Safety and Effectiveness of Guanfacine Hydrochloride Extended-Release in Adult Patients with ADHD in Japan: A Post-Marketing Surveillance Study

Akira Iwanami[1], Katsuaki Shirai[2], Hiroyuki Ida[2*]

[1]Department of Psychiatry, Showa University School of Medicine, Setagaya-ku, Tokyo, Japan

[2]Japan Medical Office, Takeda Pharmaceutical Company Limited, Tokyo, Japan

*****Corresponding author: Hiroyuki Ida
Address: Takeda Pharmaceutical Company Limited, 1-1, Nihonbashi-Honcho 2-Chome, Chuo-ku, Tokyo 103-8688, Japan
Tel: +81-3-3278-2111
Email: hiroyuki.ida@takeda.com

Supplemental Material

Supplemental Table 1. Prior ADHD medication (safety analysis population)

Prior ADHD medication	***n* (%) (*n* = 119)**
Atomoxetine only	88 (73.9)
Methylphenidate only	29 (24.4)
Methylphenidate + atomoxetine	2 (1.7)

ADHD attention-deficit/hyperactivity disorder.

Supplemental Table 2. Reasons for discontinuing ADHD medication (safety analysis population)

Prior ADHD medication	**Reason for discontinuation**	***n* (%)**
Atomoxetine	Total	88 (100.0)
	Inadequate response	55 (62.5)
	Onset of adverse reactions	29 (33.0)
	Patient request	13 (14.8)
	Other	3 (3.4)
Methylphenidate	Total	29 (100.0)
	Inadequate response	24 (82.8)
	Onset of adverse reactions	7 (24.1)
	Patient request	4 (13.8)
Methylphenidate + atomoxetine	Total	2 (100.0)
	Inadequate response	1 (50.0)
	Patient request	1 (50.0)

ADHD attention-deficit/hyperactivity disorder.

Supplemental Table 3. ADHD medications taken concomitantly with GXR (safety analysis population)

Concomitant medication	***n* (%)** **(*n* = 255)**
Methylphenidate	143 (56.1)
Atomoxetine	93 (36.5)
Methylphenidate + atomoxetine	19 (7.5)

ADHD attention-deficit/hyperactivity disorder, *GXR* guanfacine hydrochloride extended-release.

Supplemental Table 4. All ADRs

System organ class **Preferred term**	**Safety analysis population** **(*n* = 912)**
Number of patients (%)	
Any ADRs	301 (33.00)
Immune system disorders	1 (0.11)
Seasonal allergy	1 (0.11)
Psychiatric disorders	35 (3.84)
Aggression	1 (0.11)
Anger	2 (0.22)
Anxiety	2 (0.22)
Apathy	2 (0.22)
Delusion	1 (0.11)
Depressed mood	3 (0.33)
Depression	3 (0.33)
Enuresis	1 (0.11)
Hallucination	1 (0.11)
Impulsive behavior	1 (0.11)
Initial insomnia	1 (0.11)
Insomnia	4 (0.44)
Irritability	6 (0.66)
Libido decreased	1 (0.11)
Nightmare	1 (0.11)
Restlessness	1 (0.11)
Sleep disorders	5 (0.55)
Suicidal ideation	1 (0.11)
Abulia	4 (0.44)
Terminal insomnia	1 (0.11)
Nervous system disorders	202 (22.15)
Cerebral ischemia	2 (0.22)
Disturbance in attention	1 (0.11)
Dizziness	36 (3.95)
Dizziness postural	26 (2.85)

