Report on the Deliberation Results

June 3, 2019

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

Brand Name	Intuniv Tablets 1 mg Intuniv Tablets 3 mg
Non-proprietary Name	Guanfacine Hydrochloride (JAN*)
Applicant	Shionogi & Co., Ltd.
Date of Application	August 10, 2018

Results of Deliberation

In its meeting held on May 28, 2019, the First Committee on New Drugs 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 for the present application is the remainder of the re-examination period for the initial approval of the product (until March 29, 2025).

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

April 25, 2019
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	Intuniv Tablets 1 mg Intuniv Tablets 3 mg
Non-proprietary Name	Guanfacine Hydrochloride
Applicant	Shionogi & Co., Ltd.
Date of Application	August 10, 2018
Dosage Form/Strength	Tablets: Each tablet contains 1.14 mg of Guanfacine Hydrochloride (1 mg as guanfacine) or 3.42 mg of Guanfacine Hydrochloride (3 mg as guanfacine).
Application Classification	Prescription drug, (4) Drug(s) with a new indication and (6) Drug(s) with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of attention-deficit/hyperactivity disorder (AD/HD) in adults, 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 indication and dosage and administration shown below, with the following condition.

Indication

Attention-deficit/hyperactivity disorder (AD/HD) ~~in pediatric patients~~

(Strikethrough denotes deletions.)

Dosage and Administration

Patients aged <18 years:

The usual starting dose for patients aged <18 years is 1 mg/day of guanfacine administered to ~~pediatric~~ patients weighing <50 kg or 2 mg/day of guanfacine administered to ~~pediatric~~ patients weighing ≥50 kg. The dose should be increased to the maintenance dose in the table below in increments of 1 mg at intervals of ≥1 week.

The dose may be adjusted according to the symptom. The daily dose should not exceed the maximum dose in the table below. Guanfacine should be administered orally once daily.

Body weight	Starting dose	Maintenance dose	Maximum dose
≥17 kg and <25 kg	1 mg	1 mg	2 mg
≥25 kg and <34 kg	1 mg	2 mg	3 mg
≥34 kg and <38 kg	1 mg	2 mg	4 mg
≥38 kg and <42 kg	1 mg	3 mg	4 mg
≥42 kg and <50 kg	1 mg	3 mg	5 mg
≥50 kg and <63 kg	2 mg	4 mg	6 mg
≥63 kg and <75 kg	2 mg	5 mg	6 mg
≥75 kg	2 mg	6 mg	6 mg

Patients aged ≥18 years:

The usual starting dose for patients aged ≥18 years is 2 mg/day of guanfacine administered. The dose should be increased to the maintenance dose of 4 to 6 mg/day in increments of 1 mg at intervals of ≥1 week.

The dose may be adjusted according to the symptom. The daily dose should not exceed 6 mg. Guanfacine should be administered orally once daily.

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Condition

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

Attachment

Review Report (1)

March 7, 2019

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	Intuniv Tablets 1 mg Intuniv Tablets 3 mg
Non-proprietary Name	Guanfacine Hydrochloride
Applicant	Shionogi & Co., Ltd.
Date of Application	August 10, 2018
Dosage Form/Strength	Tablets: Each tablet contains 1.14 mg of Guanfacine Hydrochloride (1 mg as guanfacine) or 3.42 mg of Guanfacine Hydrochloride (3 mg as guanfacine).
Proposed Indication	Attention-deficit/hyperactivity disorder (AD/HD) ~~in pediatric patients~~ (Strikethrough denotes deletions.)

Proposed Dosage and Administration

Patients aged <18 years:

The usual starting dose for patients aged <18 years is 1 mg/day of guanfacine administered to ~~pediatric~~ patients weighing <50 kg or 2 mg/day of guanfacine administered to ~~pediatric~~ patients weighing ≥50 kg. The dose should be increased to the maintenance dose in the table below in increments of 1 mg at intervals of ≥1 week.

The dose may be adjusted according to the symptom. The daily dose should not exceed the maximum dose in the table below. Guanfacine should be administered orally once daily.

Body weight	Starting dose	Maintenance dose	Maximum dose
≥17 kg and <25 kg	1 mg	1 mg	2 mg
≥25 kg and <34 kg	1 mg	2 mg	3 mg
≥34 kg and <38 kg	1 mg	2 mg	4 mg
≥38 kg and <42 kg	1 mg	3 mg	4 mg
≥42 kg and <50 kg	1 mg	3 mg	5 mg
≥50 kg and <63 kg	2 mg	4 mg	6 mg
≥63 kg and <75 kg	2 mg	5 mg	6 mg
≥75 kg	2 mg	6 mg	6 mg

Patients aged ≥18 years:

The usual starting dose for patients aged ≥18 years is 2 mg/day of guanfacine administered. The dose should be increased to the maintenance dose of 4 to 6 mg/day in increments of 1 mg at intervals of ≥1 week.

The dose may be adjusted according to the symptom. The daily dose should not exceed 6 mg. Guanfacine should be administered orally once daily.

(Underline denotes additions. Strikethrough denotes deletions.)

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List of Abbreviations

See Appendix.

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

Guanfacine hydrochloride (hereinafter referred to as "guanfacine") is a 2,6-dichlorophenylacetate derivative selectively activating the adrenergic α_{2A} receptor and is an extended-release tablet containing guanfacine as the active ingredient. In Japan, guanfacine was approved for the indication of "attention-deficit/hyperactivity disorder (AD/HD) in pediatric patients" in March 2017. In Japan, Estulic Tablets 0.5 mg, an immediate-release preparation containing guanfacine as the active ingredient, was approved as a drug for the treatment of essential hypertension in 1984 but withdrawn from the market in 2005 owing to a commercial issue and removed from the National Health Insurance drug price list in 2007.

As of March 2018, guanfacine is approved for the treatment of AD/HD in children in 35 countries including the US and European countries, but it has not been approved for AD/HD in adults in any country or region.

In Japan, a clinical study for AD/HD in adults was initiated in [redacted] 20[redacted], and the applicant has submitted a partial change application based on the documented efficacy and safety of guanfacine in the treatment of AD/HD in adults.

In Japan, methylphenidate hydrochloride extended-release tablets and atomoxetine hydrochloride are approved for the indication of AD/HD in adults.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no quality data have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacology data were previously evaluated for the initial approval of guanfacine, and no new study data have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacokinetics data were previously evaluated for the initial approval of guanfacine, and no new study data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, the toxicity data were previously evaluated for the initial approval of guanfacine, and no new study 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 biopharmaceutics data have been submitted in this application.

Plasma guanfacine concentrations were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation, 0.05 ng/mL). In major clinical studies of guanfacine, the proposed commercial drug product (guanfacine 3 mg tablets) and the drug products for clinical studies (guanfacine 2 mg and 4 mg tablets) were used. Although guanfacine 2 mg tablets and 4 mg tablets are different from 3 mg tablets in shape, these drug products were demonstrated to have a similar dissolution behavior and bioavailability when administered in the fasted state.

6.2 Clinical pharmacology

The applicant submitted pharmacokinetic study data in Japanese healthy adults (Common Technical Document [CTD] 5.3.3.1-01, Study A3112) as evaluation data. Unless otherwise specified, an administered dose of guanfacine is equivalent to the amount of guanfacine, and of pharmacokinetic parameters, t_{max} is expressed as a median, and the other values are expressed as mean ± standard deviation (SD).

6.2.1 Investigation in Japanese healthy adults (CTD 5.3.3.1-01, Study A3112)

Table 1 shows pharmacokinetic parameters of plasma guanfacine in Japanese healthy adults following repeated oral doses of guanfacine 2, 4, 6, 7 or 8 mg once daily in a dose-escalating manner for 5 days (8 subjects included in pharmacokinetic evaluation). In a clinical pharmacology study (attached document for the initial application CTD 5.3.3.1-01, Study A3111) in which guanfacine was orally administered at 1, 2, 3 or 4 mg/day, C_{max} values were 1.66 ± 0.36, 3.05 ± 0.95, 5.60 ± 2.13, and 7.06 ± 2.98 ng/mL, respectively; and $AUC_{0\text{-}24h}$ values were 27.6 ± 5.80, 52.1 ± 18.3, 94.2 ± 36.6, and 115 ± 50.5 ng·h/mL, respectively. Based on these data, the applicant considered that the pharmacokinetic parameters of plasma guanfacine were roughly proportional to the dose.

Table 1. Pharmacokinetic parameters of plasma guanfacine in Japanese healthy adults following repeated oral doses of guanfacine

Dose (mg)	No. of subjects evaluated	C_{max} (ng/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (ng·h/mL)
2	8	2.70 ± 0.552	5.00	46.08 ± 10.47
4	8	7.71 ± 3.30	6.50	139.4 ± 58.16
6	8	11.7 ± 2.44	8.00	213.0 ± 45.79
7	8	12.2 ± 4.13	5.00	220.6 ± 83.44
8	8	14.6 ± 5.25	6.50	263.4 ± 98.31

Mean ± SD
a) Median

6.R Outline of the review conducted by PMDA

PMDA has concluded that no particular problems are found in the submitted investigation results.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from clinical studies listed in Table 2.

Table 2. List of clinical studies for efficacy and safety

Data category	Geographical location	Study Identity CTD	Phase	Study population	No. of subjects	Dosage regimen	Major endpoints
Evaluation	Japan	A3112 5.3.3.1-01	I	Healthy adults	12	Placebo or guanfacine 2-8 mg/day orally once daily for 37 days	Safety Pharmaco-kinetics
		A3132 5.3.5.1-01	III	Patients with AD/HD aged ≥18 years	201	Oral administration once daily Dose optimization period (5 weeks): Placebo or guanfacine titrated from 2 mg/day to 4 mg/day in 1 mg/day increments every week, followed by 4-6 mg/day in accordance with the dose-titration criteria. Dose maintenance period (5 weeks): continue at the last dose from the dose optimization period.	Efficacy Safety
		A3133 (long-term treatment study) 5.3.5.2-02	III	Patients with AD/HD aged ≥18 years	191	50-week oral administration once-daily Guanfacine titrated from 2 mg/day to 4 mg/day in 1 mg/day increments every week, followed by 4-6 mg/day in accordance with the dose-titration criteria.	Efficacy Safety

7.1 Japanese phase I study (CTD 5.3.3.1-01, Study A3112 [[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese healthy adults (target sample size, 12 subjects [9 in the guanfacine group, 3 in the placebo group]) to investigate the safety and pharmacokinetics of guanfacine orally administered once daily [for the pharmacokinetics, see Section 6.2.1].

In the treatment period, placebo or guanfacine 2 to 8 mg/day was orally administered once daily in the fasted state for 25 days (guanfacine was started at 2 mg/day, and the dose was increased to 4, 6, 7, and 8 mg/day every 5 days). The treatment period was followed by a 12-day tapering period (the dose was reduced to 7, 6, 4, and 2 mg/day every 3 days before withdrawal).

All of the 12 randomized subjects (3 in the placebo group, 9 in the guanfacine group) were included in the safety analysis.

Adverse events[1)] (including abnormal laboratory values) occurred in 66.7% (2 of 3) of subjects in the placebo group and 77.8% (7 of 9) of subjects in the guanfacine group. No deaths occurred. Other serious adverse event occurred in 1 subject in the guanfacine group (acute psychosis), but a causal relationship to the study drug was denied.

Adverse events (including abnormal laboratory values) for which a causal relationship to the study drug could not be ruled out occurred in 0% (0 of 3) of subjects in the placebo group and 55.6% (5 of 9) of

1) Medical Dictionary for Regulatory Activities Japanese Version (MedDRA/J) version 19.0

subjects in the guanfacine group. The major events were orthostatic hypotension (0 subjects in the placebo group, 3 subjects in the guanfacine group) and dizziness postural (0 subjects, 2 subjects).

For vital signs (blood pressure and pulse rate), changes from baseline in systolic blood pressure and diastolic blood pressure in a supine position were −3.3 and −4.3 mmHg in the placebo group and −1.3 and −5.3 mmHg in the guanfacine group (2 mg), respectively, at 4 hours after the first dose; and 1.3 and 5.0 mmHg in the placebo group and −3.3 and −4.8 mmHg in the guanfacine group (8 mg), respectively, at 4 hours post-dose on Day 25. Changes from baseline in pulse rate in a supine position were −1.0 beats per minute (bpm) in the placebo group and −0.1 bpm in the guanfacine group (2 mg) at 4 hours after the first dose; and −3.3 bpm in the placebo group and −11.8 bpm in the guanfacine group (8 mg) at 4 hours post-dose on Day 25. In electrocardiograms, there were no clinically significant abnormal findings.

Based on the above, the applicant explained that guanfacine was considered to raise no remarkable safety problem when guanfacine was orally administered once daily at 2 to 8 mg/day to Japanese healthy adults.

7.2 Japanese phase III study (CTD 5.3.5.1-01, Study A3132 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients aged ≥18 years diagnosed with AD/HD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[2)] (target sample size, 190 patients [95 per group]) to investigate the efficacy and safety of guanfacine.

