Summary Report of Benefit-Risk Assessment

TARLIGE FILM-COATED TABLET 2.5 MG, 5 MG, 10 MG, 15 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Mirogabalin besilate eqv. mirogabalin
Product Registrant	A. MENARINI SINGAPORE PTE. LTD.
Product Registration Number	SIN17575P, SIN17574P, SIN17576P, SIN17577P
Application Route	Abridged evaluation
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A INTRODUCTION

Tarlige is indicated for the treatment of neuropathic pain in adults.

The active substance, mirogabalin, is a ligand that binds strongly and specifically to calcium channel α2δ subunits. Mirogabalin exhibits its analgesic effect by reducing calcium currents through binding to the α2δ subunit, which has an auxiliary role in voltage-gated calcium channel function in the nervous system. Its analgesic effect may also involve activation of the noradrenergic pathway in the descending pain inhibitory system.

Tarlige is available as film-coated tablets containing mirogabalin besilate equivalent to 2.5 mg, 5 mg, 10 mg and 15 mg of mirogabalin. Other ingredients in the tablet core are carboxymethylcellulose calcium, citric acid hydrate, d-mannitol, magnesium aluminometasilicate, magnesium stearate, microcrystalline cellulose and tocopherol. Ingredients in the film coating include hypromellose, talc, titanium oxide, yellow ferric oxide and red ferric oxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, mirogabalin besilate, is manufactured at Daiichi Sankyo Chemical Pharma Co., Ltd., Odawara Plant, Kanagawa, Japan. The drug product, Tarlige Film-Coated Tablet, is manufactured at Taiyo Pharma Tech. Co., Ltd., Takatsuki Plant, Osaka, Japan and packaged at Synmosa Biopharma Corporation, Synmosa Plant, Hsin Chu Hsien, Taiwan.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP).

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities were either toxicologically qualified or adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 30°C with a re-test period of 36 months. The packaging is double low-density polyethylene (LDPE) bags closed with twist ties, and placed in aluminium laminated bag containing oxygen scavenger as inner containers.

Drug product:

The tablets are manufactured using a direct compression approach followed by film-coating which is considered a standard manufacturing process.

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All manufacturing sites are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were either toxicologically qualified or adequately controlled in accordance with ICH Q3B guidelines. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is an Aluminium-Aluminium blister embedded with desiccant.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of mirogabalin in the treatment of neuropathic pain was based primarily on three pivotal Phase 3 studies: J303 (Japan-Asia DPNP P3 study), J304 (Japan-Asia PHN P3 study) and J314 (Japan-Asia CNeP P3 study). All three studies were multicentre, double-blind, randomised studies of mirogabalin compared with placebo in patients with diabetic peripheral neuropathic pain (DPNP), post-herpetic neuralgia (PHN) and central neuropathic pain after spinal cord injury (CNePSCI), respectively.

The efficacy of mirogabalin was further supported by three additional studies: J313 (Japanese DPNP/PHN renal impairment safety study), J202 (Japan-Asia DPNP P2 study) and U201 (US DPNP P2 study).

J202 (Japan-Asia DPNP P2, dose-response)

Study J202 was a Phase 2, randomised, double-blind, placebo- and pregabalin-controlled, dose-finding study in Asian patients with pain associated with diabetic peripheral neuropathy. Patients were randomised in a 1:1:1:1:1 ratio, stratified by study site, to receive placebo, pregabalin 150 mg twice daily (BID), or mirogabalin 5 mg BID, 10 mg BID or 15 mg BID.

A total of 450 patients were randomised, of whom 446 were included in the Full Analysis Set (FAS): 88 in the placebo arm, 85 in the pregabalin arm, and 90, 93 and 90 in the mirogabalin 5 mg BID, 10 mg BID and 15 mg BID arms, respectively. During the 1-week titration period, patients in the pregabalin arm received 75 mg BID, while those in the mirogabalin arms received once daily dose of the respective BID doses.

For the primary endpoint of mean change from baseline to Week 7 in average daily pain score (ADPS), all mirogabalin arms showed numerical improvement compared with placebo; however, the between-arm differences were not statistically significant. For the secondary endpoint of Short-Form McGill Pain Questionnaire (SF-MPQ) visual analog scale (VAS), greater numerical reductions from baseline to Week 7 were observed in each mirogabalin arm compared with placebo. The LS mean difference versus placebo was statistically significant only in the mirogabalin 15 mg BID arm (−7.4; $p = 0.0093$).

Table 1 Summary of Efficacy Endpoints in Study J202 (FAS)

		Pregabalin	Mirogabalin

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	Placebo N = 88	150 mg BID N = 85	5 mg BID N = 90	10 mg BID N = 93	15 mg BID N = 90
ADPS					
Baseline, mean	6.01	6.07	5.78	5.85	5.91
Week 7 change from baseline, LS mean [a]	-1.45	-1.41	-1.87	-1.81	-1.74
Difference of LS mean vs placebo (95% CI)		0.03 (-0.45, 0.52)	-0.42 (-0.99, 0.15)	-0.37 (-0.93, 0.20)	-0.30 (-0.87, 0.27)
P value		0.8911	0.1995	0.2886	0.4704
SF-MPQ VAS					
Baseline, mean	61.5	63.1	60.4	61.2	62.4
Week 7 change from baseline, LS mean [a]	-16.7	-17.2	-21.9	-22.1	-24.2
Difference of LS mean vs placebo (95% CI)		-0.5 (-6.2, 5.2)	-5.2 (-10.8, 0.4)	-5.4 (-10.9, 0.2)	-7.4 (-13.0, -1.8)
P value		0.8651	0.0691	0.0577	**0.0093**

a. Missing values at Week 7 were imputed using the last observation carried forward (LOCF) approach, and the data were analysed using an ANCOVA model including treatment as a fixed effect and baseline value as a covariate.
LS: least squares

U201 (US DPNP P2, dose-response)

Study U201 was a Phase 2 randomised, double-blind, placebo- and pregabalin-controlled study conducted in US patients with DPNP. Patients were randomised in a 2:1:1:1:1:1:1 ratio to receive placebo, pregabalin 150 mg BID, or one of five mirogabalin regimens: 5 mg once daily (QD), 10 mg QD, 15 mg QD, 10 mg BID or 15 mg BID. During the 1-week titration period, patients in the pregabalin arm received 75 mg BID, while those in the mirogabalin 15 mg BID arm received 15 mg QD.

A total of 452 patients were randomised, of whom 433 were included in the FAS: 108 in the placebo arm, 50 in the pregabalin arm, and 55, 56, 51, 56 and 57 in the mirogabalin 5 mg QD, 10 mg QD, 15 mg QD, 10 mg BID and 15 mg BID arms, respectively.