Dyskinesia	1 (0.11)
Head discomfort	2 (0.22)
Headache	8 (0.88)
Memory impairment	2 (0.22)
Mental impairment	2 (0.22)
Psychomotor hyperactivity	1 (0.11)
Sedation	4 (0.44)
Somnolence	137 (15.02)
Syncope	2 (0.22)
Eye disorders	1 (0.11)
Eye pain	1 (0.11)
Ear and labyrinth disorders	2 (0.22)
Tinnitus	1 (0.11)
Vertigo	1 (0.11)
Cardiac disorders	7 (0.77)
Bradycardia	2 (0.22)
Palpitations	4 (0.44)
Tachycardia	1 (0.11)
Vascular disorders	27 (2.96)
Diastolic hypertension	1 (0.11)
Hypertension	3 (0.33)
Hypotension	14 (1.54)
Orthostatic hypotension	9 (0.99)
Respiratory, thoracic and mediastinal disorders	2 (0.22)
Dyspnea	2 (0.22)
Gastrointestinal disorders	22 (2.41)
Abdominal pain	1 (0.11)
Chronic gastritis	1 (0.11)
Constipation	13 (1.43)
Diarrhea	1 (0.11)
Irritable bowel syndrome	1 (0.11)
Nausea	8 (0.88)
Skin and subcutaneous tissue disorders	4 (0.44)
Cold sweat	1 (0.11)

Drug eruption	1 (0.11)
Hyperhidrosis	1 (0.11)
Pruritus	1 (0.11)
Musculoskeletal and connective tissue disorders	1 (0.11)
Arthralgia	1 (0.11)
Renal and urinary disorders	1 (0.11)
Pollakiuria	1 (0.11)
Reproductive system and breast disorders	1 (0.11)
Erectile dysfunction	1 (0.11)
General disorders and administration site conditions	68 (7.46)
Asthenia	2 (0.22)
Chest discomfort	1 (0.11)
Chills	1 (0.11)
Fatigue	3 (0.33)
Feeling abnormal	6 (0.66)
Feeling cold	1 (0.11)
Malaise	34 (3.73)
Edema	1 (0.11)
Pain	1 (0.11)
Pyrexia	1 (0.11)
Thirst	23 (2.52)
Investigations	17 (1.86)
Amylase increased	1 (0.11)
Blood pressure decreased	17 (1.86)
Heart rate decreased	1 (0.11)
Injury, poisoning, and procedural complications	8 (0.88)
Sedation complication	8 (0.88)

ADRs were coded using MedDRA/J version (26.1).

ADR adverse drug reaction, *MedDRA* Medical Dictionary for Regulatory Activities.

Supplemental Table 5. Individual cases of serious ADRs

ADR	Sex of patient	Age group of patient (years)	Time of ADR onset (days)	Time to outcome after ADR (days)	Outcome	Time to resolution or improvement	Daily dosage of GXR at onset (mg)	Timing of GXR administration at onset	Action taken regarding GXR
Suicidal ideation	Male	30 to <40	301	79	Resolved	>2 to <3 months	6	Evening	Dose reduced
Mental impairment	Female	≥50	1	2	Resolved	<1 week	2	Evening	Discontinued
Mental impairment	Female	30 to <40	44	24	Resolved	>1 to <2 months	2	Before sleep	Dose remained unchanged
Dizziness	Male	18 to <30	23	15	Resolved	>2 weeks to <1 month	3	Evening	Interrupted
Somnolence	Male	18 to <30	23	15	Resolved	>2 weeks to <1 month	3	Evening	Interrupted
Cerebral ischemia	Female	30 to <40	8	21	Resolved	>1 to <2 months	3	Morning	Dose remained unchanged
Bradycardia	Female	18 to <30	20	36	Resolving	>2 to <3 months	3	Evening	Dose remained unchanged
Dizziness postural	Male	40 to <50	29	33	Resolved	>2 to <3 months	3	Evening	Discontinued
Blood pressure decreased	Male	40 to <50	29	33	Resolved	>2 to <3 months	3	Evening	Discontinued
Cerebral ischemia	Female	18 to <30	2	4	Resolved	<1 week	1	Evening	Discontinued
Delusion	Female	30 to <40	35	65	Resolved	>2 to <3 months	4	Evening	Discontinued
Hallucination	Female	30 to <40	35	65	Resolved	>2 to <3 months	4	Evening	Discontinued
Psychomotor hyperactivity	Female	30 to <40	35	65	Resolved	>2 to <3 months	4	Evening	Discontinued
Syncope	Male	18 to <30	9	7	Resolved	>1 to <2 weeks	4	Evening	Discontinued
Bradycardia	Female	40 to <50	140	23	Resolved	>1 to <2 months	4	Morning	Discontinued
Syncope	Female	≥50	206	45	Resolved	>2 to <3 months	6	Before sleep	Dose reduced
Erectile dysfunction	Male	30 to <40	1	15	Resolving	>2 weeks to <1 month	2	Evening	Dose remained unchanged

ADRs were coded using MedDRA/J version (26.1).