In the dose optimization period (5 weeks), oral administration of placebo or guanfacine (2 mg/day) was started, and the dose was increased to 4 mg/day in increments of 1 mg/day every week, and then adjusted to 4 to 6 mg/day in accordance with the dose-titration criteria.[3)] In the dose maintenance period, the last dose of the dose optimization period was continued orally for 5 weeks. The treatment period was followed by the 2-week tapering period in which the dose was reduced to 2 mg/day in increments of 1 mg/day at intervals of ≥3 days before withdrawal. In addition, patients who wished to continue

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2) Patients meeting the following major inclusion criteria were included in the study: (1) patient who underwent an interview using the Japanese version of Conners' Adult ADHD Diagnostic Interview for DSM-IV™ (CAADID) and diagnosed with AD/HD (main disease requiring outpatient medical care) according to DSM-5 at screening and in childhood; (2) patient who has a total score ≥24 on the Japanese version of Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) with adult prompts and ≥2 scores on ≥5 items on inattention or hyperactivity-impulsivity subscales at baseline; and (3) patient who has a Clinical Global Impression-Severity of Illness (CGI-S) score ≥4 (moderate severity) at baseline.

3) (1) The dose was increased to 3 mg/day and 4 mg/day at Week 1 and Week 2, respectively. If the dose cannot be increased, the study treatment should be discontinued.
(2) If blood pressure and pulse rate meet any of the following (a) to (c) and (d), the dose should not be increased ([a] systolic blood pressure ≤90 mmHg and a decrease of ≥20 mmHg from baseline; [b] diastolic blood pressure ≤50 mmHg and a decrease of ≥15 mmHg from baseline; [c] pulse rate ≤50 bpm and a decrease of ≥15 bpm from baseline; and [d] newly occurring and persistent subjective symptoms related to any of [a] to [c]).
(3) If the investigator or subinvestigator determines that the subject has no particular safety problems at Week 3 and thereafter (until the end of the dose optimization period in Study A3132) (and Clinical Global Impression-Global Improvement [CGI-I] score ≥3 [mildly improved] in Study A3132), the dose can be increased by 1 mg/day ≥5 days after the previous dose increase.
(4) If the investigator or subinvestigator determines that the dose cannot be increased in light of the safety of the subject receiving guanfacine at Week 2 and thereafter, either measure of (a) or (b) should be taken as described below: (a) if the current dose can be maintained, the treatment should be continued at the same dose; or (b) if the current dose, i.e. ≥5 mg/day, cannot be maintained, the treatment should be continued at a dose reduced by 1 mg/day (the dose is reduced only once in Study A3132). Once reduced, the dose is not allowed to be increased again in Study A3132.
(5) If the investigator or subinvestigator determines that the subject has safety problems at doses of 2 to 4 mg/day (or after a dose-reduction in Study A3132), the treatment should be discontinued.

guanfacine were allowed to be transferred to the Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133) after the tapering period.

All of 201 randomized patients (100 in the placebo group, 101 in the guanfacine group) were included in the safety analysis, and 200 patients (100 patients, 100 patients), excluding 1 patient with no available data, were included in full analysis set (FAS) of the efficacy analysis population. A total of 31 patients (7 patients, 24 patients) discontinued the study treatment. The main reasons for discontinuation were adverse event in 24 patients (3 patients, 21 patients) and consent withdrawal in 4 patients (1 patient, 3 patients).

Table 3 shows the primary endpoint of the change from baseline in total score on the Japanese version of the Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) with adult prompts[4)] at Week 10 in the FAS. A statistically significant difference was observed between the placebo group and the guanfacine group ($P = 0.0005$, analysis in mixed-effects models for repeated measures [MMRM] [covariance structure of the error variance, unstructured] using the dose group, evaluation timepoints, and interaction between the dose group and evaluation timepoint as fixed effects and the total score of the ADHD-RS-IV with adult prompts at baseline [<30 or ≥30] and AD/HD disease type [mixed type, predominantly inattentive type, or predominantly hyperactive-impulsive type] as covariates).

Table 3. Change from baseline in total score on the Japanese version of the ADHD-RS-IV with adult prompts at Week 10 (FAS, MMRM)

	Total score on the Japanese version of the ADHD-RS-IV with adult prompts		Change from baseline[a)b)]	vs. placebo[b)]	
	Baseline	Last evaluation		Difference between groups [95% CI]	*P* value
Placebo	31.70 ± 6.83 (100)	23.55 ± 10.29 (93)	−7.27 ± 1.07		
Guanfacine	31.45 ± 5.92 (100)	19.53 ± 9.45 (79)	−11.55 ± 1.10	−4.28 [−6.67, −1.88]	0.0005

Mean ± SD (No. of patients evaluated)

a) Adjusted mean ± standard error (SE)

b) MMRM analysis (covariance structure of the error variance, unstructured) using the dose group, evaluation timepoints, and interaction between the dose group and evaluation timepoint as fixed effects and the total score of the ADHD-RS-IV with adult prompts at baseline (<30 or ≥30) and AD/HD disease type (mixed type, predominantly inattentive type, or predominantly hyperactive-impulsive type) as covariates.

Adverse events[1)] (including abnormal laboratory values) occurred in 62.0% (62 of 100) of patients in the placebo group and 81.2% (82 of 101) of patients in the guanfacine group. No deaths occurred, and other serious adverse event occurred in 1 patient (suicide attempt) in the guanfacine group, but a causal relationship to the study drug was denied.

Adverse events (including abnormal laboratory values) for which a causal relationship to the study drug could not be ruled out occurred in 19.0% (19 of 100) of patients in the placebo group and 71.3% (72 of 101) of patients in the guanfacine group. Major events were somnolence (7 patients in the placebo group, 33 patients in the guanfacine group), blood pressure decreased (2 patients, 21 patients), thirst (0 patients, 20 patients), dizziness postural (1 patient, 15 patients), constipation (1 patient, 9 patients), dizziness (0 patients, 8 patients), bradycardia (0 patients, 8 patients), nausea (3 patients, 3 patients), orthostatic

4) It is an 18-item scale based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for AD/HD (9 items each in subscale score for inattentive symptoms and hyperactive-impulsive symptoms). Scoring is based on a 4-point scale from 0 (no or negligible symptoms) to 3.

hypotension (0 patients, 5 patients), sinus bradycardia (1 patient, 4 patients), headache (2 patients, 3 patients), hypotension (0 patients, 4 patients), malaise (3 patients, 1 patient), and heart rate decreased (0 patients, 3 patients).

For vital signs (blood pressure and pulse rate), clinically significant changes[5)] observed were blood pressure systolic increased (9 patients, 6 patients), blood pressure systolic decreased (5 patients, 31 patients), blood pressure diastolic increased (16 patients, 13 patients), blood pressure diastolic decreased (6 patients, 41 patients), pulse rate increased (9 patients, 4 patients), and pulse rate decreased (0 patients, 1 patient). In electrocardiograms, clinically significant abnormal findings[6)] were sinus bradycardia (0 patients, 1 patient) and electrocardiogram QT prolonged (0 patients, 1 patient).

Based on the above, the applicant explained that the efficacy of guanfacine at 4 to 6 mg/day was demonstrated in the treatment of patients with AD/HD aged ≥18 years and considered to raise no major safety problems.

7.3 Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in patients who completed the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and in newly enrolled patients with AD/HD aged ≥18 years (target sample size, 190 patients) to investigate the safety and efficacy of long-term treatment with guanfacine.

In the treatment period, oral administration of guanfacine was started at 2 mg/day, and the dose was increased to 4 mg/day in increments of 1 mg/day every week, and then adjusted within a range from 4 to 6 mg/day every week in accordance with the dose-titration criteria[3)] for 50 weeks once daily. In the subsequent 2-week tapering period, the dose was reduced to 2 mg/day in increments of 1 mg/day at intervals of ≥3 days before withdrawal. All of 191 patients treated (150 patients continued from the previous study, 41 newly enrolled patients) were included in the FAS for safety and efficacy analyses. A total of 67 patients (55 patients, 12 patients) discontinued the study treatment. The main reasons for discontinuation were adverse events in 38 patients (28 patients, 10 patients), inadequate response in 15 patients (14 patients, 1 patient), and consent withdrawal in 10 patients (9 patients, 1 patient).

Table 4 shows the efficacy endpoint of the changes in total score on the Japanese version of the ADHD-RS-IV with adult prompts.

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5) For vital signs, a clinically significant change was defined as ≥1 occurrence of any of the following events:
- Blood pressure systolic increased, ≥140 mmHg and increased by ≥5 mmHg from baseline
- Blood pressure systolic decreased, <90 mmHg and decreased by ≥5 mmHg from baseline
- Blood pressure diastolic increased, ≥85 mmHg and increased by ≥5 mmHg from baseline
- Blood pressure diastolic decreased, ≤55 mmHg and decreased by ≥5 mmHg from baseline
- Pulse rate increased, ≥100 bpm and increased by ≥5 bpm from baseline
- Pulse rate decreased, <40 bpm and decreased by ≥5 bpm from baseline

6) Electrocardiogram abnormal finding assessed at the last measurement timepoint

Table 4. Change in total score on the Japanese version of the ADHD-RS-IV with adult prompts (FAS)

	Continued from the previous study		Newly enrolled	All subjects
	Placebo[a)]	Guanfacine[a)]		
Baseline	24.76 ± 10.54 (88)	22.31 ± 10.47 (62)	32.80 ± 5.94 (41)	25.69 ± 10.42 (191)
Week 1	23.43 ± 10.50 (88)	20.82 ± 9.36 (62)	30.66 ± 6.25 (41)	24.14 ± 9.99 (191)
Week 2	22.33 ± 10.64 (83)	19.64 ± 8.98 (61)	27.56 ± 7.62 (41)	22.60 ± 9.89 (185)
Week 3	21.18 ± 11.23 (80)	18.82 ± 9.62 (61)	26.39 ± 7.35 (38)	21.48 ± 10.30 (179)
Week 4	20.33 ± 11.56 (73)	18.14 ± 9.22 (58)	24.46 ± 7.58 (37)	20.48 ± 10.22 (168)
Week 5	19.14 ± 11.21 (72)	16.83 ± 8.88 (58)	21.81 ± 7.78 (37)	18.93 ± 9.86 (167)
Week 6	18.54 ± 10.95 (68)	16.07 ± 9.08 (55)	20.68 ± 6.94 (37)	18.19 ± 9.62 (160)
Week 10	17.46 ± 11.21 (63)	15.84 ± 8.95 (55)	19.22 ± 6.91 (36)	17.29 ± 9.58 (154)
Week 18	17.61 ± 11.39 (57)	14.49 ± 8.24 (51)	17.35 ± 7.07 (34)	16.43 ± 9.46 (142)
Week 26	17.15 ± 11.55 (53)	13.17 ± 8.22 (48)	16.53 ± 8.52 (32)	15.56 ± 9.85 (133)
Week 38	16.55 ± 12.19 (49)	12.13 ± 7.32 (47)	14.97 ± 8.06 (31)	14.53 ± 9.77 (127)
Week 50	15.82 ± 11.69 (49)	11.80 ± 7.43 (45)	13.93 ± 8.42 (29)	13.90 ± 9.64 (123)
Last evaluation	18.82 ± 11.06 (88)	14.44 ± 9.26 (62)	16.27 ± 9.68 (41)	16.85 ± 10.35 (191)

Mean ± SD (No. of patients evaluated)
a) Dose group in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132)

Adverse events (including abnormal laboratory values)[1)] occurred in 94.2% (180 of 191) of patients, but no deaths occurred. Serious adverse events other than deaths occurred in 2 patients (acute myeloid leukaemia and supraventricular tachycardia in 1 patient each).

Adverse events (including abnormal laboratory values) for which a causal relationship to guanfacine could not be ruled out occurred in 83.8% (160 of 191) of patients. Major events were somnolence (77 patients), thirst (58 patients), blood pressure decreased (38 patients), dizziness postural (34 patients), bradycardia (33 patients), malaise (29 patients), constipation (18 patients), dizziness (17 patients), nausea (9 patients), orthostatic hypotension (8 patients), headache (8 patients), dry mouth (6 patients), insomnia (4 patients), and sleep disorder (4 patients).

For vital signs (blood pressure and pulse rate), clinically significant changes[5)] observed were blood pressure systolic increased (15 patients, 7 patients), blood pressure systolic decreased (42 patients, 7 patients), blood pressure diastolic increased (31 patients, 14 patients), blood pressure diastolic decreased (60 patients, 17 patients), pulse rate increased (13 patients, 5 patients), and pulse rate decreased (1 patient, 0 patients). In electrocardiograms, clinically significant abnormal findings[6)] were bradycardia in 5 patients (5 patients, 0 patients).

Based on the above, the applicant explained that the long-term treatment was considered to raise no major safety problems and maintain the efficacy of guanfacine when administered at 4 to 6 mg/day to patients with AD/HD aged ≥18 years.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Assessment of AD/HD symptoms in Japanese phase III studies

In the Japanese phase III study (CTD 5.3.5.1-01, Study A3132), the Japanese version of the ADHD-RS-IV with adult prompts was selected to evaluate the primary efficacy endpoint. PMDA asked the applicant to explain the rationale and appropriateness of this selection as well as the reliability and validity of assessing AD/HD symptoms based on the Japanese version of the ADHD-RS-IV with adult prompts.

