month to <2 years in Study C0801039 was 0.80 [0.2, 2.0] in the entire age group, 0.90 [0.4, 1.8] in the high-dose group, 0.80 [0.2, 1.8] in the medium-dose group, and 0.85 [0.2, 2.0] in the low-dose group. The number of subjects aged <6 months was 13 in the entire age group, 2 in the high-dose group, 6 in the medium-dose group, and 5 in the low-dose group.

In Study C0801039, there were only 13 subjects aged <6 months, including only 1 subject in the high-dose group who did not need concomitant propofol to complete MRI, precluding full evaluation

of the efficacy of dexmedetomidine in patients aged ≥1 month to <0.4 years from the study data. However, in the high-dose group, concomitant propofol was not required in 1 of 2 subjects aged <6 months. The proposed dosage regimen specifies the administration rate based on the body weight. In addition, CL_w (geometric mean) and $V_{c,w}$ (geometric mean) by age estimated based on the PPK model constructed from the plasma drug concentration data in a foreign clinical study in pediatric patients (≥28 weeks of corrected gestational age to <17 years postpartum) requiring sedation in an intensive care setting were 1.21 L/h/kg and 0.76 L/kg, respectively, in patients aged ≥1 month to <6 months, 1.11 L/h/kg and 0.99 L/kg, respectively, in patients aged ≥6 months to <12 months, and 1.06 L/h/kg and 0.72 L/kg, respectively, in patients aged ≥12 months to <24 months, showing no significant difference in the pharmacokinetic parameter values among age groups ≥1 month to <6 months, ≥6 months to <12 months, and ≥12 months to <24 months. The results suggest that patients aged <0.4 years (approximately <5 months) receiving dexmedetomidine by the dosage regimen of the high-dose group will achieve plasma drug concentrations similar to those achieved in patients aged ≥0.4 years, along with comparable efficacy.

In Study C0801039, all adverse events observed in subjects aged <6 months were related to circulatory dynamics or respiratory status. Table 14 shows the incidences of adverse events related to circulatory dynamics and respiratory status by age groups <2 years. Strict comparison is difficult because of the limited number of subjects in each dose group, but the incidences of adverse events in subjects aged ≥1 to <6 months did not tend to differ from the incidences in subjects aged ≥6 months to <1 year or in subjects aged ≥1 to <2 years in the low-dose group (the youngest age, 0.2 years) and the medium-dose group (the youngest age, 0.2 years), including lower-age subjects than those in the high-dose group (the youngest age, 0.4 years). As mentioned earlier, no significant difference was observed in the pharmacokinetic parameter values among age groups ≥1 to <6 months, ≥6 to <12 months, and ≥12 to <24 months. These findings suggest that, also in patients aged ≥1 month to <0.4 years (approximately 5 months), dexmedetomidine is unlikely to pose safety problems when administered at the dosage regimen of the high-dose group.

Table 14. Incidences of adverse events related to circulatory dynamics and respiratory status in age subgroups <2 years (Study C0801039, safety analysis population)

	High-dose			Medium-dose			Low-dose		
	<6 months	6 months to <1 year	1 to <2 years	<6 months	6 months to <1 year	1 to <2 years	<6 months	6 months to <1 year	1 to <2 years
Number of subjects evaluated	2	8	8	6	6	9	5	7	8
Bradycardia	1 (50.0)	7 (87.5)	5 (62.5)	4 (66.7)	4 (66.7)	4 (44.4)	2 (40.0)	5 (71.4)	2 (25.0)
Bradypnoea	1 (50.0)	7 (87.5)	4 (50.0)	3 (50.0)	5 (83.3)	8 (88.9)	5 (100)	6 (85.7)	8 (100)
Diastolic hypertension	1 (50.0)	1 (12.5)	1 (12.5)	1 (16.7)	0	2 (22.2)	0	1 (14.3)	0
Hypertension	0	6 (75.0)	3 (37.5)	3 (50.0)	5 (83.3)	4 (44.4)	2 (40.0)	2 (28.6)	5 (62.5)
Hypotension	0	2 (25.0)	1 (12.5)	1 (16.7)	3 (50.0)	2 (22.2)	2 (40.0)	4 (57.1)	3 (37.5)
Systolic hypertension	0	0	1 (12.5)	1 (16.7)	0	2 (22.2)	0	0	0
Hypoxia	0	0	0	0	1 (16.7)	2 (22.2)	1 (20.0)	1 (14.3)	1 (12.5)
Tachycardia	0	0	0	0	0	1 (11.1)	1 (20.0)	0	1 (12.5)