ADR adverse drug reaction, *GXR* guanfacine hydrochloride extended-release, *MedDRA* Medical Dictionary for Regulatory Activities.

Supplemental Table 6. ADRs stratified by psychiatric comorbidities (safety analysis population)

System organ class **Preferred term**	**Major depressive disorder** **(*n* = 195)**	**Anxiety disorders** **(*n* = 162)**	**Autism spectrum disorder** **(*n* = 210)**	**Sleep disorders** **(*n* = 286)**	**Bipolar disorder** **(*n* = 147)**
Occurrences of events, *n*	79	69	77	94	50
Number of patients with events (%)					
Total	65 (33.33)	54 (33.33)	60 (28.57)	78 (27.27)	38 (25.85)
Psychiatric disorders	12 (6.15)	8 (4.94)	9 (4.29)	13 (4.55)	7 (4.76)
Aggression	0 (0.00)	0 (0.00)	1 (0.48)	0 (0.00)	0 (0.00)
Anger	1 (0.51)	0 (0.00)	1 (0.48)	1 (0.35)	0 (0.00)
Anxiety	1 (0.51)	1 (0.62)	1 (0.48)	1 (0.35)	1 (0.68)
Apathy	0 (0.00)	1 (0.62)	2 (0.95)	0 (0.00)	1 (0.68)
Delusion	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)
Depressed mood	3 (1.54)	1 (0.62)	2 (0.95)	1 (0.35)	0 (0.00)
Depression	1 (0.51)	0 (0.00)	1 (0.48)	1 (0.35)	0 (0.00)
Enuresis	1 (0.51)	0 (0.00)	1 (0.48)	0 (0.00)	0 (0.00)
Hallucination	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)
Impulsive behavior	0 (0.00)	0 (0.00)	1 (0.48)	0 (0.00)	0 (0.00)
Initial insomnia	1 (0.51)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Insomnia	2 (1.03)	0 (0.00)	0 (0.00)	1 (0.35)	0 (0.00)
Irritability	1 (0.51)	4 (2.47)	1 (0.48)	1 (0.35)	1 (0.68)
Sleep disorders	1 (0.51)	0 (0.00)	0 (0.00)	5 (1.75)	3 (2.04)
Suicidal ideation	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.35)	1 (0.68)
Abulia	3 (1.54)	2 (1.23)	1 (0.48)	2 (0.70)	0 (0.00)
Terminal insomnia	0 (0.00)	0 (0.00)	1 (0.48)	0 (0.00)	0 (0.00)
Nervous system disorders	55 (28.21)	48 (29.63)	52 (24.76)	66 (23.08)	34 (23.13)
Cerebral ischemia	1 (0.51)	1 (0.62)	2 (0.95)	1 (0.35)	0 (0.00)
Dizziness	8 (4.10)	12 (7.41)	10 (4.76)	20 (6.99)	10 (6.80)
Dizziness postural	8 (4.10)	8 (4.94)	4 (1.90)	10 (3.50)	4 (2.72)
Dyskinesia	1 (0.51)	1 (0.62)	0 (0.00)	1 (0.35)	1 (0.68)
Head discomfort	0 (0.00)	2 (1.23)	1 (0.48)	0 (0.00)	1 (0.68)
Headache	3 (1.54)	2 (1.23)	2 (0.95)	4 (1.40)	3 (2.04)

Memory impairment	1 (0.51)	0 (0.00)	0 (0.00)	2 (0.70)	0 (0.00)
Mental impairment	2 (1.03)	1 (0.62)	2 (0.95)	2 (0.70)	0 (0.00)
Psychomotor hyperactivity	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)
Sedation	0 (0.00)	0 (0.00)	1 (0.48)	0 (0.00)	1 (0.68)
Somnolence	38 (19.49)	31 (19.14)	39 (18.57)	36 (12.59)	17 (11.56)

ADRs were coded using MedDRA/J version (26.1).