For the primary endpoint of mean change from baseline to Week 5 in ADPS, statistically significant improvements versus placebo were observed in the mirogabalin 15 mg QD, 10 mg BID and 15 mg BID arms. For the SF-MPQ VAS, greater numerical reductions from baseline to Week 5 were observed across all mirogabalin arms compared with placebo. The LS mean differences versus placebo were statistically significant ($p < 0.05$) for the mirogabalin 10 mg QD, 15 mg QD and 15 mg BID arms.

Table 2 Summary of Efficacy Results in Study U201 (FAS)

	Placebo N = 108	Pregabalin 150 mg BID N = 50	Mirogabalin				
			5 mg QD N = 55	10 mg QD N = 56	15 mg QD N = 51	10 mg BID N = 56	15 mg BID N = 57
ADPS							
Baseline, mean	7.00	6.63	6.88	6.79	6.56	6.69	6.75
Week 5 change from baseline, LS mean [a]	-1.79	-1.84	-2.01	-2.32	-2.73	-2.67	-2.80
Difference of LS mean vs placebo (95% CI)		-0.05 (-0.81, 0.70)	-0.22 (-0.95, 0.51)	-0.53 (-1.25, 0.20)	-0.94 (-1.69, -0.19)	-0.88 (-1.61, -0.16)	-1.01 (-1.74, -0.29)
P value		0.8916	0.5569	0.1544	**0.0137**	**0.0171**	**0.0060**
SF-MPQ VAS							
Baseline, mean	71.12	67.68	72.64	69.64	68.63	66.82	70.75
Week 5 change from baseline, LS mean [a]	-20.34	-20.12	-26.31	-28.80	-29.19	-26.47	-32.46

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Difference of LS mean vs placebo (95% CI)		0.22 (-8.02, 8.47)	-5.97 (-13.94, 2.00)	-8.46 (-16.43, -0.49)	-8.85 (-17.04, -0.67)	-6.13 (-14.13, 1.86)	-12.12 (-20.04, -4.20)
P value		0.9576	0.1419	**0.0376**	**0.0340**	0.1324	**0.0028**

a. Missing values at Week 5 were imputed using the LOCF approach, and the data were analysed using an ANCOVA model including treatment as a fixed effect and baseline value as a covariate.

J303 (Japan-Asia DPNP P3) and J304 (Japan-Asia PHN P3)

Studies J303 and J304 were similarly-designed, Phase 3, multicentre, randomised studies of mirogabalin compared with placebo in Asian patients with peripheral neuropathic pain. Study J303 recruited patients with DPNP and J304 included PHN patients.

In the double-blind (DB) phases of J303 and J304, patients were randomised in a 1:1:1:2 ratio to receive oral mirogabalin 15 mg QD, 10 mg BID, 15 mg BID, or placebo, stratified by baseline ADPS (<6.0 or ≥6.0). The DB treatment period comprised a dose titration period of 1 to 2 weeks followed by a fixed-dose period of 12 to 13 weeks. During titration, patients in the 15 mg QD arm received mirogabalin 5 mg QD in Week 1 and 10 mg QD in Week 2, while patients in the 10 mg BID and 15 mg BID arms received 5 mg BID in Week 1 and 10 mg BID in Week 2; patients in the 15 mg BID arm were further increased to 15 mg BID from Week 3. Paracetamol was permitted as rescue medication. A placebo-controlled superiority design was considered appropriate given the high and variable placebo response typically observed in pain trials.

Both studies also included a 52-week, single-arm, open-label long-term (LT) phase. During the LT phase, mirogabalin was administered at 5 mg BID for 2 weeks, followed by 10 mg BID for 2 weeks. Thereafter, during the 48-week dose-adjustment period, the dose could be increased to 15 mg BID at the physician's discretion, with subsequent adjustments permitted between 10 mg and 15 mg BID.

The primary efficacy endpoint in the DB phase was the change from baseline to Week 14 in ADPS, assessed using an 11-point Numerical Rating Scale ranging from 0 (no pain) to 10 (worst possible pain). The daily pain scores were recorded in electronic patient diaries and averaged over a 7-day period to derive the ADPS. Key secondary efficacy endpoints included the ADPS responder rate (i.e., proportion of patients achieving ≥30% and ≥50% reduction from baseline to Week 14) and change from baseline to Week 14 in the SF-MPQ VAS, modified Brief Pain Inventory-Short Form (BPI-SF), Patient Global Impression of Change (PGIC), and average daily sleep-interference score (ADSIS). Multiplicity control was applied only to the between-group comparisons for the primary ADPS endpoint, using a prespecified gatekeeping procedure incorporating Bonferroni–Holm testing. The secondary efficacy analyses were not multiplicity-adjusted, and their *p*-values were nominal. The SF-MPQ VAS was a 100-mm patient-rated scale of pain intensity, ranging from 0 mm (no pain) to 100 mm (worst possible pain). The modified BPI-SF assessed pain severity (worst, least and average pain, and pain right now) and interference with daily functions, each on an 11-point scale from 0 to 10. The PGIC was a 7-point patient-rated assessment of overall change from baseline, ranging from 1 (very much improved) to 7 (very much worse). The ADSIS was the weekly average of daily 11-point ratings of how much pain interfered with sleep during the previous 24 hours, ranging from 0 (did not interfere) to 10 (completely interfered).

In study J303, 854 patients were randomised; 20 patients from one Korean site were excluded from all analyses due to a serious Good Clinical Practice (GCP) violation, resulting in 834 patients in the randomised analysis set. Of these, 824 were included in the modified intent-to-treat (mITT) analysis set, defined as patients in the randomised analysis set who received at

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least one dose of study drug. The mITT population comprised 164, 165, 165 and 330 patients in the mirogabalin 15 mg QD, 10 mg BID, 15 mg BID and placebo arms, respectively. The median age was 62 years (range: 26 to 84 years), most patients were male (73%), and all patients were Asian. The mean baseline ADPS was 5.58 (SD 0.963), and the median duration of painful diabetic peripheral neuropathy was 36.0 months (range: 6 to 300 months). In study J304, 765 patients were randomised and 763 were included in the mITT, comprising 152, 153, 155 and 303 patients in the mirogabalin 15 mg QD, 10 mg BID, 15 mg BID and placebo arms, respectively. The median age was 68 years (range: 25 to 89 years), most patients were male (60%), and all patients were Asian. The mean baseline ADPS was 5.71 (SD 1.069), and the median duration of post-herpetic neuralgia was 18.0 months (range: 0 to 437 months).