Number of subjects with events (incidence [%])

In a retrospective clinical study in non-Japanese pediatric patients aged 0.1 to 19.9 years undergoing MRI, dexmedetomidine was administered at a similar to or higher dose than the dose of the high-dose group in the age group <2 years in Study C0801039 (initial loading dose of 2 or 3 μg/kg over 10 minutes, followed by maintenance dose of 1, 1.5, or 2 μg/kg/h). A decrease in the heart rate or mean

arterial pressure requiring procedure was not observed. There was no relationship between age and the percentage of patients with decreased heart rate below the normal range for each age (*Paediatr Anaesth.* 2008;18:403-11).

Based on the above, the recommendation of the dosage regimen for the high-dose group of subjects aged ≥1 month to <2 years used in Study C0801039 is appropriate for use in patients in this age group, including those aged ≥1 month to <0.4 years without experience with the dosage regimen of the high-dose group in Study C0801039.

PMDA's view:

- Given the justification of the dosage regimen of Study C0801039 and the efficacy and safety results of the study, the dosage regimen for pediatric patients undergoing MRI proposed by the applicant based on the regimen of the high-dose group in Study C0801039 is acceptable.
- However, procedures or examinations other than MRI were out of the scope of Study C0801039. Some of the non-invasive procedures or examinations in non-intubated children (Table 11) may require a lower level of sedation than MRI does, and whether these procedures or examinations need the initial loading dose or a higher dose than for the approved indication is unclear. However, the use of the dosage regimen of the high-dose group in Study C0801039 may be recommended for non-invasive procedures or examinations other than MRI in non-intubated children as well, as long as safety measures are taken, including offering cautions via the package insert that the administration rate should be reduced as appropriate depending on patient condition and that dexmedetomidine must be used under appropriate management.
- Efficacy and safety evaluations in patients aged ≥1 month to <0.4 years based on the results of Study C0801039 has limitation, owing to no experience in this age group with the dosage regimen for the high-dose group of Study C0801039. However, in light of information from sources other than Study C0801039 (pharmacokinetic data in use for the approved indication, safety information from published articles on higher doses than the proposed dosage regimen), the recommendation about the use of the dosage regimen for the high-dose group of subjects aged ≥1 month to <2 years is acceptable in patients aged ≥1 month to <2 years, including those aged ≥1 month to <0.4 years, without use experience with the dosage regimen of the high-dose group in Study C0801039, on the assumption that the earlier-mentioned safety measures are taken.
- In the post-marketing setting, information should be further collected on safety of dexmedetomidine in non-invasive procedures or examinations other than MRI performed in non-intubated patients and in patients aged ≥1 month to <0.4 years.

PMDA will finalize the appropriateness of the above conclusion, taking account of comments raised in the Expert Discussion.

7.R.6 Proper use promotion measures and post-marketing investigations

7.R.6.1 Proper use promotion measures

PMDA asked the applicant to explain recommended medical system and measures to promote proper use of dexmedetomidine intended for "sedation of non-intubated children undergoing non-invasive procedures or examinations" under the recommended system.

The applicant's explanation:
In the global phase III/IV study (Study C0801039) in pediatric patients undergoing MRI, dexmedetomidine administration and patient management were in charged by an anesthesiologist (pediatric anesthesiologist) or a physician with equivalent experience, or, in the presence of a physician qualified as such, by another physician who is proficient in performing pediatric sedation. After the approval of the present application, dexmedetomidine is expected to be used by physicians in various departments including general pediatricians, not to mention anesthesiologists and intensive care specialists, for the purpose of "sedating non-intubated children undergoing non-invasive procedures or examinations" in clinical practice in Japan. The administration of dexmedetomidine involves sedation management as well as circulatory dynamics and respiratory status management, and thus it is preferably in charged by a physician with sufficient knowledge and experience in anesthesia and sedation in children. More specifically, dexmedetomidine is expected to be used by physicians who understand "Joint proposal for sedation in MRI scan [in Japanese]" (*The Journal of the Japan Pediatric Society.* 2020;124:771-805), have attended courses (PALS course, JPLS course, SECURE courses, etc.) provided by various societies or sponsored by medical societies, and have acquired emergency skills to deal with adverse events. It is also recommended that, throughout the administration, the physician should carefully and constantly manage the sedation level and systemic condition of the patient, in the presence of a healthcare professional who is engaged solely in monitoring for systemic condition including conscious state, respiratory state, and circulatory dynamics, besides the healthcare professional who performs the procedure/examination [see Section 7.R.3.2].