ADR adverse drug reaction, *MedDRA* Medical Dictionary for Regulatory Activities

Supplemental Table 7. Incidence of ADRs by patient demographics, baseline characteristics, and treatment factors (safety analysis population)

Parameters	Classifications	Total (n = 912)	Number of patients with ADR (n = 301)	Incidence of ADRs (%)	Chi-square test	Cochran–Armitage test[a]
Sex	Male	460	127	27.61	p = 0.0005	
	Female	452	174	38.50		
Age	18 to <30 years	370	127	34.32	p = 0.3150	p = 0.1187
	30 to <40 years	232	83	35.78		
	40 to <50 years	194	60	30.93		
	≥50 years	116	31	26.72		
ADHD subtype	Predominantly inattentive	442	151	34.16	p = 0.7359	
	Predominantly hyperactive-impulsive	78	26	33.33		
	Combined	386	122	31.61		
	Unknown	6	2	33.33		
Severity of ADHD[b]	Mild	374	112	29.95	p = 0.2084	p = 0.0773
	Moderate	449	155	34.52		
	Severe	89	34	38.20		
Time since diagnosis of ADHD	<1 year	561	192	34.22	p = 0.2497	p = 0.1249
	1 to <3 years	148	49	33.11		
	3 to <5 years	100	35	35.00		
	≥5 years	103	25	24.27		
Presence of ECG abnormalities	No	893	291	32.59	p = 0.9563	
	Yes	12	4	33.33		
	Unknown	7	6	85.71		
Comorbid conditions	No	280	69	24.64	p = 0.0004	
	Yes	632	232	36.71		
Psychiatric comorbidities	No	316	81	25.63	p = 0.0006	
	Yes	596	220	36.91		
Oppositional defiant disorder	No	908	299	32.93	p = 0.4688	

	Yes	4	2	50.00		
Conduct disorder	No	904	300	33.19	$p = 0.2154$	
	Yes	8	1	12.50		
Learning disability	No	904	300	33.19	$p = 0.2154$	
	Yes	8	1	12.50		
Major depressive disorder	No	717	224	31.24	$p = 0.0299$	
	Yes	195	77	39.49		
Bipolar disorder	No	765	248	32.42	$p = 0.3905$	
	Yes	147	53	36.05		
Autism spectrum disorder	No	702	224	31.91	$p = 0.1983$	
	Yes	210	77	36.67		
Anxiety disorders	No	750	229	30.53	$p = 0.0006$	
	Yes	162	72	44.44		
Tic	No	909	300	33.00	$p = 0.9903$	
	Yes	3	1	33.33		
Sleep disorders	No	626	188	30.03	$p = 0.0047$	
	Yes	286	113	39.51		
Hypotension, orthostatic hypotension, or bradycardia	No	907	297	32.75	$p = 0.0250$	
	Yes	5	4	80.00		
Cardiovascular disease	No	842	269	31.95	$p = 0.0186$	
	Yes	70	32	45.71		
Hypertension	No	862	281	32.60	$p = 0.2792$	
	Yes	50	20	40.00		
Arrhythmia	No	899	293	32.59	$p = 0.0275$	
	Yes	13	8	61.54		
Ischemic heart disease	No	909	301	33.11	$p = 0.2233$	
	Yes	3	0	0.00		
Cerebrovascular accident	No	912	301	33.00		
	Yes	0				
Hepatic impairment	No	910	300	32.97	$p = 0.6089$	