In J303, the primary analysis of change from baseline in Week 14 ADPS showed a statistically significant improvement versus placebo only in the mirogabalin 15 mg BID arm, with LS mean changes of −1.81 and −1.31 in the mirogabalin 15 mg BID and placebo arms, respectively (difference in LS mean vs placebo: −0.50; p = 0.0027). Statistical significance was not demonstrated for the mirogabalin 10 mg BID or 15 mg QD arms, for which the LS mean changes from baseline were −1.47 and −1.34, respectively, with corresponding differences versus placebo of −0.15 (95% CI: −0.48, 0.17) and −0.03 (95% CI: −0.35, 0.30). The sensitivity analyses, including analyses using the Per Protocol Set (PPS), alternative shifting parameters, alternative imputation methods, and mixed-effect model with repeated measures (MMRM) using observed data only, were generally consistent with the primary analysis. In J304, all three mirogabalin dose arms demonstrated statistically significant improvement in Week 14 ADPS compared with placebo, with LS mean differences versus placebo of −0.41 for 15 mg QD, −0.47 for 10 mg BID and −0.77 for 15 mg BID (all $p < 0.02$). The sensitivity analyses were consistent with the primary analysis, supporting the robustness of the findings. A dose-response relationship was observed in both studies. Although a statistically significant treatment effect on the primary endpoint was not demonstrated for mirogabalin 10 mg BID in J303, this was not considered a major concern, as the posology allows dose adjustment between 10 mg and 15 mg BID according to individual patient symptoms and tolerability.

In J303, the Week 14 ADPS responder rates were numerically higher with mirogabalin 15 mg BID than placebo. The proportions of patients achieving ≥30% reduction from baseline in ADPS were 36.7%, 35.8% and 44.8% in the placebo, mirogabalin 10 mg BID and mirogabalin 15 mg BID arms, respectively. The corresponding ≥50% responder rates were 19.4%, 20.0% and 30.9%, with nominal statistical significance versus placebo demonstrated only for the mirogabalin 15 mg BID arm (OR 1.86; p = 0.0048). In J304, the ≥30% responder rates were 35.0%, 45.1% and 49.7% in the placebo, mirogabalin 10 mg BID and mirogabalin 15 mg BID arms, respectively, with nominal significance versus placebo observed for both mirogabalin 10 mg BID (OR 1.52; p = 0.0405) and 15 mg BID (OR 1.81; p = 0.0035). The corresponding ≥50% responder rates were 19.8%, 26.8% and 29.0%, with nominal significance versus placebo observed only for the mirogabalin 15 mg BID arm (OR 1.63; p = 0.0336).

The efficacy of mirogabalin was further supported by numerical improvements and/or nominally significant differences versus placebo across secondary endpoints based on multidimensional pain assessments, including the SF-MPQ VAS and modified BPI-SF.

Table 3 Summary of Key Efficacy Results in Studies J303 and J304 (mITT Analysis Set)

	J303 (DPNP)				J304 (PHN)			
		Mirogabalin				Mirogabalin		
	Placebo N = 330	15 mg QD N = 164	10 mg BID N = 165	15 mg BID N = 165	Placebo N = 303	15 mg QD N = 152	10 mg BID N = 153	15 mg BID N = 155
Primary endpoint, Change in ADPS								

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Baseline ADPS, mean	5.59	5.59	5.57	5.55	5.75	5.69	5.70	5.65
Week 14 change from baseline, LS mean [a]	-1.31	-1.34	-1.47	-1.81	-1.20	-1.61	-1.68	-1.97
Difference of LS mean vs placebo (95% CI)		-0.03 (-0.35, 0.30)	-0.15 (-0.48, 0.17)	-0.50 (-0.82, -0.17)		-0.41 (-0.74, -0.07)	-0.47 (-0.81, -0.14)	-0.77 (-1.10, -0.44)
P value		0.8773	0.3494	**0.0027**		**0.0170**	**0.0058**	**<0.0001**
Secondary endpoints[c]								
≥30% reduction in ADPS at Week 14 from baseline, n (%)	121 (36.7)	64 (39.0)	59 (35.8)	74 (44.8)	106 (35.0)	69 (45.4)	69 (45.1)	77 (49.7)
Odds Ratio (95% CI)		1.11 (0.75, 1.63)	0.96 (0.65, 1.42)	1.41 (0.96, 2.05)		1.54 (1.03, 2.29)	1.52 (1.02, 2.27)	1.81 (1.21, 2.69)
P value		0.6102	0.8437	0.0792		**0.0363**	**0.0405**	**0.0035**
≥50% reduction in ADPS at Week 14 from baseline, n (%)	64 (19.4)	34 (20.7)	33 (20.0)	51 (30.9)	60 (19.8)	35 (23.0)	41 (26.8)	45 (29.0)
Odds Ratio (95% CI)		1.09 (0.68, 1.74)	1.04 (0.65, 1.66)	1.86 (1.21, 2.85)		1.20 (0.75, 1.93)	1.48 (0.93, 2.34)	1.63 (1.04, 2.56)
P value		0.7218	0.8754	**0.0048**		0.4526	0.0964	**0.0336**
Baseline SF-MPQ VAS, mean	58.5	58.0	57.3	58.7	59.4	58.5	59.3	59.0
Week 14 change from baseline, LS mean [b]	-16.6	-16.8	-18.1	-22.5	-13.6	-18.7	-19.3	-21.4
Difference of LS mean vs placebo (95% CI)		-0.4 (-4.1, 3.3)	-1.9 (-5.6, 1.7)	-5.9 (-9.5, -2.2)		-5.1 (-8.8, -1.4)	-5.7 (-9.4, -1.9)	-7.8 (-11.5, -4.1)
P value		0.8307	0.2980	**0.0018**		**0.0076**	**0.0030**	**<0.0001**
Baseline modified BPI-SF Average Pain, mean	5.1	5.2	5.1	5.1	5.4	5.2	5.3	5.3
Week 14 change from baseline, LS mean [b]	-1.4	-1.4	-1.6	-1.6	-1.2	-1.7	-1.6	-1.8
Difference of LS mean vs placebo (95% CI)		0.0 (-0.3, 0.3)	-0.1 (-0.4, 0.2)	-0.2 (-0.5, 0.1)		-0.5 (-0.8, -0.2)	-0.4 (-0.8, -0.1)	-0.6 (-0.9, -0.3)
P value		0.9700	0.4307	0.1702		**0.0023**	**0.0062**	**0.0002**
PGIC much improved or better at Week 14, n (%) [d]	86 (26.1)	44 (26.8)	49 (29.7)	66 (40.0)	80 (26.2)	55 (36.2)	51 (33.3)	53 (34.2)
Odds Ratio (95% CI)		1.04 (0.68, 1.59)	1.20 (0.79, 1.81)	1.89 (1.27, 2.81)		1.58 (1.04, 2.40)	1.39 (0.91, 2.13)	1.45 (0.95, 2.20)
P value		0.8551	0.3921	**0.0016**		**0.0318**	0.1233	0.0830
PGIC minimally improved or better at Week 14, n (%) [d]	194 (58.8)	108 (65.9)	106 (64.2)	116 (70.3)	165 (54.5)	95 (62.5)	106 (69.3)	107 (69.0)
Odds Ratio (95% CI)		1.35 (0.92, 2.00)	1.26 (0.86, 1.85)	1.66 (1.11, 2.47)		1.39 (0.94, 2.08)	1.89 (1.25, 2.85)	1.86 (1.24, 2.81)
P value		0.1298	0.2421	**0.0129**		0.1025	**0.0025**	**0.0028**
Week 14 ADSIS change from baseline, LS mean [b]	-0.86	-1.00	-1.02	-1.39	-0.84	-1.37	-1.29	-1.62
Difference of LS mean vs placebo (95% CI)		-0.12 (-0.39, 0.15)	-0.19 (-0.47, 0.08)	-0.64 (-0.92, -0.37)		-0.44 (-0.72, -0.16)	-0.39 (-0.67, -0.11)	-0.70 (-0.98, -0.43)
P value		0.3899	0.1666	**<0.0001**		**0.0022**	**0.0062**	**<0.0001**