The above recommendation will be presented in the package insert to call attention. The following (a) to (c) are the measures to promote the proper use based on the recommendation, which will be implemented in coordination with related academic societies.

(a) Preparation and distribution of reference materials for healthcare professionals (proper use guide)
Reference materials will be prepared for healthcare professionals, distributed and explained to medical facilities to be supplied with dexmedetomidine. The materials will explain the pharmacological action of dexmedetomidine and provide information according to "Joint proposal for sedation in MRI scan [in Japanese]," "Practical guide for safe sedation (revised version, June 2022)" (Japanese Society of Anesthesiologists; 2022), etc., including (1) points for sedation management in non-invasive procedures or examinations in non-intubated children (applicable procedures or examinations, necessity of judging the need of sedative, medical system including as equipment and personnel, etc.); and (2) cautionary advice pertaining to before, during, and after administration (recommended monitoring items, measures to be taken for inadequate sedative effect of dexmedetomidine alone, precautions for concomitant use of other sedatives, etc.).

(b) Proper use promotion program
An e-learning content explaining the above proper use guide will be prepared. Physicians other than anesthesiologists and sedation specialists will be asked to view the e-learning content before using dexmedetomidine. In case the use of dexmedetomidine without viewing the e-learning content or

under an inappropriate management system is identified, the concerned party will be requested to view the e-learning content or to use dexmedetomidine under an appropriate management system.

(c) Surveillance on proper use

In order to evaluate the practice of the use of dexmedetomidine under appropriate medical system, surveillance will be conducted involving physicians other than anesthesiologists and sedation management specialists who have administered dexmedetomidine for the purpose of "sedation of non-intubated children undergoing non-invasive procedures or examinations." The surveillance is will investigate what departments the physicians belong to, attendance history at the proper use promotion program, attendance history at advanced life support training, the presence/absence of the healthcare professional to engage in monitoring of patient's systemic condition during dexmedetomidine administration and their specialty, monitoring system for the systemic condition of patients (use/non-use of monitoring equipment for sedation management/respiratory management/circulatory management), and the availability of appropriate instruments and equipment to effectively respond to emergencies.

PMDA's view:

During MRI, access to the patient inside the MRI scanner is restricted. Magnetic medical devices are kept out of the MRI room and that limits possible emergency measures taken inside the room. For these reasons, adverse drug reactions related to circulatory dynamics or respiratory status can be highly risky particularly in MRI among non-invasive procedures or examinations in non-intubated children. Once becomes available for "non-invasive procedures or examinations in non-intubated children," dexmedetomidine will be used by general pediatricians with no or little experience in the use of dexmedetomidine for the approved indication. Therefore, it is crucial to take measures for the promotion of proper use of dexmedetomidine under an appropriate medical system. Although there is no major problem in the proper use promotion measures proposed by the applicant, the conclusion on the need of additional measures, etc. will be finalized taking account of comments raised in the Expert Discussion.

7.R.6.2 Post-marketing investigations

The applicant plans to conduct use-results surveillance (target sample size, 100 subjects) to investigate the safety, particularly that related to circulatory dynamics and respiratory status, of dexmedetomidine in clinical practice in Japan.

PMDA's view:

Based on the reviews in Sections 7.R.3 and 7.R.5, the investigation of the safety of dexmedetomidine in clinical practice, particularly that related to circulatory dynamics and respiratory status, through the post-marketing surveillance is appropriate. The surveillance should also aim to gather safety data of dexmedetomidine used in combination with other sedatives and of dexmedetomidine used for non-invasive procedures or examinations other than MRI in non-intubated patients. The conclusion on the appropriateness of the post-marketing investigations will be finalized taking account of comments raised in the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. The results and the conclusions of PMDA will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. The results and the conclusion of PMDA will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that dexmedetomidine has a certain level of efficacy in sedation of non-intubated children during non-invasive procedures or examinations, and that dexmedetomidine has acceptable safety in view of its benefits. Dexmedetomidine is clinically meaningful because it offers a novel option as a sedative for non-intubated children undergoing non-invasive procedures or examinations. Efficacy, safety, clinical positioning and indication, dosage regimen, proper use promotion measures, the appropriateness of post-marketing investigations, etc. need to be further discussed at the Expert Discussion.