The applicant's explanation about the concerned selection:
In Japan, confirmatory studies had been conducted using the Japanese version of the Conners' Adult ADHD Rating Scale (CAARS)-Screening Version to evaluate the primary efficacy endpoint in adult patients with AD/HD. However, at the time of developing guanfacine for adult patients, the Japanese version of the CAARS long form was being widely used, and the Screening Version was no longer acceptable for clinical studies. The CAARS long form is composed of 66 items and is difficult to be used in assessing the symptoms of the study subject on every visit, but the ADHD-RS-IV with adult prompts is composed of 18 items based on the AD/HD diagnosis criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and enables patient assessment on each visit. In light of the above, the ADHD-RS-IV with adult prompts was selected for evaluation of the primary endpoint in Study A3132. Given that the ADHD-RS-IV with adult prompts had been validated outside Japan, its Japanese translation was prepared, and the accuracy of translation was confirmed before the start of study. Furthermore, a validation study was conducted in adult patients with AD/HD and healthy adults, thereby demonstrating intra-rater and inter-rater reliability and validity of the Japanese version of the ADHD-RS-IV with adult prompts (*Clinical psychiatry.* 2018;60:399-409).

Before the start of Study A3132, investigators and subinvestigators received training on the use of this assessment scale to minimize inter-rater variability.

Based on the above, assessment according to the Japanese version of the ADHD-RS-IV with adult prompts in Study A3132 was appropriate.

PMDA concluded that there is no major problem with choosing the Japanese version of the ADHD-RS-IV with adult prompts as the primary endpoint in Study A3132 because reliability and validity of the Japanese version of the ADHD-RS-IV with adult prompts was demonstrated, the assessment procedure was standardized prior to the study, and appropriate measures were taken to minimize variability.

7.R.1.2 Effects of sedation on efficacy evaluation

Sedation-related adverse events were reported in patients receiving guanfacine [see Section 7.R.2.3]. PMDA asked the applicant to explain whether the concerned events might have resulted in spurious improvement, affecting the efficacy evaluation of guanfacine.

The applicant's explanation:
Table 5 shows the results of change from baseline to Week 10 in total score and each subscale score of the ADHD-RS-IV with adult prompts in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) examined by the presence of sedation-related adverse events.[7)] In the guanfacine group, the changes tended to be greater in the subgroup of patients with sedation-related adverse events than those in the subgroup without such events, and the changes in the subgroup without such events were still greater than those in the placebo group, indicating considerable improvement. The inattention subscale score of

7) Events that fall under the following MedDRA preferred terms (PTs):
Somnolence, sedation, fatigue, lethargy, asthenia, hypersomnia, malaise, apathy, decreased activity, listless, and sluggishness

the ADHD-RS-IV with adult prompts is presumed to worsen due to sedation-related adverse events, but the score actually improved in the subgroup with such events in the guanfacine group. This finding, thereby suggesting the efficacy of guanfacine irrespective of such events rather than sedation-related adverse events concealed the AD/HD symptoms and lead to spurious improvements in the guanfacine group.

Table 5. Mean change from baseline to Week 10 in total score and each subscale score of the ADHD-RS-IV with adult prompts by presence of sedation-related adverse events in Study A3132 (FAS, MMRM)

				Score[a]		Change from baseline[b]
				Baseline	Week 10	
Total score	Placebo			31.70 ± 6.83 (100)	23.55 ± 10.29 (93)	−7.27 ± 1.07
	Guanfacine	Overall population		31.45 ± 5.92 (100)	19.53 ± 9.45 (79)	−11.55 ± 1.10
		Sedation-related adverse events	Yes	31.26 ± 6.25 (35)	15.78 ± 8.57 (27)	−15.65 ± 1.60
			No	31.55 ± 5.78 (65)	21.48 ± 9.37 (52)	−9.45 ± 1.25
Inattention subscale score	Placebo			21.88 ± 3.53 (100)	16.62 ± 6.46 (93)	−4.89 ± 0.76
	Guanfacine	Overall population		21.24 ± 3.42 (100)	13.82 ± 6.39 (79)	−7.39 ± 0.79
		Sedation-related adverse events	Yes	20.89 ± 4.03 (35)	11.33 ± 5.86 (27)	−9.46 ± 1.15
			No	21.43 ± 3.06 (65)	15.12 ± 6.32 (52)	−6.34 ± 0.90
Hyperactivity-impulsivity subscale score	Placebo			9.82 ± 5.84 (100)	6.92 ± 5.84 (93)	−2.10 ± 0.52
	Guanfacine	Overall population		10.21 ± 5.60 (100)	5.71 ± 5.03 (79)	−3.84 ± 0.54
		Sedation-related adverse events	Yes	10.37 ± 5.79 (35)	4.44 ± 4.39 (27)	−5.85 ± 0.75
			No	10.12 ± 5.54 (65)	6.37 ± 5.26 (52)	−2.74 ± 0.61

a) Mean ± SD (No. of patients evaluated)
b) Adjusted mean ± SE
MMRM analysis (covariance structure of the error variance, unstructured) using the dose group, evaluation timepoints, and interaction between the dose group and evaluation timepoint as fixed effects and the total score of the ADHD-RS-IV with adult prompts at baseline (<30 or ≥30) and AD/HD disease type (mixed type, predominantly inattentive type, or predominantly hyperactive-impulsive type) as covariates.

PMDA accepted the above explanation.

7.R.1.3 Factors affecting the efficacy of guanfacine

7.R.1.3.1 Effect of AD/HD disease type

PMDA asked the applicant to explain whether the efficacy of guanfacine would differ depending on the AD/HD disease type.

The applicant's explanation:
Subgroup analyses were conducted on change from baseline to Week 10 in total score and each subscale score of the ADHD-RS-IV with adult prompts in Japanese phase III study (CTD 5.3.5.1-01, Study A3132). Table 6 shows the results of subgroup analyses by AD/HD disease type. Although the number of patients evaluated was as small as 2 in each dose group for the subgroup of predominantly hyperactive-impulsive type and interpretation of the results was difficult, guanfacine consistently improved the symptoms in both subgroups of mixed type and predominantly inattentive type. Thus the AD/HD disease type was considered unlikely to affect the efficacy of guanfacine.

Table 1. Change from baseline in total score and each subscale score of the ADHD-RS-IV with adult prompts in Study A3132 by AD/HD disease type (FAS, MMRM)

	Disease type	Dose group	Score[a]		Change from baseline[b)c)]	Difference from score in the placebo[c)] [95% CI]
			Baseline	Week 10		
Total score	Mixed type	Placebo	35.49 ± 7.41 (49)	26.56 ± 11.49 (48)	−8.56 ± 1.43	
		Guanfacine	34.73 ± 5.72 (51)	21.54 ± 9.46 (41)	−13.56 ± 1.47	−5.00 [−8.97, −1.04]
	Predominantly inattentive type	Placebo	27.94 ± 3.34 (49)	20.00 ± 7.74 (43)	−7.85 ± 0.99	
		Guanfacine	27.83 ± 3.59 (47)	16.72 ± 8.47 (36)	−11.28 ± 1.07	−3.42 [−6.24, −0.61]
	Predominantly hyperactive-impulsive type	Placebo	31.00 ± 7.07 (2)	27.50 ± 2.12 (2)	−3.50 ± 3.45	
		Guanfacine	33.00 ± 8.49 (2)	29.00 ± 15.56 (2)	−4.00 ± 3.45	−0.50 [−15.58, 14.58]
Inattention subscale score	Mixed type	Placebo	22.43 ± 3.10 (49)	17.04 ± 6.56 (48)	−5.45 ± 0.84	
		Guanfacine	21.43 ± 3.32 (51)	14.29 ± 5.90 (41)	−7.72 ± 0.86	−2.28 [−4.66, 0.11]
	Predominantly inattentive type	Placebo	21.84 ± 2.92 (49)	16.44 ± 6.32 (43)	−5.23 ± 0.83	
		Guanfacine	21.49 ± 2.69 (47)	13.44 ± 6.90 (36)	−8.05 ± 0.88	−2.81 [−5.22, −0.41]
	Predominantly hyperactive-impulsive type	Placebo	9.50 ± 6.36 (2)	10.50 ± 7.78 (2)	1.12 ± 0.80	
		Guanfacine	10.50 ± 6.36 (2)	11.00 ± 9.90 (2)	0.38 ± 0.80	−0.74 [−3.15, 1.67]
Hyperactivity-impulsivity subscale score	Mixed type	Placebo	13.06 ± 5.43 (49)	9.52 ± 6.13 (48)	−3.71 ± 0.65	
		Guanfacine	13.29 ± 4.39 (51)	7.24 ± 4.97 (41)	−6.46 ± 0.68	−2.75 [−4.62, −0.88]
	Predominantly inattentive type	Placebo	6.10 ± 3.20 (49)	3.56 ± 2.77 (43)	−2.53 ± 0.33	
		Guanfacine	6.34 ± 3.75 (47)	3.28 ± 3.14 (36)	−3.16 ± 0.36	−0.63 [−1.61, 0.34]
	Predominantly hyperactive-impulsive type	Placebo	21.50 ± 0.71 (2)	17.00 ± 5.66 (2)	−5.67 ± 4.57	
		Guanfacine	22.50 ± 2.12 (2)	18.00 ± 5.66 (2)	−3.33 ± 4.57	2.35 [−37.45, 42.15]

a) Mean ± SD (No. of patients evaluated)
b) Adjusted mean ± SE
c) MMRM analysis (covariance structure of the error variance, unstructured; in the predominantly hyperactive-impulsive type subgroup, compound symmetry structure was applied to the inattention subscale score and heterogeneous AR (1) structure was applied to the hyperactivity-impulsivity subscale score) using the dose group, evaluation timepoint, and interaction between the dose group and evaluation timepoint as fixed effects and the subscale score of the ADHD-RS-IV with adult prompts at baseline as a covariate.

7.R.1.3.2 Effect of prior therapy

PMDA asked the applicant to explain an effect of prior therapy on the efficacy of guanfacine.

The applicant's explanation about an effect of prior therapy status on the efficacy of guanfacine:
Subgroup analyses were conducted on change from baseline to Week 10 in total score and each subscale score of the ADHD-RS-IV with adult prompts in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132). Table 7 shows the results of subgroup analyses by prior AD/HD therapy status. With respect to the total score, the guanfacine group showed more improvement than the placebo group irrespective of the prior therapy status. With respect to the subscale score, the guanfacine group consistently showed more improvement than the placebo group except for the hyperactivity-impulsivity subscale score in patients who had previously received non-central stimulants. The prior AD/HD therapy status was therefore considered unlikely to affect the efficacy of guanfacine.

Table 2. Change from baseline in total score and each subscale score of the ADHD-RS-IV with adult prompts in Study A3132 by prior AD/HD therapy status (FAS, MMRM)

	Prior therapy	Dose group	Score[a]		Change from baseline[b)c)]	Difference from score in the placebo[c)] [95% CI]
			Baseline	Week 10		
Total score	Central stimulant	Placebo	31.48 ± 7.03 (25)	25.39 ± 8.04 (23)	−5.45 ± 2.33	
		Guanfacine	31.95 ± 6.42 (22)	17.74 ± 8.96 (19)	−12.62 ± 2.27	−7.16 [−12.02, −2.31]
	Non-central stimulant	Placebo	31.27 ± 6.97 (22)	21.20 ± 9.84 (20)	−8.61 ± 2.40	
		Guanfacine	29.52 ± 4.81 (21)	19.47 ± 10.61 (17)	−10.23 ± 2.35	−1.62 [−7.20, 3.96]
	None	Placebo	31.98 ± 6.80 (53)	23.64 ± 11.32 (50)	−7.79 ± 1.49	
		Guanfacine	31.96 ± 6.04 (57)	20.35 ± 9.29 (43)	−12.22 ± 1.58	−4.44 [−7.85, −1.02]
Inattention subscale score	Central stimulant	Placebo	22.24 ± 2.79 (25)	18.43 ± 5.31 (23)	−3.86 ± 1.72	
		Guanfacine	20.23 ± 4.10 (22)	12.47 ± 6.37 (19)	−7.27 ± 1.82	−3.41 [−6.66, −0.17]
	Non-central stimulant	Placebo	21.95 ± 2.94 (22)	15.85 ± 5.98 (20)	−5.44 ± 1.72	
		Guanfacine	20.14 ± 3.10 (21)	12.35 ± 6.18 (17)	−8.15 ± 1.75	−2.71 [−6.79, 1.37]
	None	Placebo	21.68 ± 4.06 (53)	16.10 ± 7.06 (50)	−5.34 ± 1.06	
		Guanfacine	22.04 ± 3.07 (57)	15.00 ± 6.39 (43)	−7.64 ± 1.12	−2.30 [−4.64, 0.04]
Hyperactivity-Impulsivity subscale score	Central stimulant	Placebo	9.24 ± 5.72 (25)	6.96 ± 5.05 (23)	−2.08 ± 1.22	
		Guanfacine	11.73 ± 5.39 (22)	5.26 ± 4.99 (19)	−5.27 ± 1.21	−3.19 [−5.53, −0.86]
	Non-central stimulant	Placebo	9.32 ± 5.82 (22)	5.35 ± 5.13 (20)	−3.66 ± 1.12	
		Guanfacine	9.38 ± 5.48 (21)	7.12 ± 5.56 (17)	−3.02 ± 1.11	0.64 [−1.88, 3.16]
	None	Placebo	10.30 ± 5.96 (53)	7.54 ± 6.39 (50)	−2.19 ± 0.70	
		Guanfacine	9.93 ± 5.71 (57)	5.35 ± 4.86 (43)	−4.27 ± 0.74	−2.08 [−3.64, −0.52]

a) Mean ± SD (No. of patients evaluated)
b) Adjusted mean ± SE
c) MMRM analysis (covariance structure of the error variance, unstructured) using the dose group, evaluation timepoint, and interaction between the dose group and evaluation timepoint as fixed effects and the subscale score of the ADHD-RS-IV with adult prompts at baseline as a covariate

PMDA considers unlikely for the prior AD/HD therapy status to affect the efficacy of guanfacine with a clinical significance because improvement in terms of the total score of the ADHD-RS-IV with adult prompts was observed irrespective of the prior therapy, although no improvement in the hyperactivity-impulsivity subscale score was observed in subjects who had previously received non-central stimulants.