a. Multiple Imputation using Pattern Mixture Model with Shifting Parameters of [adverse event, lack of efficacy, all other reasons] = [1.0, 1.0, 0.5] and MMRM Analysis.
b. Missing value at Week 14 was imputed using LOCF approach and the data was analysed based on ANCOVA model including treatment arm as a fixed effect and baseline value as a covariate.

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c. For secondary endpoints, bold *p*-values indicate nominal statistical significance ($p < 0.05$); no adjustment for multiplicity was applied.
d. Missing value at Week 14 was imputed using LOCF approach.

Maintenance of treatment effect was demonstrated in the long-term phases of J303 and J304, which included 214 and 237 patients, respectively. At Week 66, with missing values imputed using the LOCF approach, the mean (SD) change from baseline in SF-MPQ VAS was −9.8 (14.06) in J303 and −12.4 (16.13) in J304.

J314 (Japan-Asia CNeP P3 study)

Study J314 was a Phase 3, multicentre, randomised study of mirogabalin compared with placebo in patients with CNePSCI. In the DB phase, patients were randomised in a 1:1 ratio to receive oral mirogabalin or placebo, stratified by baseline weekly ADPS (<6.0 or ≥6.0) and region (Japan or others). The study drug administration period comprised a 2-week dose-titration period followed by a 12-week maintenance-dose period. Patients with creatinine clearance (CLcr) ≥60 mL/min received mirogabalin 5 mg BID in Week 1 and 10 mg BID in Week 2; from Week 3, the dose could be increased to 15 mg BID as tolerated, with subsequent dose adjustments permitted between 10 mg and 15 mg BID. Patients with CLcr 30 to <60 mL/min received half of the corresponding dose. Paracetamol was permitted as rescue medication.

The study also included a single-arm, 52-week, open-label, LT phase, which enrolled patients with central post-stroke pain (CPSP) or central neuropathic pain in Parkinson's disease (CNePPD), in addition to those continuing from the DB phase. During the LT phase, patients with CLcr ≥60 mL/min received mirogabalin 5 mg BID for 2 weeks, followed by 10 mg BID for another 2 weeks. Thereafter, during the 47-week maintenance-dose period, the dose could be increased to 15 mg BID at the physician's discretion, with subsequent adjustments permitted between 10 mg and 15 mg BID. During the 1-week taper period, the dosage was reduced to once daily administration of the corresponding BID dose. Patients with CLcr 30 to <60 mL/min received half of the corresponding dose administered to patients with CLcr ≥60 mL/min throughout the treatment period.

The primary efficacy endpoint in the DB phase was the change from baseline to Week 14 in ADPS. Key secondary efficacy endpoints included the ADPS responder rate (i.e., proportion of patients achieving ≥30% and ≥50% reduction from baseline to Week 14) and change from baseline to Week 14 in the SF-MPQ VAS, PGIC, ADSIS, and Neuropathic Pain Symptom Inventory (NPSI). As no multiplicity adjustment was applied in the statistical analyses, all secondary endpoint *p*-values were nominal. The NPSI was specifically developed and validated for the assessment of neuropathic pain and was considered appropriate for evaluating treatment effects on neuropathic symptoms.

A total of 300 patients were randomised, of whom 299 were included in the mITT analysis set: 150 patients in the mirogabalin arm and 149 patients in the placebo arm. The median age was 60 years (range: 20 to 82 years), the majority of patients were male (86%), and all patients were Asian. The mean (SD) baseline ADPS was 6.06 (1.29), and the median duration of CNePSCI was 57.0 months (range: 3 to 499 months).

The primary analysis of change from baseline to Week 14 in ADPS demonstrated a statistically significant improvement with mirogabalin compared with placebo. The LS mean changes from baseline were −1.23 in the mirogabalin arm and −0.52 in the placebo arm, corresponding to an LS mean difference versus placebo of −0.71 ($p = 0.0001$). Nominal significance ($p < 0.05$)

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was also achieved in the mirogabalin arm across sensitivity analyses using different shifting parameters, as well as supplemental analyses using alternative imputation methods, and analysis using the PPS. These analyses were consistent with the primary analysis and supported the robustness of the primary efficacy finding.

The ≥30% ADPS responder rate was higher in the mirogabalin arm than in the placebo arm (30.7% versus 18.8%; OR 1.91; p = 0.0192), as was the ≥50% ADPS responder rate (14.0% versus 6.0%; OR 2.52; p = 0.0269). In addition, improvements versus placebo (p < 0.01) were observed across the NPSI subscores, including spontaneous pain, paroxysmal pain, evoked pain, paraesthesia/dysaesthesia, and the total score.