PMDA has concluded that dexmedetomidine may be approved if dexmedetomidine is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

October 14, 2022

Product Submitted for Approval

Brand Name	Precedex Intravenous Solution 200 μg "Pfizer," Precedex Intravenous Solution 200 μg /50 mL Syringe "Pfizer"
Non-proprietary Name	Dexmedetomidine Hydrochloride
Applicant	Pfizer Japan Inc.
Date of Application	March 30, 2022

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

Based on the reviews in Sections "7.R.1 Plan of global phase III/IV study (Study C0801039)" and "7.R.2 Efficacy" in the Review Report (1), PMDA concluded that in Study C0801039, the primary endpoint "the percentage of subjects not requiring concomitant propofol to complete MRI" was statistically significantly high in the high-dose group as compared with the low-dose group, demonstrating a certain level of efficacy of dexmedetomidine alone in pediatric patients undergoing MRI when administered according to the dosage regimen of the high-dose group. Presumably, however, a certain percentage of patients will not achieve adequate sedation with dexmedetomidine alone, and appropriate advice on the measures for such cases should be offered [See Section 1.2].

This conclusion was supported by the expert advisors at the Expert Discussion.

1.2 Safety

PMDA's view:
The following are the observations on the safety of dexmedetomidine, based on the review in Section "7.R.3 Safety" in the Review Report (1). These conclude that the safety in sedation of non-intubated children undergoing procedures or examinations with dexmedetomidine is manageable, despite the need of attention to its impact particularly on circulatory dynamics and respiratory status, as long as appropriate cautionary advice, i.e., dexmedetomidine must be used by physicians who are proficient in

sedation management in non-intubated children and under a system in which patients are monitored for such possible impact, etc., is offered.

- The occurrence of adverse events in the global phase III/IV study (Study C0801039) and the foreign phase IV study (Study DEX-10-16) does not suggest that dexmedetomidine, when used in non-intubated children undergoing procedures or examinations, may cause adverse events which were not observed in its use for the approved indications or bring concerns specific to Japanese patients.
- Based on the occurrence of adverse events related to circulatory dynamics and respiratory status in Study C0801039, these events are manageable as long as dexmedetomidine is administered carefully under the supervision of a physician who is proficient in sedation management in non-intubated children, and in the presence of a healthcare professional who is engaged in systemic condition monitoring, by whom circulatory dynamics and respiratory status are monitored, while the procedure or examination is performed by another healthcare professional. The concomitant use of other sedatives may increase the risk of adverse events related to circulatory dynamics and respiratory status. Thus, as proposed by the applicant, the package insert should offer advice on extra caution to be exercised in the use of other sedatives, in view of the increased risk of adverse drug reactions by supplementary use of other sedatives.
- Results of Study C0801039, etc. indicate the possibility that dexmedetomidine administered to children undergoing procedures or examinations may prolong time to awakening as compared with barbiturates or midazolam, or dexmedetomidine administered to adults undergoing surgery or procedures. Time to awakening after MRI largely varied among subjects in Study C0801039. Give these findings, the package insert should note the possible delay in time to awakening, along with advice to the effect that patients be placed under supervision until recovery after procedure or examination, as proposed by the applicant.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. At the same time, the following comments were raised by the expert advisors:

- The monitoring items required during dexmedetomidine administration include the respiratory rate, heart rate (pulse rate), blood pressure, ECG, SpO_2, $EtCO_2$, etc. Study C0801039, however, did not reveal the occurrence of apnoea[12)] based on $EtCO_2$ measurements, suggesting that SpO_2 values and respiratory rates will suffice to evaluate respiratory impact. Also, there is a concern that $EtCO_2$ monitoring can be an obstacle in the use of dexmedetomidine for the proposed indication at many medical institutions if it is a requirement. Therefore, whether the package insert should include advice related to $EtCO_2$ monitoring is subject to reconsideration.
- "JCS 2018 Guideline on the Clinical Examinations for Decision Making of Diagnosis and Drug therapy in Pediatric Patients with Congenital Heart Disease and Cardiovascular Disorder, revised version" (Japanese Circulation Society Joint Working Group; 2019) states that dexmedetomidine may cause severe bradycardia when co-administered with calcium antagonists or beta blockers. Because children have less reserve capacity for cardiac contraction (low-age group in particular) than adults, cardiac output depends on heart rate and is largely affected by bradycardia. Whether the package insert needs to offer any caution about the co-administration of dexmedetomidine with calcium antagonists or beta blockers should be discussed.