	Yes	2	1	50.00		
Renal impairment	No	911	300	32.93	$p = 0.1540$	
	Yes	1	1	100.00		
Other	No	724	221	30.52	$p = 0.0018$	
	Yes	188	80	42.55		
Status of prior ADHD treatment	No prior ADHD treatment	570	189	33.16	$p = 0.2987$	
	Discontinued prior treatment	119	32	26.89		
	Continued prior treatment in addition to receiving GXR	208	73	35.10		
	Other	15	7	46.67		
Initial daily dose	<1 mg	11	2	18.18	$p = 0.4216$	$p = 0.1218$
	1 to <2 mg	445	139	31.24		
	2 to <3 mg	449	157	34.97		
	≥3 mg	7	3	42.86		
Maximum daily dose	<1 mg	4	1	25.00	$p = 0.6143$	$p = 0.6649$
	1 to <2 mg	184	59	32.07		
	2 to <3 mg	267	91	34.08		
	3 to <4 mg	205	67	32.68		
	4 to <5 mg	136	52	38.24		
	5 to <6 mg	43	10	23.26		
	6 mg	73	21	28.77		
Total dose	<90 mg	235	123	52.34	$p < 0.0001$	$p < 0.0001$
	90 to <270 mg	137	51	37.23		
	270 to <540 mg	137	36	26.28		
	540 to <1080 mg	237	52	21.94		
	≥1080 mg	166	39	23.49		
Duration of GXR treatment	<1 month	174	101	58.05	$p < 0.0001$	$p < 0.0001$
	1 to <3 months	143	58	40.56		
	3 to <6 months	92	32	34.78		

	6 to <12 months	108	33	30.56		
	≥12 months	395	77	19.49		
Used concomitant medications (excluding medications to treat adverse events)	No	281	70	24.91	$p = 0.0005$	
	Yes	631	231	36.61		
Concomitant ADHD medications	No	657	205	31.20	$p = 0.0632$	
	Yes	255	96	37.65		
Psychotropic medications (excluding ADHD medications)	No	426	120	28.17	$p = 0.0036$	
	Yes	486	181	37.24		
Cardiovascular medications	No	889	288	32.40	$p = 0.0151$	
	Yes	23	13	56.52		

[a]A Cochran–Armitage test was performed for all parameters with ordinal scales that have more than three categories.
[b]Based on the guidelines in the American Psychiatric Association's Diagnostic and Statistical Manual Fifth Edition (DSM-5).
ADHD attention-deficit/hyperactivity disorder, *ADR* adverse drug reaction, *GXR* guanfacine hydrochloride extended-release.

Supplemental Table 8. Change in ADHD-RS-IV total and subscale scores at 12 months by autism spectrum disorder status (safety analysis population)

	ADHD-RS-IV total score					**Inattention subscale score**					**Hyperactivity-impulsivity subscale score**				
	Baseline	**At 12 months**				**Baseline**	**At 12 months**				**Baseline**	**At 12 months**			
	Mean (SD)	**Mean (SD)**	**Change from baseline, mean (SD)**	**Change from baseline (95% CI)**	***P* value[a]**	**Mean (SD)**	**Mean (SD)**	**Change from baseline, mean (SD)**	**Change from baseline (95% CI)**	***P* value[a]**	**Mean (SD)**	**Mean (SD)**	**Change from baseline, mean (SD)**	**Change from baseline (95% CI)**	***P* value[a]**
With autism spectrum disorder (n = 77)	26.0 (8.6)	15.4 (7.9)	−10.6 (8.3)	(−12.5, −8.7)	$p <$ 0.0001	17.5 (4.9)	10.5 (5.1)	−6.9 (5.4)	(−8.2, −5.7)	$p <$ 0.0001	8.6 (5.4)	4.9 (4.1)	−3.7 (4.5)	(−4.7, −2.6)	$p <$ 0.0001
Without autism spectrum disorder (n = 208)	26.7 (9.9)	14.0 (8.2)	−12.8 (8.4)	(−13.9, −11.6)	$p <$ 0.0001	17.8 (5.0)	9.6 (4.9)	−8.3 (5.0)	(−8.9, −7.6)	$p <$ 0.0001	8.9 (6.3)	4.4 (4.3)	−4.5 (4.7)	(−5.2, −3.9)	$p <$ 0.0001

[a]Mean ADHD-RS-IV total and subscale scores at 12 months were compared with mean baseline values using two-sided paired *t*-tests.
ADHD-RS-IV Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; *SD* standard deviation; *CI* confidence interval.