7.R.2 Safety

7.R.2.1 Difference in safety profile between adult and pediatric AD/HD

PMDA asked the applicant to explain the difference in safety profile of guanfacine between adult and pediatric AD/HD.

The applicant's explanation:

Table 8 shows major adverse events in Japanese clinical studies in adult or pediatric patients with AD/HD.[8)] The incidence of adverse events such as thirst, blood pressure decreased, dizziness postural, bradycardia, dizziness, insomnia, and dry mouth tended to be higher in adult patients than in pediatric patients. All-time oral dryness tends to be increasingly perceived with aging in general (*Ann Jpn Prosthodont Soc.* 2015;7:136-41), and most of other adverse events were also subjective symptoms. Such characteristics of thirst and dry mouth were considered to have led to higher incidence in adult patients than in pediatric patients. Furthermore, adverse events leading to discontinuation occurred more commonly in adult patients than in pediatric patients, but most of these events were mild or moderate in severity and resolved or were resolving without treatment.

8) In adult patients, short-term treatment study (CTD 5.3.5.1-01, Study A3132), long-term treatment study (CTD 5.3.5.2-02, Study A3133)
In pediatric patients, short-term treatment study (initial application data CTD 5.3.5.1-01, Study A3122), long-term treatment study (initial application data CTD 5.3.5.2-06, Study A3131)

Table 8. Incidence of adverse events in adult or pediatric patients with AD/HD in Japanese clinical studies

	Short-term treatment						Long-term treatment	
	Adult patients		Pediatric patients				Adult patients	Pediatric patients
	Study A3132		Study A3122				Study A3133	Study A3131
	Placebo	Guanfacine	Placebo	Guanfacine			Guanfacine	Guanfacine
				0.04 mg/kg	0.08 mg/kg	0.12 mg/kg		
No. of subjects evaluated	100	101	67	66	65	66	191	222
All adverse events	62 (62.0)	82 (81.2)	41 (61.2)	50 (75.8)	53 (81.5)	61 (92.4)	180 (94.2)	215 (96.8)
Serious adverse events	0	1 (1.0)	0	0	0	0	2 (1.0)	6 (2.7)
Adverse events leading to discontinuation	3 (3.0)	20 (19.8)	2 (3.0)	1 (1.5)	1 (1.5)	10 (15.2)	38 (19.9)	13 (5.9)
Major adverse events								
Thirst	0	22 (21.8)	0	0	0	1 (1.5)	59 (30.9)	3 (1.4)
Blood pressure decreased	2 (2.0)	21 (20.8)	0	1 (1.5)	2 (3.1)	8 (12.1)	38 (19.9)	18 (8.1)
Dizziness postural	1 (1.0)	15 (14.9)	0	0	0	1 (1.5)	36 (18.8)	5 (2.3)
Constipation	1 (1.0)	11 (10.9)	0	0	1 (1.5)	5 (7.6)	21 (11.0)	15 (6.8)
Dizziness	0	8 (7.9)	0	1 (1.5)	1 (1.5)	1 (1.5)	20 (10.5)	6 (2.7)
Bradycardia	0	8 (7.9)	1 (1.5)	0	2 (3.1)	7 (10.6)	33 (17.3)	6 (2.7)
Nausea	4 (4.0)	5 (5.0)	2 (3.0)	0	3 (4.6)	2 (3.0)	15 (7.9)	8 (3.6)
Insomnia	0	5 (5.0)	0	0	1 (1.5)	1 (1.5)	9 (4.7)	5 (2.3)
Orthostatic hypotension	0	5 (5.0)	0	0	0	1 (1.5)	8 (4.2)	6 (2.7)
Malaise	3 (3.0)	1 (1.0)	2 (3.0)	2 (3.0)	1 (1.5)	5 (7.6)	30 (15.7)	15 (6.8)
Heart rate decreased	0	3 (3.0)	0	0	0	1 (1.5)	2 (1.0)	3 (1.4)
Palpitations	0	2 (2.0)	0	0	0	0	4 (2.1)	1 (0.5)
Vertigo	0	2 (2.0)	0	1 (1.5)	0	0	3 (1.6)	1 (0.5)
Initial insomnia	1 (1.0)	1 (1.0)	0	0	0	2 (3.0)	5 (2.6)	4 (1.8)
Terminal insomnia	0	2 (2.0)	0	0	0	0	0	1 (0.5)
Abdominal discomfort	1 (1.0)	1 (1.0)	0	0	0	0	4 (2.1)	1 (0.5)
Fatigue	0	1 (1.0)	0	1 (1.5)	0	0	3 (1.6)	2 (0.9)
Abdominal pain upper	0	1 (1.0)	0	0	0	0	3 (1.6)	1 (0.5)
Nasal congestion	0	1 (1.0)	0	0	0	0	1 (0.5)	1 (0.5)
Dry mouth	0	0	0	0	0	0	6 (3.1)	1 (0.5)
Blood bilirubin increased	2 (2.0)	0	0	0	0	0	5 (2.6)	1 (0.5)
Blood pressure increased	0	0	0	0	0	0	3 (1.6)	3 (1.4)
Hypoaesthesia	0	0	0	0	0	0	4 (2.1)	2 (0.9)
Sleep disorder	1 (1.0)	0	1 (1.5)	0	0	0	4 (2.1)	1 (0.5)
Asthenia	0	0	0	0	0	0	3 (1.6)	1 (0.5)

No. of subjects with event (incidence, %)

Then, the applicant explained individual adverse events related to the following matters, taking the safety profile of guanfacine into account: The cardiovascular system, central nervous system, fall and traumatic injury, syncope, weight increased and decreased, gastrointestinal system, abnormal glucose metabolism, abnormal lipid metabolism, suicide, and hostility and aggression. The details are described below.

7.R.2.2 Cardiovascular adverse events

The applicant's explanation:

Table 9 shows changes in blood pressure (systolic and diastolic) and pulse rate in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132). In the guanfacine group, decreased blood pressure and pulse rate were observed during the treatment period; the level of blood pressure and pulse rate decreased immediately after the start of guanfacine treatment and dose increases and returned to the baseline level at the end of the tapering period.

Table 9. Changes in blood pressure (systolic, diastolic) and pulse rate in Study A3132

		Baseline	End of treatment (Week 10)		End of tapering (Week 12)	
		Measured value	Measured value	Change from baseline	Measured value	Change from baseline
Blood pressure systolic (mmHg)	Placebo	114.67 ± 14.30 (100)	114.78 ± 13.65 (93)	−0.21 ± 7.61	114.43 ± 14.33 (91)	−0.41 ± 10.59
	Guanfacine	116.21 ± 12.13 (101)	107.07 ± 13.51 (79)	−10.31 ±11.69	117.98 ± 13.39 (76)	0.76 ± 11.48
Blood pressure diastolic (mmHg)	Placebo	73.44 ± 11.07 (100)	73.35 ± 10.36 (93)	−0.48 ± 7.02	72.03 ± 10.43 (91)	−1.67 ± 7.85
	Guanfacine	73.24 ± 10.74 (101)	65.79 ± 10.51 (79)	−8.21 ± 10.30	74.71 ± 10.69 (76)	0.72 ± 9.00
Pulse rate (bpm)	Placebo	76.06 ± 10.00 (100)	74.51 ± 8.88 (93)	−1.81 ± 9.71	74.05 ± 9.29 (91)	−2.12 ± 9.63
	Guanfacine	74.86 ± 9.80 (101)	66.18 ± 10.70 (79)	−8.64 ± 12.22	73.48 ± 10.96 (76)	−1.32 ± 9.73

Mean ± SD (No. of patients evaluated); Number of patients evaluated for changes was the same as that of patients subjected to measurement at each timepoint.

Table 10 shows the proportion of subjects who experienced decreased blood pressure (systolic, diastolic) and pulse rate in the Japanese clinical studies[8)] in adult or pediatric patients with AD/HD. The proportion of subjects who experienced ≥20 mmHg decreased systolic blood pressure tended to be higher in adult patients than in pediatric patients, but this trend was potentially attributable to high blood pressure at baseline in adult patients, especially patients aged ≥40 years. Furthermore, no differences were observed in incidence of ≥20 mmHg decreased diastolic blood pressure or ≥20 bpm decreased pulse rate between the studies.

Table 10. Incidence of decreased blood pressure (systolic, diastolic) and pulse rate from baseline in adult patients or pediatric patients with AD/HD in Japanese clinical studies

		Short-term treatment				Long-term treatment		
		Adult patients		Pediatric patients		Adult patients		Pediatric patients
		Study A3132		Study A3122		Study A3133		Study A3131
		Placebo	Guanfacine 4-6 mg/day	Placebo	Guanfacine 1-6 mg/day pooled	Continued from the previous study	Newly enrolled	Guanfacine 1-6 mg/day
No. of subjects evaluated		100	100	67	197	150	41	222
Systolic Blood pressure decreased (mmHg)	≥5 and <10	31 (31.0)	7 (7.0)	16 (23.9)	37 (18.8)	16 (10.7)	4 (9.8)	22 (9.9)
	≥10 and <15	19 (19.0)	17 (17.0)	24 (35.8)	42 (21.3)	22 (14.7)	8 (19.5)	47 (21.2)
	≥15 and <20	6 (6.0)	21 (21.0)	4 (6.0)	34 (17.3)	34 (22.7)	6 (14.6)	39 (17.6)
	≥20	10 (10.0)	47 (47.0)	8 (11.9)	57 (28.9)	67 (44.7)	21 (51.2)	89 (40.1)
Diastolic Blood pressure decreased (mmHg)	≥5 and <10	31 (31.0)	10 (10.0)	16 (23.9)	42 (21.3)	27 (18.0)	7 (17.1)	34 (15.3)
	≥10 and <15	23 (23.0)	22 (22.0)	16 (23.9)	44 (22.3)	34 (22.7)	14 (34.1)	44 (19.8)
	≥15 and <20	6 (6.0)	29 (29.0)	5 (7.5)	34 (17.3)	42 (28.0)	8 (19.5)	41 (18.5)
	≥20	5 (5.0)	30 (30.0)	6 (9.0)	45 (22.8)	35 (23.3)	12 (29.3)	73 (32.9)
Pulse rate decreased (bpm)	≥5 and <10	29 (29.0)	11 (11.0)	13 (19.4)	26 (13.2)	13 (8.7)	4 (9.8)	19 (8.6)
	≥10 and <15	25 (25.0)	27 (27.0)	11 (16.4)	35 (17.8)	41 (27.3)	7 (17.1)	42 (18.9)
	≥15 and <20	7 (7.0)	21 (21.0)	7 (10.4)	36 (18.3)	31 (20.7)	10 (24.4)	41 (18.5)
	≥20	7 (7.0)	34 (34.0)	14 (20.9)	76 (38.6)	54 (36.0)	18 (43.9)	108 (48.6)

No. of subjects with event (incidence, %)

Table 11 shows the proportion of subjects whose blood pressure and pulse rate at the end of the tapering period were higher than the baseline levels. In Study A3132, the proportion of subjects who experienced ≥5 mmHg increased diastolic and systolic blood pressures tended to be higher in the guanfacine group than in the placebo group, but no considerable difference was observed in the above proportion between adult patients with AD/HD and pediatric patients with AD/HD, raising no clinically major problems with rebound hypertension. In addition, no considerable difference in the proportion to subjects who experienced increased pulse rate was observed between the placebo group and guanfacine group or

between adult patients with AD/HD and pediatric patients with AD/HD in Study A3132, raising no clinically major problem with rebound pulse rate.