PMDA's view:
In light of the recommendation on the practice of $EtCO_2$ monitoring by "Joint proposal for sedation in MRI scan [in Japanese]" (*The Journal of the Japan Pediatric Society.* 2020;124:771-805) and "Practical guide for safe sedation (revised version, June 2022)" (Japanese Society of Anesthesiologists; 2022), etc. published by related academic societies, the advice on $EtCO_2$ monitoring will be beneficial. Nevertheless, taking into account the comment of the expert advisors, PMDA suggested that the clinical settings should be advised via the package insert to monitor $EtCO_2$ where possible, in addition to SpO_2, respiratory rate, heart rate (pulse rate), blood pressure, and ECG, to ensure careful patient monitoring during procedures or examinations. The applicant responded appropriately.

PMDA asked the applicant to explain whether the co-administration of dexmedetomidine with calcium antagonists or beta blockers is suggestive of increased risk of adverse events and whether it is necessary to raise caution about such use of dexmedetomidine.

The applicant's explanation:
In Study C0801039 and in the Japanese study (Study C0801017) in pediatric patients requiring sedation in an intensive care setting, concomitant calcium antagonists or beta blockers was used in only a limited number of subjects, precluding conclusion on the impact of these drugs on the onset of adverse events. The post-marketing surveillance on the approved indications has not yielded data showing the influence of cardiovascular drugs to the onset of adverse drug reactions of dexmedetomidine. No published articles were found on the investigation of the risk of adverse events by the co-administration of dexmedetomidine with calcium antagonists or beta blockers. Hence, there is no need to provide caution about the co-administration of dexmedetomidine with calcium antagonists or beta blockers via the package insert. On the other hand, in children (particularly in the low-age group), because of their less reserve capacity for cardiac contraction than in adults, their cardiac output depends on the heart rate and is markedly affected by bradycardia. Caution should be raised about bradycardia in children receiving dexmedetomidine. The package insert will advise that dexmedetomidine should be administered to children under careful observation because of significant effect of bradycardia particularly in lower-age children, whose cardiac output is dependent on heart rate.

PMDA accepted the above measures proposed by the applicant. This conclusion of PMDA was supported by the expert advisors.

1.3 Clinical positioning and indication

PMDA's conclusions:
On the basis of the review in Section "7.R.4 Clinical positioning and indication" described in the Review Report (1), dexmedetomidine may be regarded as one of the sedatives to be used in children undergoing non-invasive procedures or examinations, and the indication of dexmedetomidine "sedation of non-intubated children undergoing non-invasive procedures or examinations," including those other than MRI investigated in the global phase III/IV study (Study C0801039), is acceptable. Meanwhile, the efficacy of dexmedetomidine in procedures or examinations requiring pain relief or local anesthesia or its safety in the co-administration with analgesics or local anesthetics have not been

investigated. The package insert should provide the cautionary note that efficacy and safety have not been established in procedures or examinations requiring pain relief or local anesthesia.

These conclusions were supported by the expert advisors at the Expert Discussion.

PMDA thus instructed the applicant to provide the cautionary note in "Precautions concerning indication" in the package insert that efficacy and safety have not been established in procedures or examinations requiring pain relief or local anesthesia, and the applicant responded appropriately.

1.4 Dosage and administration

Based on the evaluation in Section "7.R.5 Dosage and administration" described in the Review Report (1), PMDA concluded that the dosage regimen of dexmedetomidine for sedation of children undergoing non-invasive procedures or examinations should be determined based on the dosage regimen for the high-dose group in the global phase III/IV study (Study C0801039).

The conclusion was supported by the expert advisors at the Expert Discussion.