Table 4 Summary of Key Efficacy Results in Study J314 (mITT Analysis Set)

	Placebo N=149	Mirogabalin N = 150
Primary endpoint, Change in ADPS		
Baseline ADPS, mean	6.09	6.04
Week 14 change from baseline, LS mean [a]	-0.52	-1.23
Difference of LS mean vs placebo (95% CI)		-0.71 (-1.08, -0.34)
P value		**0.0001**
Key Secondary Endpoints[c]		
≥30% reduction in ADPS at Week 14 from baseline, n (%)	28 (18.8)	46 (30.7)
Odds Ratio (95% CI)		1.91 (1.11, 3.27)
P value		**0.0192**
≥50% reduction in ADPS at Week 14 from baseline, n (%)	9 (6.0)	21 (14.0)
Odds Ratio (95% CI)		2.52 (1.11, 5.71)
P value		**0.0269**
Baseline SF-MPQ VAS, mean	63.8	63.3
Week 14 change from baseline, LS mean [b]	-7.4	-14.2
Difference of LS mean vs placebo (95% CI)		-6.9 (−11.1, -2.7)
P value		**0.0013**
PGIC much improved or better at Week 14, n (%) [d]	11 (7.4)	26 (17.3)
Odds Ratio (95% CI)		2.63 (1.25, 5.54)
P value		**0.0110**
PGIC minimally improved or better at Week 14, n (%) [d]	55 (36.9)	82 (54.7)
Odds Ratio (95% CI)		2.06 (1.30, 3.27)
P value		**0.0022**
Week 14 ADSIS change from baseline, LS mean [b]	-0.35	-1.14
Difference of LS mean vs placebo (95% CI)		-0.71 (-1.04, -0.38)
P value		**<0.0001**
Week 14 NPSI		
Change from baseline in Spontaneous Pain, LS mean [b]	-1.5	-4.2
Difference of LS mean vs placebo (95% CI)		-2.8 (-4.0, -1.6)
P value		**<0.0001**
Change from baseline in Paroxysmal Pain, LS mean [b]	-0.9	-2.5
Difference of LS mean vs placebo (95% CI)		-1.6 (-2.5, -0.7)
P value		**0.0006**
Change from baseline in Evoked Pain, LS mean [b]	-1.0	-2.6
Difference of LS mean vs placebo (95% CI)		-1.8 (-3.1, -0.5)
P value		**0.0059**
Change from baseline in Paresthesia/Dysesthesia, LS mean [b]	-1.2	-2.7
Difference of LS mean vs placebo (95% CI)		-1.5 (-2.4, -0.7)
P value		**0.0004**
Change from baseline in Total Score, LS mean [b]	-4.5	-12.0
Difference of LS mean vs placebo (95% CI)		-7.7 (-11.1, -4.4)
P value		**<0.0001**

a. Multiple Imputation using Pattern Mixture Model with Shifting Parameters of [adverse event, lack of efficacy, all other reasons] = [1.0, 1.0, 0.5] and ANCOVA Analysis

b. Missing value at Week 14 was imputed using LOCF approach and the data was analysed based on ANCOVA model including treatment arm as a fixed effect and baseline value as a covariate.

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c. For secondary endpoints, *p*-values are nominal; no adjustment for multiplicity was applied.
d. Missing value at Week 14 was imputed using LOCF approach.

Maintenance of treatment effect was demonstrated in the long-term phase (N = 210), with a mean (SD) change from baseline in SF-MPQ VAS of −9.6 (24.70) at Week 52.

J313 (Japanese DPNP/PHN renal impairment safety)

Study J313 was a Phase 3, multicentre, single-arm, open-label study that evaluated the safety and efficacy of mirogabalin in patients with DPNP or PHN and moderate to severe renal impairment. The treatment period comprised a 2-week titration period followed by a 12-week fixed-dose period. During titration, patients with moderate renal impairment (CLcr 30 to 59 mL/min) received mirogabalin 2.5 mg BID in the first week and 5 mg BID in the second week, while patients with severe renal impairment (CLcr 15 to 29 mL/min) received mirogabalin 2.5 mg QD in the first week and 5 mg QD in the second week. During the fixed-dose period, mirogabalin was administered at 7.5 mg BID in patients with moderate renal impairment and 7.5 mg QD in patients with severe renal impairment.

A total of 35 patients were enrolled, including 30 patients with moderate renal impairment and 5 patients with severe renal impairment. The mean baseline ADPS was 5.70. Baseline CLcr was 51.8 mL/min in the moderate renal impairment arm and 22.0 mL/min in the severe renal impairment arm. At Week 14, LS mean changes from baseline in ADPS ranged from −1.79 to −2.07 across the moderate and severe renal impairment arms. These efficacy results were generally comparable to those observed in the pivotal studies J303 and J304, which enrolled patients with CLcr >60 mL/min.

Table 5 Efficacy Results in Study J313 (efficacy analysis set)

	Moderate renal impairment N = 30	Severe renal impairment N = 5	Total N = 35
Change in ADPS			
Baseline, mean	5.65	5.97	5.70
Week 14 change from baseline [a] LS Mean (95 % CI)	-1.79 (-2.45, -1.14)	-2.07 (-3.77, -0.36)	-1.93 (-2.84, -1.01)
SF-MPQ VAS Score			
Baseline, mean	59.1	62.8	59.6
Week 14 change from baseline, mean [b]	-20.8	-26.0	-21.5

a. Multiple Imputation using Pattern Mixture Model with Shifting Parameters of [adverse event, lack of efficacy, all other reasons] = [1.0, 1.0, 0.5] and MMRM analysis.
b. Missing Week 14 values were imputed using the LOCF approach.

Overall, the clinical efficacy of mirogabalin in adults with neuropathic pain was supported by three pivotal Phase 3 studies, J303, J304 and J314, conducted in patients with DPNP, PHN and CNePSCI, respectively. In all three studies, mirogabalin demonstrated statistically significant improvement versus placebo in the primary endpoint of change from baseline in ADPS at Week 14. Additional support was provided by nominally significant improvements versus placebo in the NPSI in J314 for assessing neuropathic pain symptoms. Maintenance of treatment effect was also demonstrated in the long-term phases of the pivotal studies, as assessed by the SF-MPQ VAS at Week 66 in J303 and J304 and at Week 52 in J314. While extrapolation from selected neuropathic pain models to a general neuropathic pain indication may be limited by the heterogeneity of neuropathic pain aetiologies, pathophysiology and treatment response, this approach was considered acceptable as efficacy was demonstrated independently across 3 distinct and clinically relevant neuropathic peripheral and central pain models.

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D ASSESSMENT OF CLINICAL SAFETY

The clinical safety assessment of mirogabalin was primarily based on the three pivotal Phase 3 studies, J303, J304 and J314, in which 1,886 patients received at least one dose of study treatment during the double-blind phase, comprising 1,105 patients in the mirogabalin arms and 781 patients in the placebo arms. The overall safety database also provided adequate long-term exposure of mirogabalin in the LT phases of the studies, with 567 patients treated for at least 24 weeks and 410 patients treated for at least 52 weeks. The median treatment duration was 99 days during the DB phases and 364 to 365 days during the LT phases.