Table 11. Incidences of increased blood pressure (systolic, diastolic) and pulse rate from baseline in adult patients or pediatric patients with AD/HD in Japanese clinical studies

		Short-term treatment				Long-term treatment		
		Adult patients		Pediatric patients		Adult patients		Pediatric patients
		Study A3132		Study A3122		Study A3133		Study A3131
		Placebo	Guanfacine 4-6 mg/day	Placebo	Guanfacine 1-6 mg/day pooled	Continued from the previous study	Newly enrolled	Guanfacine 1-6 mg/day
No. of subjects evaluated		91	76	63	183	95	29	191
Systolic Blood pressure increased (mmHg)	≥5 and <10	7 (7.7)	12 (15.8)	7 (11.1)	26 (14.2)	18 (18.9)	7 (24.1)	23 (12.0)
	≥10 and <15	11 (12.1)	7 (9.2)	6 (9.5)	22 (12.0)	9 (9.5)	2 (6.9)	30 (15.7)
	≥15 and <20	8 (8.8)	4 (5.3)	5 (7.9)	9 (4.9)	6 (6.3)	5 (17.2)	26 (13.6)
	≥20	1 (1.1)	3 (3.9)	5 (7.9)	15 (8.2)	9 (9.5)	2 (6.9)	26 (13.6)
Diastolic Blood pressure increased (mmHg)	≥5 and <10	10 (11.0)	15 (19.7)	8 (12.7)	28 (15.3)	16 (16.8)	9 (31.0)	27 (14.1)
	≥10 and <15	5 (5.5)	8 (10.5)	12 (19.0)	21 (11.5)	10 (10.5)	3 (10.3)	24 (12.6)
	≥15 and <20	2 (2.2)	2 (2.6)	3 (4.8)	14 (7.7)	8 (8.4)	4 (13.8)	17 (8.9)
	≥20	0	1 (1.3)	4 (6.3)	11 (6.0)	3 (3.2)	0	29 (15.2)
Pulse rate increased (bpm)	≥5 and <10	10 (11.0)	15 (19.7)	10 (15.9)	27 (14.8)	22 (23.2)	8 (27.6)	24 (12.6)
	≥10 and <15	7 (7.7)	3 (3.9)	4 (6.3)	20 (10.9)	7 (7.4)	2 (6.9)	19 (9.9)
	≥15 and <20	0	3 (3.9)	7 (11.1)	10 (5.5)	7 (7.4)	2 (6.9)	16 (8.4)
	≥20	2 (2.2)	2 (2.6)	7 (11.1)	16 (8.7)	9 (9.5)	0	26 (13.6)

No. of subjects with event (incidence, %)

The applicant's explanation about the effects on the cardiovascular system, based on the finding of blood pressure decreased and pulse rate decreased associated with guanfacine:

- Table 12 shows the incidence of cardiovascular adverse events[9)] in Japanese clinical studies[8)] in adult patients or pediatric patients with AD/HD. In Study A3132, adverse events such as blood pressure decreased, bradycardia, orthostatic hypotension, sinus bradycardia, and hypotension occurred more commonly in the guanfacine group than in the placebo group. While 1 subject discontinued the treatment due to adverse events in the placebo group, 10 subjects discontinued in the guanfacine group. All of the adverse events leading to treatment discontinuation occurred during the dose optimization period, and thus the initial forced up-titration to 4 mg/day was considered to be responsible.

9) Events that fall under MedDRA system organ class (SOC) "cardiac disorders" and "vascular disorders," and high-level group terms (HLGT) "cardiac and vascular investigations (excl enzyme tests)"

Table 12. Incidence of cardiovascular adverse events in adult patients or pediatric patients with AD/HD in Japanese clinical studies

	Short-term treatment						Long-term treatment	
	Adult patients		Pediatric patients				Adult patients	Pediatric patients
	Study A3132		Study A3122				Study A3133	Study A3131
	Placebo	Guanfacine	Placebo	Guanfacine			Guanfacine	Guanfacine
				0.04 mg/kg	0.08 mg/kg	0.12 mg/kg		
No. of subjects evaluated	100	101	67	66	65	66	191	222
Cardiovascular adverse events	4 (4.0)	40 (39.6)	1 (1.5)	6 (9.1)	4 (6.2)	22 (33.3)	77 (40.3)	46 (20.7)
Major adverse events								
Blood pressure decreased	2 (2.0)	21 (20.8)	0	1 (1.5)	2 (3.1)	8 (12.1)	38 (19.9)	18 (8.1)
Bradycardia	0	8 (7.9)	1 (1.5)	0	2 (3.1)	7 (10.6)	33 (17.3)	6 (2.7)
Orthostatic hypotension	0	5 (5.0)	0	0	0	1 (1.5)	8 (4.2)	6 (2.7)
Sinus bradycardia	1 (1.0)	4 (4.0)	0	2 (3.0)	0	3 (4.5)	2 (1.0)	2 (0.9)
Hypotension	0	4 (4.0)	0	1 (1.5)	2 (3.1)	6 (9.1)	2 (1.0)	8 (3.6)
Palpitations	0	2 (2.0)	0	0	0	0	4 (2.1)	1 (0.5)
Heart rate decreased	0	3 (3.0)	0	0	0	1 (1.5)	2 (1.0)	3 (1.4)
Blood pressure increased	0	0	0	0	0	0	3 (1.6)	3 (1.4)

No. of subjects with event (incidence, %)

- The incidence of cardiovascular adverse events was higher in adult patients than in pediatric patients, and adverse events related to decreased blood pressure and pulse rate commonly occurred. Although subgroup analyses were performed on incidences by dividing the study population according to the age bracket, baseline blood pressure, or baseline pulse rate, no clear differences were observed in incidence of adverse events between subgroups divided by these patient characteristics. Factors responsible for such high incidence of adverse events in adult patients were not identified. All the adverse events related to decreased blood pressure and pulse rate were non-serious and mild or moderate, except for bradycardia in 1 patient (severe) in Study A3133.

- With respect to QT interval in electrocardiogram, Fridericia-corrected QT Interval (QTcF interval) exceeding 450 ms occurred in 2.0% (2 of 99) of subjects in the placebo group and in 1.0% (1 of 98) of subjects in the guanfacine group at Week 5, but no subjects experienced QTcF interval exceeding 480 ms in Study A3132. A change in QTcF interval from baseline to Week 5 exceeding 30 ms occurred in 3.0% (3 of 99) of subjects in the placebo group and in 1.0% (1 of 98) of subjects in the guanfacine group, but no subjects experienced the change exceeding 60 ms. In Study A3133, QTcF interval exceeding 450 ms by the final measurement occurred in 4.7% (4 of 86) of subjects in the placebo population in Study A3132, in 3.3% (2 of 60) of subjects in the guanfacine population in Study A3132, and in 2.5% (1 of 40) of subjects newly enrolled, but no subjects experienced QTcF interval exceeding 480 ms. A change in QTcF interval from baseline to the final measurement exceeding 30 ms occurred in 5.8% (5 of 86) of subjects in the placebo population in Study A3132, in 5.0% (3 of 60) of subjects in the guanfacine population in Study A3132, and in 5.0% (2 of 40) of subjects newly enrolled, but no subjects experienced the change exceeding 60 ms.

Based on the above, the applicant considered it is unnecessary to provide further cautions about monitoring of patients receiving guanfacine for the following reasons: The package insert has already

included precautionary statements that (1) blood pressure and pulse rate should be measured before the start of treatment, 1 to 2 weeks after any dose change, and approximately once every 4 weeks after optimal dose is determined; (2) electrocardiography should be performed for any abnormality before start of the treatment; if any abnormality is found, the use of guanfacine should be carefully considered; and (3) if patient has a cardiovascular disease or a history of such diseases, or if any abnormality is found in electrocardiogram before the first dose, patients should be carefully monitored through periodic electrocardiography.

7.R.2.3 Adverse events in the central nervous system

The applicant's explanation:

Table 13 shows the incidence of adverse events in the central nervous system[10)] and sedation-related adverse events[7)] in Japanese clinical studies[8)] in adult patients or pediatric patients with AD/HD. Somnolence commonly occurred, and adverse events such as dizziness postural and dizziness more commonly occurred in the guanfacine group in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and in the Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133) in adult patients than in pediatric patients. Although adverse events did not greatly differ between adult patients and pediatric patients, the severity differed. All the events in pediatric patients with AD/HD in clinical studies were mild or moderate in severity. In adult patients, however, severe adverse events occurred in 2 patients (suicide attempt and dizziness in 1 patient each) in Study A3132 and in 1 patient (dependence in 1 patient) in Study A3133; and a serious adverse event occurred in 1 patient (suicide attempt in 1 patient) in Study A3132. The causal relationship to the study drug was denied in all these cases. The higher incidences in adult patients than in pediatric patients were considered attributable to the nature of the adverse events in the central nervous system, which were reported as a complaint of subjective symptom, and thus the safety was considered to have no clinically significant difference between pediatric patients and adult patients.

10) Events that fall under MedDRA SOC "nervous system disorders" and "psychiatric disorders"

Table 13. Incidence of adverse events in the central nervous system in adult patients or pediatric patients with AD/HD in Japanese clinical studies

	Short-term treatment						Long-term treatment	
	Adult patients		Pediatric patients				Adult patients	Pediatric patients
	Study A3132		Study A3122				Study A3133	Study A3131
	Placebo	Guanfacine	Placebo	Guanfacine			Guanfacine	Guanfacine
				0.04 mg/kg	0.08 mg/kg	0.12 mg/kg		
No. of subjects evaluated	100	101	67	66	65	66	191	222
Adverse events in the central nervous system	16 (16.0)	54 (53.5)	9 (13.4)	29 (43.9)	32 (49.2)	40 (60.6)	122 (63.9)	147 (66.2)
Major adverse events								
Somnolence	8 (8.0)	35 (34.7)	4 (6.0)	22 (33.3)	24 (36.9)	36 (54.5)	80 (41.9)	127 (57.2)
Dizziness postural	1 (1.0)	15 (14.9)	0	0	0	1 (1.5)	36 (18.8)	6 (2.7)
Dizziness	0	8 (7.9)	0	1 (1.5)	1 (1.5)	1 (1.5)	20 (10.5)	6 (2.7)
Headache	5 (5.0)	3 (3.0)	4 (6.0)	5 (7.6)	8 (12.3)	9 (13.6)	14 (7.3)	31 (14.0)
Insomnia	0	5 (5.0)	0	0	1 (1.5)	1 (1.5)	9 (4.7)	5 (2.3)
Initial insomnia	1 (1.0)	1 (1.0)	0	0	0	2 (3.0)	5 (2.6)	4 (1.8)
Middle insomnia	2 (2.0)	1 (1.0)	0	2 (3.0)	1 (1.5)	3 (4.5)	3 (1.6)	13 (5.9)
Sedation-related adverse events	10 (10.0)	35 (34.7)	5 (7.5)	23 (34.8)	24 (36.9)	37 (56.1)	95 (49.7)	133 (59.9)
Major adverse events								
Somnolence	8 (8.0)	35 (34.7)	4 (6.0)	22 (33.3)	24 (36.9)	36 (54.5)	80 (41.9)	127 (57.2)
Fatigue	0	1 (1.0)	0	1 (1.5)	0	0	3 (1.6)	2 (0.9)
Malaise	3 (3.0)	1 (1.0)	2 (3.0)	2 (3.0)	1 (1.5)	5 (7.6)	30 (15.7)	15 (6.8)

No. of subjects with event (incidence, %)

Given that sedation-related adverse events such as somnolence are considered to be caused by attenuation of sympathetic nervous activities following treatment with guanfacine, the package insert has already included a precaution that patients receiving guanfacine should not be engaged in potentially hazardous machine operations including driving. No additional precaution was considered necessary.

7.R.2.4 Adverse events related to fall and traumatic injury

The applicant's explanation:

The incidence of adverse events related to fall and traumatic injury[11] in Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133) were 1.0% (1 of 100) of patients (contusion and wound in 1 patient each) in the placebo group and in 2.0% (2 of 101) of patients (ligament sprain and contusion in 1 patient each) in the guanfacine group in Study A3132; and 4.7% (9 of 191) of patients (contusion and wound in 4 patients each, ligament sprain in 2 patients, laceration in 1 patient) in Study A3133. The incidence of such events did not tend to be higher in adult patients than in pediatric patients.

Table 14 shows adverse events related to fall and traumatic injury reported in the post-marketing safety information in Japan and overseas.[12]. Because estimated exposures in person-years remain unknown for adult patients and pediatric patients, it is not possible to compare the reported rate per person-years between adult patients and pediatric patients, but the number of reported adverse events related to fall

[11] Events that fall under the following MedDRA PTs:
Internal injury, birth trauma, wound, wound haemorrhage, wound infection, wound contamination, wound haematoma, wound complication, wound necrosis, post-traumatic pain, post-traumatic osteoporosis, traumatic shock, traumatic haemorrhage, traumatic amputation, traumatic ulcer, traumatic haematoma, multiple injuries, injury, musculoskeletal injury, soft tissue injury, fall, bone contusion, skeletal injury, contusion, ligament sprain, laceration, and fracture

[12] Tabulation data in Japan covered from May 26, 2017 to September 17, 2018 (estimated exposure to be 75,105 person-years), and tabulation data overseas covered from September 2009 to September 17, 2018 (estimated exposure to be 1,126,691 person-years)

and traumatic injury was small in both adult and pediatric patients. Accordingly, the adverse events in adult patients were considered to be not different from those in pediatric patients.