1.5 Measures for promoting proper use and post-marketing investigations

Taking account of the review in Section "7.R.6 Proper use promotion measures and post-marketing investigations" in the Review Report (1), PMDA concluded that it is crucial to take measures to promote the proper use of dexmedetomidine under an appropriate medical system, and that there are no major problems with offering advice on recommended medical system in the package insert and implementing the following measures in coordination with related academic societies:

- Preparation and distribution of materials for healthcare professionals (a proper use guide)
- Implementation of the proper use promotion program
- Surveillance on proper use

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. At the same time, the following comment was raised by the expert advisors:

- In the proper use promotion program, the requirements for physicians who use dexmedetomidine should be more clearly defined, including mandatory viewing of e-learning contents for physicians other than anesthesiologists who will use dexmedetomidine for the proposed indication. The applicant should discuss how to verify that physicians are qualified and whether medical facilities have appropriate equipment and system.

Based on the above, PMDA instructed the applicant, in the proper use promotion program, to more clearly define the requirements for physicians who will be using dexmedetomidine for the proposed indication, and to discuss a strategy to verify the eligibility of physicians and medical facilities using dexmedetomidine in terms of the sufficiency of equipment and system.

The applicant's explanation about their action plan:

- In coordination with related academic societies (Japan Pediatric Society and the Japanese Society of Pediatric Anesthesiology), the applicant will define the requirements for facilities, physicians

who will administer sedation, and healthcare professionals to be engaged solely in patient monitoring, which ensure the proper use of dexmedetomidine for the proposed indication.

- The requirements for facilities will include the availability of equipment for monitoring of circulatory dynamics and respiratory status, capability for emergency response, and the availability of a system to allocate a physician qualified to perform sedation and a healthcare professional to be engaged in patient monitoring (see below).
- General pediatricians, etc. with no experience in sedation with dexmedetomidine, unlike anesthesiologists/intensive care specialists/emergency physicians well experienced in the use of dexmedetomidine, must meet all of the following requirements to perform sedation: (1) attendance at a course of emergency medical care for children, familiarity with the emergency medical care and ability to perform it to deal with adverse events; (2) accessibility to support from another physician who is proficient in the use of dexmedetomidine; and (3) attendance at the proper use program (viewing of the e-learning content) and adequate understanding of the safety profile of dexmedetomidine based on its pharmacological characteristics, necessary preparation, and points to be checked before dexmedetomidine administration. The requirements for healthcare professionals to be engaged solely in patient monitoring are: attendance at a course of emergency medical care for children, familiarity with the emergency medical care and ability to perform it to deal with adverse events.
- In the proper use promotion program, every facility to be supplied with dexmedetomidine will be advised to use dexmedetomidine only when the requirements for facilities, physicians who perform sedation, and healthcare professionals to engage in patient monitoring are all met. The applicant must assure that facilities intending to use dexmedetomidine for the proposed indication comply with these requirements. In parallel, a fact-finding survey on the proper use will be conducted. When any incompliance with the requirements is identified in the use of dexmedetomidine for the proposed indication through these activities, the applicant will promptly request for proper use.
- As soon as possible after the approval of dexmedetomidine for the proposed indication, cooperation on the proper use promotion, including the announcement of the requirements for facilities, physicians who perform sedation, and healthcare professionals to engage in patient monitoring, as well as the proper use promotion program, will be requested through the related academic societies (Japan Pediatric Society and the Japanese Society of Pediatric Anesthesiology)

PMDA accepted the measures proposed by the applicant, and this conclusion was supported by the expert advisors.

1.6 Risk management plan (draft)

Based on the discussion in Section "7.R.6 Proper use promotion measures and post-marketing investigations" in the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for dexmedetomidine should include the safety specification presented in Table 15, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 16.

Table 15. Safety and efficacy specifications in the risk management plan (draft) [a)]

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Bradycardia • Hypotension • Hypertension • Hyperglycaemia • Withdrawal syndrome • Respiratory depression	• Atrioventricular block • Cardiac arrest • Convulsion • Cortisol suppression • Hypothermia • Ischaemic heart disease • Tachypnoea	• Safety in co-administration of other sedatives in children
Efficacy specification		
None		

a) Include safety and efficacy specifications relevant to the present application only.

Table 16. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft) [a)]

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals (a proper use guide) • Implement the proper use promotion program

a) Include additional pharmacovigilance activities and additional risk minimization activities relevant to the present application only.