Table 6 Overview of Safety Profile in Peripheral Neuropathy Studies (DB Phases)

	J303				J304			
		Mirogabalin				Mirogabalin		
	Placebo N = 330	15 mg QD N = 164 n (%)	10 mg BID N = 165 n (%)	15 mg BID N = 165 n (%)	Placebo N = 303	15 mg QD N = 152 n (%)	10 mg BID N = 153 n (%)	15 mg BID N = 155 n (%)
Any AE	202 (61.2)	112 (68.3)	113 (68.5)	128 (77.6)	157 (51.8)	92 (60.5)	102 (66.7)	113 (72.9)
Related	34 (10.3)	38 (23.2)	31 (18.8)	60 (36.4)	39 (12.9)	43 (28.3)	54 (35.3)	69 (44.5)
Severe	7 (2.1)	6 (3.7)	5 (3.0)	4 (2.4)	4 (1.3)	3 (2.0)	3 (2.0)	5 (3.2)
SAE	11 (3.3)	4 (2.4)	8 (4.8)	11 (6.7)	5 (1.7)	5 (3.3)	2 (1.3)	3 (1.9)
Related	1 (0.3)	0 (0.0)	2 (1.2)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to discontinuation	13 (3.9)	4 (2.4)	7 (4.2)	16 (9.7)	12 (4.0)	8 (5.3)	16 (10.5)	12 (7.7)
Related	4 (1.2)	3 (1.8)	3 (1.8)	13 (7.9)	3 (1.0)	3 (2.0)	14 (9.2)	10 (6.5)
AE leading to deaths	0	0	2 (1.2)	0	0	0	0	0
Related	0	0	0	0	0	0	0	0

Table 7 Overview of Safety Profile in Peripheral Neuropathy Studies (LT Phases)

	J303			J304		
	5 mg BID modal N = 4 n (%)	10 mg BID modal N = 35 n (%)	15 mg BID modal N = 175 n (%)	5 mg BID modal N = 10 n (%)	10 mg BID modal N = 42 n (%)	15 mg BID modal N = 185 n (%)
Any AE	3 (75.0)	35 (100.0)	157 (89.7)	6 (60.0)	41 (97.6)	156 (84.3)
Related	2 (50.0)	28 (80.0)	29 (16.6)	4 (40.0)	30 (71.4)	60 (32.4)
Severe	1 (25.0)	3 (8.6)	12 (6.9)	0	5 (11.9)	5 (2.7)
SAE	1 (25.0)	4 (11.4)	19 (10.9)	1 (10.0)	7 (16.7)	12 (6.5)
Related	0	0	3 (1.7)	0	0	0
AE leading to discontinuation	3 (75.0)	7 (20.0)	18 (10.3)	4 (40.0)	10 (23.8)	6 (3.2)
Related	2 (50.0)	6 (17.1)	5 (2.9)	2 (20.0)	6 (14.3)	4 (2.2)
AE leading to deaths	0	0	1 (0.6)	0	0	0
Related	0	0	1 (0.6)	0	0	0

Table 8 Overview of Safety Profile in Central Neuropathy Study - J314 (DB Phase)

	Placebo N = 148 n (%)	Mirogabalin N = 151 n (%)
Any AE	82 (55.4)	118 (78.1)
Related	19 (12.8)	62 (41.1)
Severe	1 (0.7)	6 (4.0)
Severe, related	0	0

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SAE	7 (4.7)	9 (6.0)
Related	1 (0.7)	0
AE leading to discontinuation	6 (4.1)	14 (9.3)
Related	2 (1.4)	8 (5.3)
AE leading to deaths	0	1 (0.7)
Related	0	0

Table 9 Overview of Safety Profile in Central Neuropathy Study - J314 (LT Phase)

	Modal dose		
	Low N=12 n (%)	**Middle N=18** n (%)	**High N=180** n (%)
Any AE	9 (75.0)	18 (100.0)	151 (83.9)
Related	8 (66.7)	17 (94.4)	59 (32.8)
Severe	1 (8.3)	3 (16.7)	9 (5.0)
Severe, related	0	0	1 (0.6)
SAE	1 (8.3)	4 (22.2)	23 (12.8)
Related	0	0	2 (1.1)
AE leading to discontinuation	9 (75.0)	3 (16.7)	12 (6.7)
Related	7 (58.3)	1 (5.6)	6 (3.3)
AE leading to deaths	0	0	0
Related	0	0	0

Across the DB phases of the three pivotal studies J303, J304 and J314 (Tables 6 and 8), treatment-emergent adverse events (AEs) were reported more frequently in the mirogabalin arms than in the placebo arms. In J303 and J304, the incidence of AEs was highest in the mirogabalin 15 mg BID arms, at 77.6% and 72.9%, respectively. Across studies J303, J304 and J314, the most commonly reported AEs with mirogabalin, compared with placebo, were nasopharyngitis (7.9% to 16.4% versus 5.4% to 12.7%), somnolence (8.5% to 29.8% versus 3.6% to 5.4%), dizziness (4.9% to 15.5% versus 2.1% to 3.4%), peripheral oedema (2.0% to 8.5% versus 0.3% to 1.4%) and weight increased (2.4% to 7.3% versus 0.3% to 0.7%). The most common AEs leading to treatment discontinuation in the mirogabalin arms, compared with placebo, were dizziness (0% to 2.4% versus 0% to 0.3%), somnolence (0.6% to 4.0% versus 0% to 0.3%) and peripheral oedema (0% to 2.0% versus 0%).

Across the DB and LT phases of the three pivotal studies, four AEs leading to death were reported in the mirogabalin arms. One event of drowning in the mirogabalin 15 mg BID modal arm during the J303 long-term phase (Table 7) was considered related to study drug by the investigator, given the known central nervous system activity of mirogabalin. In the DB phases, the incidence of serious AEs (SAEs) was numerically higher in some mirogabalin arms than in placebo, ranging from 1.3% to 6.7% across mirogabalin arms compared with 1.7% to 4.7% in placebo arms. However, treatment-related SAEs were uncommon and were reported only in J303, occurring in 1.2% of patients in the 10 mg BID and 15 mg BID arms. These comprised loss of consciousness and oedema in the 10 mg BID arm, and diplopia, alanine aminotransferase increased and aspartate aminotransferase increased in the 15 mg BID arm. No SAEs were considered related to study drug in the mirogabalin arms of the DB phases of J304 or J314.

Adverse events of clinical interest evaluated across Studies J303, J304 and J314 included hepatic-related events, suicide-related events, central nervous system (CNS) effects, weight gain, oedema and visual disturbance. Among these, CNS-related events were the most frequently reported with mirogabalin. Dizziness-related events were reported in up to 15.5% of patients in the mirogabalin arms compared with 2.1% to 4.1% in the placebo arms, and somnolence-related events in up to 31.1% of patients in the mirogabalin arms compared with

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3.6% to 6.1% in the placebo arms. However, treatment discontinuations due to dizziness and somnolence were relatively infrequent, occurring in up to 2.4% and 4.0% of mirogabalin-treated patients, respectively, compared with 0% to 0.3% for either event in the placebo arms. In the LT phases of J303, J304 and J314, the incidences of AEs related to falls and injuries were 20.6%, 8.4% and 25.7%, respectively. Given that neuropathic pain is commonly treated in an older patient population, a warning on the risk of falls and the need for caution has been included in the package insert.