Table 14. Adverse events related to fall and traumatic injury in post-marketing safety information in Japan and overseas

	Japan			Overseas		
	Adult patients	Pediatric patients	Age unknown	Adult patients	Pediatric patients	Age unknown
Number of all adverse events	33 (7)	4044 (158)	346 (13)	738 (40)	8272 (889)	2856 (239)
Adverse events related to fall and traumatic injury	0	6 (0)	0	5 (0)	10 (1)	4 (1)
Major event						
Fall	0	6 (0)	0	3 (0)	7 (1)	3 (1)
Ligament sprain	0	0	0	1 (0)	0	0
Contusion	0	0	0	1 (0)	2 (0)	1 (0)
Wound haemorrhage	0	0	0	0	1 (0)	0

Number of events (No. of serious events)

The package insert has already included a caution against adverse events related to fall and traumatic injury, and no additional caution was considered necessary.

7.R.2.5 Adverse events related to syncope

The applicant's explanation about:

The incidence of adverse events related to syncope[13)] were only 1.0% (1 of 100) of patients (syncope in 1 patient) in the placebo group in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and 0.5% (1 of 191) of patients (loss of consciousness in 1 patient) in the Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133). The incidence of such events did not tend to be higher in adult patients than in pediatric patients.

Table 15 shows adverse events related to syncope reported in the post-marketing safety information in Japan and overseas.[12)] Because estimated exposures in person-years by adult patients and pediatric patients remain unknown, it is not possible to compare the reported rate per person-years between adult patients and pediatric patients, but the adverse events in adult patients were considered to be not different from those in pediatric patients.

Table 15. Adverse events related to syncope in post-marketing safety information in Japan and overseas

	Japan			Overseas		
	Adult patients	Pediatric patients	Age unknown	Adult patients	Pediatric patients	Age unknown
Number of all adverse events	33 (7)	4044 (158)	346 (13)	738 (40)	8272 (889)	2856 (239)
Adverse events related to syncope	0	14 (2)	1 (0)	5 (5)	109 (99)	38 (34)
Syncope	0	11 (0)	1 (0)	4 (4)	68 (66)	28 (28)
Loss of consciousness	0	3 (2)	0	1 (1)	25 (25)	5 (5)
Presyncope	0	0	0	0	12 (4)	5 (1)
Depressed level of consciousness	0	0	0	0	3 (3)	0
Consciousness fluctuating	0	0	0	0	1 (1)	0

Number of events (No. of serious events)

13) Events that fall under the following MedDRA PTs:
Syncope, loss of consciousness, presyncope, depressed level of consciousness, and consciousness fluctuating

The package insert has already included a caution against adverse events related to syncope, and no additional caution was considered necessary.

7.R.2.6 Adverse events related to weight increased or decreased

The applicant's explanation:

Table 16 shows change in body weight following guanfacine treatment in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133). The proportion of patients who experienced body weight increased or decreased by ≥7% did not tend to increase with the guanfacine treatment, and thus no clinically significant change in body weight were observed.

Table 16. Change in body weight in adult patients with AD/HD in Japanese clinical studies

Evaluation timepoints[a)]	Placebo/guanfacine[b)]			Guanfacine/guanfacine		
	No. of subjects evaluated	Decrease by ≥7%	Increase by ≥7%	No. of subjects evaluated	Decrease by ≥7%	Increase by ≥7%
Week 4-5	111	0	0	84	0	0
Week 10	99	2 (2.0)	1 (1.0)	79	0	0
Week 22	86	3 (3.5)	1 (1.2)	55	2 (3.6)	1 (1.8)
Week 30	82	4 (4.9)	0	51	3 (5.9)	1 (2.0)
Week 38	80	5 (6.3)	2 (2.5)	48	3 (6.3)	2 (4.2)
Week 50	78	4 (5.1)	3 (3.8)	47	5 (10.6)	5 (10.6)
Week 64/last dose	125	6 (4.8)	8 (6.4)	98	7 (7.1)	7 (7.1)

No. of subjects with event (incidence, %)

a) Time from the start of guanfacine treatment (start of Study A3133 for the placebo/guanfacine group, start of Study A3132 for the guanfacine/guanfacine group)

b) Including patients newly enrolled in Study A3133

The applicant's explanation:

Adverse events related to weight increased or decreased[14)] occurred in 0% (0 of 100) of patients in the placebo group and in 1.0% (1 of 101) of patients (weight increased in 1 patient) in the guanfacine group in Study A3132; and in 1.6% (3 of 191) of patients (weight increased in 3 patients) in Study A3133. No clinically significant effects were observed.

The package insert has already included a caution against body weight increased, which was observed in pediatric patients with AD/HD receiving guanfacine, but no effects related to body weight increased or decreased were observed in adult patients. No additional caution was therefore considered necessary.

7.R.2.7 Adverse events in the gastrointestinal system

The applicant's explanation:

Table 17 shows the incidence of adverse events in the gastrointestinal system[15)] in adult patients or pediatric patients with AD/HD in Japanese clinical studies[8)]. Although adverse events such as constipation occurred more commonly in the guanfacine group than in the placebo group in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132), all of these were mild or moderate in severity and non-serious. A profile of these events did not tend to differ between adult patients and pediatric patients.

14) Events that fall under the following MedDRA PTs:
Abnormal weight gain, central obesity, obesity, overweight, and weight increased

15) Events fall under MedDRA SOC "gastrointestinal disorders"

Table 17. Incidence of adverse events in the gastrointestinal system in adult patients or pediatric patients with AD/HD in Japanese clinical studies

	Short-term treatment						Long-term treatment	
	Adult patients		Pediatric patients				Adult patients	Pediatric patients
	Study A3132		Study A3122				Study A3133	Study A3131
	Placebo	Guanfacine	Placebo	Guanfacine			Guanfacine	Guanfacine
				0.04 mg/kg	0.08 mg/kg	0.12 mg/kg		
No. of subjects evaluated	100	101	67	66	65	66	191	222
Adverse events in the gastrointestinal system	12 (12.0)	27 (26.7)	11 (16.4)	10 (15.2)	14 (21.5)	16 (24.2)	65 (34.0)	90 (40.5)
Major adverse events								
Constipation	1 (1.0)	11 (10.9)	0	0	1 (1.5)	5 (7.6)	21 (11.0)	15 (6.8)
Nausea	4 (4.0)	5 (5.0)	2 (3.0)	0	3 (4.6)	2 (3.0)	15 (7.9)	8 (3.6)
Diarrhoea	3 (3.0)	4 (4.0)	3 (4.5)	3 (4.5)	3 (4.6)	4 (6.1)	9 (4.7)	21 (9.5)
Abdominal pain	1 (1.0)	3 (3.0)	1 (1.5)	6 (9.1)	2 (3.1)	4 (6.1)	5 (2.6)	24 (10.8)
Dental caries	1 (1.0)	3 (3.0)	1 (1.5)	0	3 (4.6)	1 (1.5)	4 (2.1)	19 (8.6)
Abdominal discomfort	1 (1.0)	1 (1.0)	0	0	0	0	4 (2.1)	1 (0.5)
Dry mouth	0	0	0	0	0	0	6 (3.1)	1 (0.5)
Stomatitis	1 (1.0)	1 (1.0)	2 (3.0)	0	1 (1.5)	0	4 (2.1)	9 (4.1)
Vomiting	1 (1.0)	0	1 (1.5)	1 (1.5)	1 (1.5)	4 (6.1)	4 (2.1)	11 (5.0)

No. of subjects with event (incidence, %)

Based on the above, no additional caution against gastrointestinal adverse events was considered necessary.

7.R.2.8 Adverse events related to glucose metabolism abnormal

The applicant's explanation about the risk of glucose metabolism abnormal associated with guanfacine:

- In the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133), data on fasting plasma glucose were not collected, and only data on sugar in urine were collected. Subjects in whom the sugar in urine was normal at baseline but became abnormal (outside of the reference range) after the start of guanfacine treatment accounted for 3.0% (3 of 99) of patients in the placebo group and 4.3% (4 of 94) of patients in the guanfacine group in Study A3132; and 6.0% (11 of 191) of patients in Study A3133.

- In Studies A3132 and A3133, no adverse events related to glucose metabolism abnormal[16)] occurred. According to the post-marketing safety information in Japan and overseas,[12)] only 1 adverse event related to glucose metabolism abnormal (13.31 per million person-years, including 0 serious events) was reported in pediatric patient (blood glucose increased) in Japan. Outside Japan, 17 events (15.09 per million person-years, including 8 serious events) were reported, including 9 events in pediatric patients (4 serious events), 2 events in adult patients (0 serious events), and 6 events in patients unknown for age (4 serious events). Major adverse events were 4 events of blood glucose increased (3 events in pediatric patients, 1 event in adult patient, 0 events in patient unknown for age) and 3 events of hypoglycaemia (2 events in pediatric patients, 0 events in adult patients, 1 event in patient unknown for age). Because estimated exposures in person-years remain unknown for adult patients and pediatric patients, it is not possible to compare the reported rate per person-years between adult patients and pediatric patients, but the number of reported adverse events related to glucose

[16)] Events that fall under MedDRA HLGT "glucose metabolism disorders (incl diabetes mellitus)" and high-level terms (HLT) "carbohydrate tolerance analyses (incl diabetes mellitus)"

metabolism abnormal was small in both adult and pediatric patients. Accordingly, the adverse events in adult patients were considered to be not different from those in pediatric patients.

Based on the above, no additional caution against adverse events related to glucose metabolism abnormal was considered necessary.

7.R.2.9 Adverse events related to suicide and adverse events related to hostility and aggression

7.R.2.9.1 Adverse events related to suicide

The applicant's explanation:

The incidence of adverse events related to suicide[17] in Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133) was only 1.0% (1 of 101) of patients (suicide attempt in 1 patient) in the guanfacine group in Study A3132 and 0.5% (1 of 191) of patients (intentional self-injury in 1 patient) in Study A3133. In addition, no such events occurred in the Japanese phase III study in pediatric patients (initial application data CTD 5.3.5.1-01, Study A3122), and in the Japanese long-term treatment study in pediatric patients (initial application data CTD 5.3.5.2-06, Study A3131), the events occurred in 0.9% (2 of 222) of patients (suicidal ideation in 1 patient and self-injurious behavior in 1 patient).

Table 18 shows reported adverse events related to suicide in the post-marketing safety information in Japan and overseas.[12] Because estimated exposures in person-years remains unknown for adult patients and pediatric patients, it is not possible to compare the reported rate per person-years between adult patients and pediatric patients, but the adverse events in adult patients were considered to be not different from those in pediatric patients.

Table 18. Adverse events related to suicide in post-marketing safety information in Japan and overseas

	Japan			Overseas		
	Adult patients	Pediatric patients	Age unknown	Adult patients	Pediatric patients	Age unknown
Number of all adverse events	33 (7)	4044 (158)	346 (13)	738 (40)	8272 (889)	2856 (239)
Adverse events related to suicide	1 (0)	16 (3)	2 (0)	11 (10)	73 (65)	22 (19)
Major event						
Intentional overdose	1 (0)[a)]	11 (0)[a)]	1 (0)[a)]	1 (1)	12 (10)	3 (2)
Intentional self-injury	0	0	0	2 (1)	13 (8)	2 (1)
Suicidal ideation	0	3 (1)	1 (0)	6 (6)	32 (32)	14 (13)
Suicide attempt	0	2 (2)	0	0	6 (6)	1 (1)
Self-injurious ideation	0	0	0	1 (1)	6 (5)	0
Suicidal behaviour	0	0	0	0	3 (3)	2 (2)

Number of events (No. of serious events)

a) Because intentional overdose is not assessed for seriousness in Japan, this event was uniformly handled as non-serious event.

A risk of adverse events related to suicide in adult patients did not tend to be different from that in pediatric patients, and the package insert has already included a caution against such events. No additional caution was considered necessary.

[17] Events that fall under MedDRA standardized MedDRA queries (SMQ) "hostility/aggression (broad)"

7.R.2.9.2 Adverse events related to hostility and aggression

The applicant's explanation:

The incidence of adverse events related to hostility and aggression[18)] in the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133) were only 1.0% (1 of 101) of patients (aggression in 1 patient) in the guanfacine group in Study A3132 and 0.5% (1 of 191) of patients (irritability and laceration in 1 patient) in Study A3133.

Table 19 shows reported adverse events related to hostility and aggression in the post-marketing safety information in Japan and overseas.[12)] Because estimated exposures in person-years remains unknown for adult patients and pediatric patients, it is not possible to compare the report rate per person-years between adult patients and pediatric patients, but the adverse events in adult patients were considered to be not different from those in pediatric patients.