PMDA instructed the applicant to conduct post-marketing surveillance to investigate the safety and efficacy specifications.

The applicant explained their plan for the specified use-results survey shown in Table 17.

Table 17. Outline of specified use-results survey (draft)

Objective	To investigate safety in clinical practice
Survey method	Sequential survey method
Population	Pediatric patients (≥1 month to <18 years of age) receiving dexmedetomidine for "sedation of non-intubated children undergoing non-invasive procedures or examinations"
Observation period	From patient evaluation before the start through the end of dexmedetomidine administration or up to 1 hour after discontinuation
Target sample size	100 patients for safety analysis
Main survey items	• Patient characteristics (sex, age [including months in those <2 years of age]), body weight, procedures/examinations requiring sedation with dexmedetomidine, medical history (prior and concurrent), etc. • Use of dexmedetomidine (administration rate, reason for change in the administration rate, etc.) • Use of concomitant drugs (name of the drug, route of administration, etc.) • Occurrence of adverse events

PMDA accepted the above plan.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA concluded that the product may be approved for the indications and the dosage and administration as shown below, with the following approval condition. Because the product is designated as a specific use drug, the re-examination period for the indications and the dosage and administration of the present application should be 5 years and 10 months.

Indications

Sedation during and after mechanical ventilation in an intensive care setting
Sedation of non-intubated adult patients during surgical and other procedures under local anesthesia
Sedation of non-intubated pediatric patients during non-invasive procedures or examinations

(Underlines denote addition.)

Dosage and administration

1. Sedation during and after mechanical ventilation in an intensive care setting

Adults: Usually, dexmedetomidine is infused intravenously at 6 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 0.2 to 0.7 μg/kg/h as maintenance dose to achieve the optimal sedation level depending on the patient's condition (maintenance administration). The administration may be started with the maintenance dose.
Children aged ≥6 years: Usually, dexmedetomidine is infused intravenously at 0.2 μg/kg/h continuously, followed by a continuous infusion at 0.2 to 1.0 μg/kg/h to achieve the optimal sedation level depending on the patient's condition.
Children with corrected gestational age (gestational age + postnatal age) of ≥45 weeks to <6 years postpartum: Usually, dexmedetomidine is infused intravenously at 0.2 μg/kg/h continuously, followed by a continuous infusion at 0.2 to 1.4 μg/kg/h to achieve the optimal sedation level depending on the patient's condition.
The infusion rate should be decreased depending on the patient's condition.

2. Sedation of non-intubated adult patients during surgical and other procedures under local anesthesia

Adults: Usually, dexmedetomidine is infused intravenously at 6 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 0.2 to 0.7 μg/kg/h as maintenance dose to achieve the optimal sedation level (maintenance administration). The infusion rate should be decreased depending on the patient's condition.

3. Sedation of non-intubated pediatric patients during non-invasive procedures or examinations

Children aged ≥2 years: Usually, dexmedetomidine is infused intravenously at 12 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 1.5 μg/kg/h as maintenance dose (maintenance administration).
Children aged ≥1 month to <2 years: Usually, dexmedetomidine is infused intravenously at 9 μg/kg/h continuously over 10 minutes (initial loading administration), followed by a continuous infusion at 1.5 μg/kg/h as maintenance dose (maintenance administration).
The infusion rate should be decreased depending on the patient's condition.

(Underlines denote addition.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ASA	American Society of Anesthesiologists
CI	Confidence Interval
CL_w	Weight-adjusted Clearance
C_{max}	Maximum Concentration
CT	Computed Tomography
CTD	Common Technical Document
Dexmedetomidine	Dexmedetomidine hydrochloride
$EtCO_2$	End-tidal Carbon Dioxide
FAS	Full Analysis Set
FDA	Food and Drug Administration
MRI	Magnetic Resonance Imaging
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population Pharmacokinetics
PREA	Pediatric Research Equity Act
Precedex	Precedex Intravenous Solution 200 μg "Pfizer," Precedex Intravenous Solution 200 μg/50 mL Syringe "Pfizer"
PSSS	Pediatric Sedation State Scale
SpO_2	Saturation of Peripheral Oxygen
TTE	Transthoracic Echocardiogram
$V_{c,w}$	Weight-adjusted Volume of distribution of the central compartment