Peripheral oedema was reported in 2.0% to 8.5% of patients in the mirogabalin arms of the DB phase of the pivotal studies, compared with 0.3% to 1.4% in the placebo arms; most events were mild or moderate in severity, and discontinuations due to peripheral oedema were infrequent (≤2.0%). Hepatic-related AEs were reported in 0% to 5.8% of patients in the mirogabalin arms compared with 1.0% to 2.0% in the placebo arms, but none of the events assessed by the Hepatic Adjudication Committee met Hy's Law criteria. Visual disorder-related AEs were reported in 0.7% to 2.6% of patients in the mirogabalin arms compared with 0% to 0.7% in the placebo arms. One serious AE of diplopia was reported in the mirogabalin 15 mg BID arm of J303 that was considered related to study drug and resolved. Suicide-related AEs were uncommon, occurring in 0% to 1.3% of patients in the mirogabalin arms and 0% to 2.0% in the placebo arms; these events comprised mild suicidal ideation and were not considered related to mirogabalin. AEs related to drug abuse were infrequent, with reported incidences ranging from 0% to 1.3% in the mirogabalin arms and 0% to 0.3% in the placebo arms across the DB phase of the studies; all such events were reported as "feeling abnormal". Dedicated drug abuse potential studies did not show a significant difference between mirogabalin at therapeutic doses and placebo in terms of abuse potential.

Overall, the safety profile of mirogabalin was considered manageable and generally consistent with that of other gabapentinoids, with no major safety concerns identified. The main safety risks, including CNS effects such as dizziness and somnolence with associated risks of impaired driving, falls and fractures, weight gain, withdrawal symptoms, visual disorders, and drug abuse and dependencehave been adequately addressed through warnings and precautions in the package insert. In addition, the package insert includes information on a limited number of serious respiratory depression events reported during post-marketing use of mirogabalin, including in patients with contributory risk factors.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Treatment of neuropathic pain remains challenging, as many patients achieve inadequate or only partial pain relief despite available therapies. Current first-line pharmacological options include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and gabapentinoids, with sequential treatment trials recommended when initial therapy is ineffective or not tolerated. However, treatment responses are often incomplete and may diminish over time, supporting the need for additional therapeutic options.

The clinical efficacy of mirogabalin for neuropathic pain was supported by three pivotal studies, J303, J304 and J314, conducted in patients with DPNP, PHN and CNePSCI, respectively. The selection of the three distinct and clinically relevant neuropathic peripheral and central pain models was considered acceptable.

In J303, mirogabalin 15 mg BID demonstrated a statistically significant improvement versus placebo in the primary endpoint of change from baseline in ADPS at Week 14, with LS mean

changes of −1.81 and −1.31, respectively (LS mean difference vs placebo: −0.50; 95% CI: −0.82, −0.17; $p = 0.0027$). In J304, all three mirogabalin dose arms demonstrated statistically significant improvements versus placebo, with LS mean changes of −1.97, −1.68 and −1.61 for mirogabalin 15 mg BID, 10 mg BID and 15 mg QD, respectively, compared with −1.20 in the placebo arm. The corresponding LS mean differences versus placebo were −0.77 (95% CI: −1.10, −0.44; $p < 0.0001$), −0.47 (95% CI: −0.81, −0.14; $p = 0.0058$) and −0.41 (95% CI: −0.74, −0.07; $p = 0.0170$), respectively. A dose-response relationship was observed in both J303 and J304.

In J314, mirogabalin demonstrated statistically significant superiority over placebo for change from baseline in ADPS at Week 14, with LS mean changes of −1.23 and −0.52, respectively (LS mean difference vs placebo: −0.71; 95% CI: −1.08, −0.34; $p = 0.0001$). Across the three pivotal studies, reductions in ADPS from baseline in the mirogabalin arms ranged from 1.23 to 1.97 points, corresponding to improvements of 20.4% to 34.9%, exceeding the commonly accepted clinically relevant thresholds of a 1-point reduction and 15% to 20% improvement in chronic pain assessment. Additional supportive evidence was provided by nominally significant improvements ($p < 0.01$) versus placebo in the NPSI, a validated instrument for assessing neuropathic pain symptoms. In the Phase 2 studies J202 and U201, the observed treatment effects of mirogabalin on ADPS were generally numerically larger than those observed with pregabalin 150 mg BID. Maintenance of treatment effect was supported in the long-term phases of the pivotal studies, based on SF-MPQ VAS assessments at Week 66/52.

The safety profile of mirogabalin was generally consistent with that expected for gabapentinoids. Across the pivotal studies, AEs were reported more frequently in the mirogabalin arms than in the placebo arms, with the highest incidence observed in the 15 mg BID arms of J303 and J304. The most commonly reported AEs with mirogabalin were nasopharyngitis, somnolence, dizziness, peripheral oedema and weight increased. One fatal event of drowning in the mirogabalin 15 mg BID modal arm during the J303 LT phase was considered related to study drug by the investigator, in view of the known CNS effects of mirogabalin. AEs of clinical interest included events related to hepatic dysfunction, suicidality, CNS effects, weight gain, oedema and visual disturbance. These risks were considered manageable and have been adequately addressed in the local package insert through relevant warnings and precautions, including advice on dose adjustment or discontinuation where clinically indicated. Overall, no major safety concerns were identified.

Overall, the benefit-risk profile of mirogabalin in the treatment of neuropathic pain in adults was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tarlige for the treatment of neuropathic pain in adults was deemed favourable and approval of the product registration was granted on 06 July 2026.