Table 19. Adverse events related to hostility and aggression in post-marketing safety information in Japan and overseas

	Japan			Overseas		
	Adult patients	Pediatric patients	Age unknown	Adult patients	Pediatric patients	Age unknown
Number of all adverse events	33 (7)	4044 (158)	346 (13)	738 (40)	8272 (889)	2856 (239)
Adverse events related to hostility and aggression	1 (0)	120 (1)	19 (0)	22 (1)	830 (69)	247 (17)
Major event						
Aggression	0	26 (0)	32 (3)	4 (1)	176 (12)	64 (0)
Irritability	0	43 (0)	5 (0)	5 (0)	122 (2)	39 (0)
Psychomotor excitability	0	0	0	4 (0)	93 (2)	28 (2)
Agitation	0	19 (0)	3 (0)	1 (0)	64 (9)	25 (0)
Impulsive behaviour	0	0	0	2 (0)	66 (1)	14 (2)
Disturbance in social behaviour	0	0	0	1 (0)	62 (0)	12 (1)
Anger	0	12 (1)	2 (0)	2 (2)	54 (2)	15 (0)
Affect lability	1 (0)	13 (0)	1 (0)	0	51 (2)	13 (2)
Abnormal behaviour	0	1 (0)	0	1 (0)	31 (5)	9 (0)
Psychotic disorder	0	0	0	1 (0)	12 (8)	7 (6)

Number of events (No. of serious events)

A risk of adverse events related to hostility and aggression in adult patients did not tend to be different from that in pediatric patients, and the package insert has already included a caution against such events. No additional caution was considered necessary.

PMDA's view on the safety of guanfacine:

- Blood pressure decreased and pulse rate decreased occurred more commonly in adult patients with AD/HD than in pediatric patients with AD/HD, and cardiovascular adverse events leading to treatment discontinuation occurred during the dose optimization period. Based on the findings, the package insert should include a caution about the risk of hypotension and bradycardia including differences in incidence between adult and pediatric patients with AD/HD, and any patient should be appropriately monitored during treatment with guanfacine.

[18)] Events that fall under MedDRA SMQ "hostility/aggression (broad)"

- Although cardiovascular adverse events commonly occurred in adult patients with AD/HD, most of these events were not severe or serious. Accordingly, it is acceptable to monitor adult patients with AD/HD as done for pediatric patients.

- Since adult patients with AD/HD who have comorbidity in the cardiovascular system or use drugs potentially affecting the cardiovascular system are expected to receive guanfacine, etc. the cardiovascular safety of long-term treatment with guanfacine should be continuously investigated through post-marketing activities.

- A management strategy for cardiovascular risks and post-marketing investigation will be finalized, taking account of comments raised in the Expert Discussion.

- For other adverse events, the safety profiles are unlikely to differ considerably between adult and pediatric patients with AD/HD, and thus no additional caution is necessary in the package insert.

7.R.3 Clinical positioning

PMDA asked the applicant to explain clinical positioning of guanfacine in adult patients with AD/HD based on its treatment experience in pediatric patients with AD/HD.

The applicant's explanation:

- According to an epidemiological investigation, adult patients with AD/HD are estimated to be 1.65% of the adult population, and no large difference is found in estimated prevalence between males and females (1.67% of males, 1.53% of females) (*Japanese Journal of Psychiatric Treatment*. 2013;28:155-62). Because a number of AD/HD cases tend to be found within a family, involvement of genetic factors is suggested, but contribution of specific genes is considered to be small. In addition, development of AD/HD is interpreted as follows: Intrauterine and perinatal environmental factors (smoking and stress of the mother, low birth weight, poor nutrient intake, abuse, etc.) are involved, and consequent neurobiological functional impairment (functional impairment in the frontal lobe, reward system, etc.) contributes to the development. The neurobiological condition characteristic to AD/HD in adults is suggested to be similar to that in pediatric patients (*J Int Neuropsychological Soc.* 2019;18:728-37, *Child Psychol Psychiatry.* 2009;50:669-78), and AD/HD in 30% to 50% of children are reported to persist even after they become adults.

- Drugs used to treat AD/HD in adults are classified into central stimulants and non-central stimulants as with ones for pediatric patients. Outside Japan, multiple central stimulants and non-central stimulants have been approved. In the clinical practice guidelines issued by the National Institute for Health and Care Excellence and Canadian ADHD Resource Alliance, central stimulants (methylphenidate hydrochloride, lisdexamfetamine, amphetamine, etc.) are recommended as the first-line drugs and non-central stimulant (atomoxetine hydrochloride) is recommended for patients who are intolerant or have not responded sufficiently to central stimulants. Outside Japan, multiple treatment options are available, and there is relatively low needs for a new drug targeting adult

patients with AD/HD. Thus guanfacine is not developed as a drug targeting adult patients with AD/HD.

- In Japan, no clinical practice guidelines specialized in AD/HD in adults have been published, but in the diagnosis and clinical practice guideline for AD/HD in children, methylphenidate hydrochloride of central stimulant and atomoxetine hydrochloride of non-stimulant are both positioned as the first-line drugs in consideration of the limited drug therapy options in Japan. In clinical settings, drugs are selected according to the patient's condition (Study Group for AD/HD diagnosis and clinical practice guideline. *Clinical practice guideline for the diagnosis and treatment of attention deficit hyperactivity disorder [ADHD]*. Edition 4. Jiho Inc., 2016). Currently available drugs with the indication of AD/HD in adults are limited to methylphenidate hydrochloride and atomoxetine hydrochloride. Based on the above, these drugs are considered to be used for the treatment of AD/HD in adult patients as done for pediatric patients with AD/HD.

PMDA asked the applicant to explain clinical positioning of guanfacine based on clinical study data of guanfacine.

The applicant's explanation:

- The Japanese phase III study (CTD 5.3.5.1-01, Study A3132) demonstrated the efficacy of guanfacine in adult patients with AD/HD [see Section 7.2]. In the guanfacine group in Study A3132, the total score in the Japanese version of the ADHD-RS-IV with adult prompts was decreased from baseline by 11.55 (−11.55, mean value) or approximately 36.7%. In clinical studies of many drugs in patients with AD/HD, responders are defined as patients achieving a decrease in endpoint parameter by 25% to 30% (*Clinical Therapeutics.* 2006;28:1892-1908). In studies using ADHD-RS-IV with adult prompts (*J ClinPsychiatry.* 2008;69:1364-73, *Neuropsychopharmacology.* 2015;40:2745-52), responders were also defined as patients achieving a decrease in score by 30%. The change observed in Study A3132 is considered to have a clinical significance.

- The safety profile of guanfacine is different from approved drugs. Although guanfacine showed effects on pulse and blood pressure, cardiovascular events, and adverse events in the central nervous system [see Section 7.R.2], neither abuse nor dependence is suggested.

- Based on the above, guanfacine can be used in adult patients with AD/HD as the first-line drug as in the cases of approved drugs.

PMDA's view:

- There are no major problems with positioning guanfacine as the first-line drug for adult patients with AD/HD as in the cases of approved drugs in consideration that (1) guanfacine has demonstrated its efficacy in adult patients with AD/HD in Japanese clinical studies, showing clinically significant improvement in AD/HD symptoms as in the cases of approved drugs; (2) guanfacine is positioned as the first-line drug in pediatric patients with AD/HD as in the cases of approved drugs; and (3)

therapeutic options for AD/HD in adults are limited, and thus drugs are selected based on clinical practice for treatment of AD/HD in children.

- In patients receiving guanfacine, however, adverse events of blood pressure decreased by >20 mmHg and pulse rate decreased by >20 bpm occurred, and the incidence of cardiovascular events was higher in adult patients with AD/HD in clinical studies than that in pediatric patients with AD/HD [see Section 7.R.2.2]. Many patients discontinued the treatment due to adverse events during early dosing period [see Section 7.R.5.1]. In light of the safety profile characteristic to guanfacine described above, etc., the necessity of positioning guanfacine as the second-line drug will be finalized, taking account of comments raised in the Expert Discussion, although guanfacine is positioned as the first-line drug for the treatment of AD/HD in children.

7.R.4 Indication

PMDA considers that there are no particular problems with the proposed indication (attention-deficit/hyperactivity disorder [AD/HD]) but will finalize the indication based on the review on clinical positioning [see Section 7.R.3].

7.R.5 Dosage and administration

7.R.5.1 Starting dose and up-titration method

PMDA asked the applicant to justify the starting dose of guanfacine and the up-titration method.

The applicant's explanation:
Dosage regimens of guanfacine for pediatric patients with AD/HD are established according to the body weight. The starting dose for adult patients with AD/HD, however, was uniformly proposed to be the same dose as the starting dose for pediatric patients with AD/HD weighing ≥50 kg (2 mg/day) because the mean body weight of adults aged ≥18 years is ≥50 kg for both males and females (Japan's National Health and Nutrition Survey Report in 2016, Part 2 Data from physical examination, Ministry of Health, Labour and Welfare, 2016, p.102). The up-titration method was established so that the dose was to be increased in increments of 1 mg/day every week as done for pediatric patients with AD/HD.

Then, the proposed starting dose and up-titration method were justified based on results from the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133) as follows:

- Table 20 shows the incidence of adverse events leading to treatment discontinuation in Studies A3132 and A3133. In Study A3132, the dose was forced to be increased to 4 mg/day in increments of 1 mg/day every week during the dose optimization period, but many subjects discontinued the treatment at 3 mg/day owing to the adverse events. Adverse events leading to treatment discontinuation included somnolence and blood pressure decreased (5 events each), bradycardia and thirst (2 events each), sinus bradycardia, orthostatic hypotension, suicide attempt, dizziness postural, dizziness, anxiety, poor quality sleep, insomnia, abdominal pain upper, and palpitations (1 event each) in the guanfacine group; and somnolence, sinus bradycardia, and malaise (1 event each) in the placebo group in Study A3132; somnolence (9 events), blood pressure decreased (8 events), malaise

(6 events), bradycardia (4 events), dizziness postural and dizziness (3 events each), middle insomnia and thirst (2 events each), and supraventricular tachycardia, influenza, headache, abdominal pain, diarrhoea, heart rate decreased, nasopharyngitis, electrocardiogram abnormal, white blood cell count decreased, neutrophil percentage decreased, depressed mood, nausea, orthostatic intolerance, and peripheral swelling (1 event each) in Study A3133. Adverse events in the cardiovascular system and central nervous system, which were attributable to the pharmacological action of guanfacine, commonly occurred.

Table 20. Incidence of adverse events leading to treatment discontinuation in Studies A3132 and A3133 (safety analysis set)

		Study A3132[a)]		Study A3133[a)b)]
		Placebo	Guanfacine	
No. of subjects evaluated		100	101	191
Number of subjects leading to discontinuation		3 (3.0)	20 (19.8)	38 (19.8)
Time to onset	≤1 week	2 (2.0)	11 (10.9)	25 (13.1)
	>1 week and ≤2 weeks	0	12 (11.8)	21 (11.0)
	>2 weeks and ≤3 weeks	1 (1.0)	4 (4.0)	14 (7.3)
	>3 weeks and ≤4 weeks	0	5 (5.0)	9 (4.7)
	>4 weeks and ≤5 weeks	0	2 (2.0)	5 (2.6)
Dose at the onset	2 mg/day	0	11 (10.9)	19 (9.9)
	3 mg/day	0	11 (10.9)	21 (11.0)
	4 mg/day	0	6 (5.9)	17 (8.9)
	5 mg/day	0	4 (4.0)	8 (4.2)
	6 mg/day	0	0	10 (5.2)
Severity	Mild	2 (2.0)	14 (13.9)	35 (18.3)
	Moderate	1 (1.0)	13 (12.9)	29 (15.2)
	Severe	0	2 (2.0)	2 (1.0)
Causal relationship to the study drug	Unrelated	0	7 (7.0)	17 (8.9)
	Related	3 (3.0)	19 (18.8)	36 (18.8)

No. of subjects with event (incidence, %)
a) Includes all adverse events in subjects who experienced at least 1 event leading to treatment discontinuation.
b) Includes subjects with ongoing adverse events from Study A3132

- Subgroup analyses were performed to identify patient characteristics in subjects who discontinued the study treatment. The results revealed that subjects with comorbidity accounted for 95.0% (19 of 20) of discontinued subjects in the guanfacine group in Study A3132, which tended to be higher than 74.3% (75 of 101) of subjects in the overall subjects in the guanfacine group. In addition, females accounted for 60.0% (12 of 20) of discontinued subjects, which was higher than 34.7% (35 of 101) of subjects in the overall subjects in the guanfacine group; and subjects weighing <50 kg accounted for 25.0% (5 of 20) of discontinued subjects, which tended to be higher than 9.9% (10 of 101) of subjects in the overall subjects in the guanfacine group.

- Regarding the starting dose and up-titration method of guanfacine, measures such as provision of the following statements were considered appropriate: (1) At the start and dose adjustment of guanfacine, the dose should be determined according to the patient's condition, and dosage regimens for patients aged <18 years should be taken into account as appropriate; and (2) for up-titration method, the dose should be increased in increments of 1 mg at intervals of ≥1 week, and for patients with the above characteristics, the interval for up-titration should be designed to be long enough.

Provided that patients and physicians are adequately informed of adverse events characteristic to guanfacine and given a precautionary statement that the dose should be carefully titrated in increments of 1 mg at intervals of ≥1 week, it would be possible to set the starting dose of guanfacine as 2 mg/day and up-titrate in increments of 1 mg at intervals of ≥1 week.

7.R.5.2 Maintenance dose

PMDA asked the applicant to explain the basis for the maintenance dose of guanfacine.

The applicant's explanation:

The Japanese phase III study in pediatric patients with AD/HD (initial application data CTD 5.3.5.1-01, Study A3122) demonstrated the efficacy of guanfacine in the 0.05 to 0.08 mg/kg group and 0.08 to 0.12 mg/kg group. Then, in Study A3122, the maximum dose per body weight specified for each group was administered, and the 0.05 to 0.08 mg/kg group demonstrated the efficacy and safety of guanfacine administered at 4 mg/day (0.08 mg/kg) to patients weighing 50 kg; and the dose in Study A3122 was designed not to exceed 6 mg/day. Based on the above, it was considered appropriate for the Japanese phase III study in adult patients with AD/HD (CTD 5.3.5.1-01, Study A3132) to be conducted at the maintenance dose of 4 to 6 mg/day in the guanfacine group.

The efficacy of guanfacine at 4 to 6 mg/day in the dose maintenance period was demonstrated in Study A3132 [see Section 7.2]. Table 21 shows the incidence of adverse events by dose in the dose maintenance period, in which none of the serious adverse events, severe adverse events, and adverse events leading to discontinuation occurred. The incidence of adverse events did not tend to increase with higher doses in the dose maintenance period. At the last evaluation, 25, 22, and 32 subjects received guanfacine at 4, 5, and 6 mg/day, respectively, showing an even distribution of the maintenance dose without any imbalance in the low dose or high dose.

Table 21. Incidence of adverse events by dose in the dose maintenance period in Study A3132

	Placebo	Guanfacine (by dose in the dose maintenance period)		
		4 mg	5 mg	6 mg
No. of subjects evaluated	95	27	23	33
Major event				
Nasopharyngitis	12 (12.6)	4 (14.8)	1 (4.3)	2 (6.1)
Somnolence	0	0	0	2 (6.1)
Dizziness	0	0	1 (4.3)	1 (3.0)
Constipation	0	0	1 (4.3)	1 (3.0)
Thirst	0	0	1 (4.3)	1 (3.0)
Diarrhoea	1 (1.1)	0	2 (8.7)	0
Blood pressure decreased	0	0	2 (8.7)	0
Initial insomnia	1 (1.1)	0	1 (4.3)	0
Influenza	2 (2.1)	0	0	0

No. of subjects with event (incidence, %)

Accordingly, it was considered appropriate to specify the maintenance dose at 4 to 6 mg/day in light of the following findings: (1) the efficacy of guanfacine was demonstrated within a dose range from 4 to 6 mg/day, and the number of subjects at each maintenance dose did not largely vary; and (2) no major safety problems have been identified at ≥4 mg/day.

Based on the above, the dosage and administration of guanfacine were established as shown below.

Dosage and administration
The usual starting dose for patients aged ≥18 years is 2 mg/day of guanfacine administered. The dose should be increased to the maintenance dose of 4 to 6 mg/day in increments of 1 mg at intervals of ≥1 week. The dose may be adjusted according to the symptom. The daily dose should not exceed 6 mg. Guanfacine should be administered orally once daily.

PMDA's view:

- Taking into account that many subjects discontinued the treatment due to adverse events associated with the pharmacological action of guanfacine during the dose optimization period in Studies A3132 and A3133, appropriate information should be provided so that adverse events can be reduced or avoided during the early dosing period. In the meantime, the applicant explained to caution that the dosage regimen for patients aged <18 years should also be considered appropriately. However, given that the proportion of subjects who discontinued the guanfacine treatment also differed depending on the presence of comorbidity, there is no adequate evidence for only considering the dosage regimen for patients aged <18 years according to the body weight. Although many subjects discontinued the treatment due to adverse events in the dose optimization period, neither severe nor serious adverse events occurred. On the assumption that appropriate cautions and information about the initial dosing regimen of guanfacine and the management strategy for cardiovascular risks [see Section 7.R.2.2] are provided, there are no major problems with the proposed dosage and administration that the dose is started at 2 mg/day irrespective of the patient's characteristics and then increased in increments of 1 mg at intervals of ≥1 week.

- There are no major problems with the maintenance dose of 4 to 6 mg/day, taking into account that major safety problem was not reported with guanfacine at 4 to 6 mg/day in subjects who had tolerated guanfacine during the dose optimization period.

- The dosage and administration reviewed above will be finalized, taking account of comments raised in the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant has explained that additional pharmacovigilance activities as described below are planned to be conducted to investigate the effects of guanfacine on the cardiovascular system in adult patients with AD/HD.

- A specified use-results survey with the target sample size of 750 adult patients with AD/HD will be conducted to evaluate the safety and efficacy of guanfacine in clinical use, and in this survey, each patient will be followed up for 1 year.

PMDA will finalize the main survey items, target sample size, and follow-up period in the specified use-results survey, 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 assessment is ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

The assessment is ongoing. The results and PMDA's conclusion 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 guanfacine has efficacy in the treatment of AD/HD in adults, and that guanfacine has acceptable safety in view of its benefits. Guanfacine can be one of the therapeutic options in the treatment of AD/HD in adults, and thus it has a clinical significance. PMDA considers that the management strategy for cardiovascular risks, clinical positioning, dosage and administration, and post-marketing investigations should be further discussed at the Expert Discussion.

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

Review Report (2)

April 24, 2019

Product Submitted for Approval

Brand Name	Intuniv Tablets 1 mg Intuniv Tablets 3 mg
Non-proprietary Name	Guanfacine Hydrochloride
Applicant	Shionogi & Co., Ltd.
Date of Application	August 10, 2018

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).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Review Report (1).

PMDA also discussed the following points and took action as necessary.

1.1 Management strategy for cardiovascular risks

The following view by PMDA was supported by the expert advisors: In the Japanese phase III study (CTD 5.3.5.1-01, Study A3132) and Japanese long-term treatment study (CTD 5.3.5.2-02, Study A3133) of guanfacine in adult patients with AD/HD, the proportion of patients with cardiovascular adverse events such as blood pressure decreased and pulse rate decreased tended to be higher than that in pediatric patients with AD/HD, and there were cardiovascular adverse events leading to treatment discontinuation during the dose optimization period. Thus, the package insert should include a caution about the risk of hypotension and bradycardia including differences in the incidences between adult and pediatric patients with AD/HD. The proportion of severe or serious adverse events, however, tended to be low. In consideration of the above, the expert advisors supported PMDA's view that there are no major problems with monitoring adult patients with AD/HD as done for pediatric patients with AD/HD [see Section 7.R.2 of the Review Report (1)].

The following view by PMDA was supported by the expert advisors: Since adult patients with AD/HD who have comorbidity in the cardiovascular system or use drugs potentially affecting the cardiovascular system may receive guanfacine, the safety in the cardiovascular system should be continuously investigated in patients receiving guanfacine for an extended period through post-marketing activities [see Section 7.R.2 of the Review Report (1)]. Patients who are expected to receive guanfacine are mostly young adults, and patients who have comorbidity in the cardiovascular system or use drugs potentially affecting the cardiovascular system concomitantly is assumed to be limited; expert advisors, therefore, commented that some measures should be taken to ensure that these patients are appropriately included in the post-marketing surveillance.

Based on the above, PMDA asked the applicant to explain investigations in the post-marketing surveillance.

The applicant's explanation:
The specified use-results survey (Table 24) with the target sample size of 750 adult patients with AD/HD is planned to include 35 patients who have comorbidity in the cardiovascular system and 25 patients who use drugs potentially affecting the cardiovascular system concomitantly, in light of characteristics of the patients receiving drugs in the same class.

PMDA accepted the above applicant's action.

1.2 Clinical positioning

The expert advisors supported PMDA's view that there are no major problems with positioning guanfacine as the first-line drug for adult patients with AD/HD as in the cases of approved drugs [see Section 7.R.3 of the Review Report (1)].

1.3 Dosage and administration

The following view by PMDA was supported by the expert advisors: Based on the assumption that appropriate cautions and information about the initial dosing regimen of guanfacine are provided, there are no major problems with the proposed regimen that the dose is started at 2 mg/day irrespective of the patient's characteristics and then increased in increments of 1 mg at intervals of ≥1 week [see Section 7.R.5 of the Review Report (1)]. There are no major problems with the maintenance dose of 4 to 6 mg/day [see Section 7.R.5 of the Review Report (1)].

Based on the above, PMDA instructed the applicant to include cautions for dose adjustment during the guanfacine treatment (especially, at the start of treatment and at dose adjustment) in the package insert. The applicant responded appropriately.

1.4 Risk management plan (draft)

In view of the discussion presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for guanfacine should include the safety specifications presented in

Table 22, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 23.

Table 22. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypotension and bradycardia • Syncope • Blood pressure increased after discontinuation of the treatment • Sedation	• QT prolonged • Dehydration • Cardiac valvulopathy • Suicidal behaviour/suicidal ideation • Hostility/aggression • Glucose metabolism abnormal (hypoglycaemia, blood glucose increased)	None
Efficacy specification		
None		

Table 23. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities[a)]	Additional risk minimization activities[a)]
• Early post-marketing phase vigilance (adults) • Specified use-results survey (adults)	• Early post-marketing phase vigilance (adults) • Preparation and distribution of materials for healthcare professionals (guide for proper use and reference sheet for Intuniv® dosing regimen) • Preparation and distribution of materials for patients, parents and guardians (“Guide for use of Intuniv®” brochure for proper use and materials for instructing how to use the drug)

a) Only additional pharmacovigilance activities and risk minimization activities related to this application are described.

Based on the above, PMDA asked the applicant to conduct the post-marketing surveillance to investigate the above specification.

The applicant explained that the specified use-results survey targeting adult patients with AD/HD as presented in Table 24 will be conducted.

Table 24. Outline of specified use-results survey (draft)

Objective	To survey cardiovascular events in clinical use
Survey method	Central registry system
Population	Adult patients with AD/HD who use guanfacine for the first time
Observation period	12 months
Planned sample size	750 patients (including 35 patients who have comorbidity in the cardiovascular system and 25 patients who use drugs potentially affecting the cardiovascular system concomitantly)
Main survey items	• Patient characteristics (age, sex, presence of electrocardiogram abnormality before guanfacine is started, timing of diagnosis, AD/HD status when guanfacine is started, severity, comorbidity, etc.) • Guanfacine treatment status (dose, daily dose, treatment duration, reason for discontinuation, etc.) • Prior therapy, concomitant drugs, concomitant therapy • Adverse events • Vital signs • Electrocardiography • ADHD-RS-IV with adult prompts, CGI-I, PGI-I

PMDA accepts the above, but results obtained from this survey, when available, should be provided to healthcare professionals immediately.

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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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 5.3.5.1-01, CTD 5.3.5.2-02) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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 has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following condition. Although this application is for a new indication and a new dosage, ≥4 years of the initially defined re-examination period remains, and thus the appropriate re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until March 29, 2025).

Indication

Attention-deficit/hyperactivity disorder (AD/HD) ~~in pediatric patients~~

(Strikethrough denotes deletions.)

Dosage and administration

Patients aged <18 years:

The usual starting dose for patients aged <18 years is 1 mg/day of guanfacine administered to ~~pediatric~~ patients weighing <50 kg or 2 mg/day of guanfacine administered to ~~pediatric~~ patients weighing ≥50 kg. The dose should be increased to the maintenance dose in the table below in increments of 1 mg at intervals of ≥1 week.

The dose may be adjusted according to the symptom. The daily dose should not exceed the maximum dose in the table below. Guanfacine should be administered orally once daily.

Body weight	Starting dose	Maintenance dose	Maximum dose
≥17 kg and <25 kg	1 mg	1 mg	2 mg
≥25 kg and <34 kg	1 mg	2 mg	3 mg
≥34 kg and <38 kg	1 mg	2 mg	4 mg
≥38 kg and <42 kg	1 mg	3 mg	4 mg
≥42 kg and <50 kg	1 mg	3 mg	5 mg
≥50 kg and <63 kg	2 mg	4 mg	6 mg
≥63 kg and <75 kg	2 mg	5 mg	6 mg
≥75 kg	2 mg	6 mg	6 mg

Patients aged ≥18 years:

The usual starting dose for patients aged ≥18 years is 2 mg/day of guanfacine administered. The dose should be increased to the maintenance dose of 4 to 6 mg/day in increments of 1 mg at intervals of ≥1 week.

The dose may be adjusted according to the symptom. The daily dose should not exceed 6 mg. Guanfacine should be administered orally once daily.

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Condition

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

Appendix

List of Abbreviations

AD/HD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder Rating Scale IV
AUC	Area Under Concentration-time Curve
CAARS	Conners' Adult ADHD rating Scale
CGI-I	Clinical Global Impression-Global Improvement
CGI-S	Clinical Global Impression-Severity of Illness
C_{max}	Maximum Concentration
CTD	Common Technical Document
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FAS	Full Analysis Set
HLGT	High-Level Group Terms
HLT	High-Level Terms
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese Version
MMRM	Mixed-effects Models for Repeated Measures
PGI-I	Patient Global Impression - Improvement
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Terms
QTcF interval	Fridericia-corrected QT Interval
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
t_{max}	Time to Reach Maximum Concentration
Intuniv	Intuniv Tablets 1 mg, Intuniv Tablets 3 mg
Guanfacine	Guanfacine Hydrochloride