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MIROGABALIN Besilate

TARLIGE® FILM-COATED TABLETS 2.5 mg
TARLIGE® FILM-COATED TABLETS 5 mg
TARLIGE® FILM-COATED TABLETS 10 mg
TARLIGE® FILM-COATED TABLETS 15 mg

1. COMPOSITION AND PRODUCT DESCRIPTION

1.1 Composition

Brand Name	Active Ingredient(s)	Excipients
TARLIGE Film-coated Tablets 2.5 mg	In 1 tablet 4.39 mg of mirogabalin besilate (equivalent to 2.5 mg of mirogabalin)	D-mannitol, microcrystalline cellulose, carmellose calcium, tocopherol, citric acid hydrate, magnesium aluminometasilicate, magnesium stearate, hypromellose, titanium oxide, talc, yellow ferric oxide, red ferric oxide
TARLIGE Film-coated Tablets 5 mg	In 1 tablet 8.78 mg of mirogabalin besilate (equivalent to 5 mg of mirogabalin)	
TARLIGE Film-coated Tablets 10 mg	In 1 tablet 17.56 mg of mirogabalin besilate (equivalent to 10 mg of mirogabalin)	
TARLIGE Film-coated Tablets 15 mg	In 1 tablet 26.34 mg of mirogabalin besilate (equivalent to 15 mg of mirogabalin)	

1.2 Product Description

Brand Name	Dosage Form	Color	Externals		
			Size (mm)	Thickness (mm)	Weight (mg)
TARLIGE Film-coated Tablets 2.5 mg	Film-coated tablets	Peach	6.7 (diameter)	About 3.4	About 105
TARLIGE Film-coated Tablets 5 mg	Film-coated tablets (oblong / scored*)	Grayish red	10.8 (long diameter) 5.7 (short diameter)	About 3.8	About 208
TARLIGE Film-coated Tablets 10 mg	Film-coated tablets (oblong / scored*)	Peach	12.2 (long diameter) 6.5 (short diameter)	About 4.4	About 311
TARLIGE Film-coated Tablets 15 mg	Film-coated tablets (oblong / scored*)	Grayish red	12.2 (long diameter) 6.5 (short diameter)	About 4.4	About 311

**The score line serves to facilitate breaking of the tablet for ease of swallowing and does not divide the tablet into equal half doses.*

2. INDICATIONS

Treatment of neuropathic pain in adults (See clinical studies section).

3. DOSAGE AND ADMINISTRATION

Administer mirogabalin at an initial oral dose of 5 mg twice daily, and then increase the dose by 5 mg per dosing with an interval of at least 1 week up to 15 mg twice daily. The dose may be increased or decreased appropriately in the range between 10 mg and 15 mg twice daily, based on individual patient age or symptoms.

4. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

For patients with renal impairment, the dose and dosing intervals should be adjusted, referring to creatinine clearance levels listed in the table below. Treatment should be started at a low dose, and the dose should be increased in patients who show confirmed tolerability but insufficient effect.

		Severity grade of renal impairment (creatinine clearance [CLcr]: mL/min)		
		Mild (60 ≤ CLcr < 90)	Moderate (30 ≤ CLcr < 60)	Severe (including patients on hemodialysis) (CLcr < 30)
Daily dose		10 mg to 30 mg	5 mg to 15 mg	2.5 mg to 7.5 mg
Initial dose		5 mg twice daily	2.5 mg twice daily	2.5 mg once daily
Effective dose	Minimum dose	10 mg twice daily	5 mg twice daily	5 mg once daily
	Recommended dose	15 mg twice daily	7.5 mg twice daily	7.5 mg once daily

5. IMPORTANT WARNINGS AND PRECAUTIONS

5.1 Mirogabalin besilate (TARLIGE) may cause event(s) (e.g., dizziness, somnolence, loss of consciousness), which could increase the occurrence of accidental injury (fall). Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication. Patients being treated with Mirogabalin besilate (TARLIGE) must be warned not to operate potentially dangerous machinery, such as driving a car.

5.2 Treatment with Mirogabalin besilate (TARLIGE) may cause weight gain. Caution should therefore be exercised for potential occurrence of obesity. If signs of obesity are noted, appropriate measures, such as diet and/or exercise therapy, should be taken. In particular, since weight gain may be associated with dose increase or long-term use, body weight should be measured regularly.

5.3 Mirogabalin besilate (TARLIGE) provides symptomatic treatment of neuropathic pain and does not treat the underlying cause. Therefore, the underlying condition causing the pain should be diagnosed and treated concurrently.

5.4 Abrupt discontinuation of treatment with Mirogabalin besilate (TARLIGE) may cause drug withdrawal symptoms (e.g., insomnia, nausea, diarrhea, decreased appetite). Treatment with Mirogabalin besilate (TARLIGE) should be discontinued in a careful manner, such as gradual dose reduction.

5.5 Treatment with Mirogabalin besilate (TARLIGE) may cause ophthalmic disorders (e.g., amblyopia, abnormal vision, vision blurred, diplopia). Caution should therefore be exercised for potential occurrence of ophthalmic disorders in medical examinations including careful history taking.

5.6 Drug abuse and Drug dependence with Mirogabalin besilate (TARLIGE)

Mirogabalin showed no abuse potential at doses up to 45 mg. The abuse potential of supratherapeutic doses of mirogabalin 60 mg and 105 mg was observed to be comparable to pregabalin 200 and 450 mg.

Cases of misuse, abuse and dependence have been reported in the post-marketing database with other gabapentinoids. As with any central nervous system (CNS) active drug, carefully evaluate patients for history of drug abuse and/or psychiatric disorders. Caution should be applied when considering mirogabalin use in patients with current substance abuse or a history of substance abuse, who are at higher risk for mirogabalin abuse.

Abrupt discontinuation of treatment with this drug may cause drug withdrawal symptoms (e.g., insomnia, nausea, diarrhea, decreased appetite) and that treatment with this drug should be discontinued in a careful manner, such as gradual dose reduction.

6. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

6.1 Patients with Renal Impairment

The dose and dosing intervals should be adjusted according to creatinine clearance levels. Mirogabalin concentrations in plasma may increase in these patients, possibly increasing the risk of adverse reactions.

6.2 Pregnant Women

For pregnant women and women who may be pregnant, Mirogabalin besilate **(**TARLIGE**)** should be administered only if the expected therapeutic benefits outweigh the possible risks associated with treatment. An animal study (in rats) has shown that mirogabalin crossed the placenta. In animal reproduction studies, Mirogabalin was not teratogenic in rats at doses up to 1000 mg/kg/day and in rabbits up to 100 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) for embryo-fetal and pre-/post-natal development was 10 mg/kg/day, providing a 4.3 to 5.2-fold safety margin relative to the maximum recommended human dose (MRD).

6.3 Breastfeeding Women

Because the effect on the nursing infant is unknown, caution should be exercised when mirogabalin is administered to a nursing mother. The continuation or discontinuation of breastfeeding should be considered while taking account of the expected therapeutic benefits and the benefits of maternal feeding. An animal study (in rats) has shown that mirogabalin transferred to breast milk.

6.4 Pediatric Use

Clinical studies in children have not been conducted.

6.5 Geriatric Use

6.5.1 Mirogabalin besilate (TARLIGE) should be administered with care, and dose and dosing interval adjustment based on creatinine clearance levels is required. Elderly patients often have reduced renal function.

6.5.2 Elderly patients tend to experience falls resulting in fractures, etc. led by events (e.g., dizziness, somnolence, loss of consciousness).

7. INTERACTIONS

Mirogabalin is predominantly excreted by renal glomerular filtration and tubular secretion. The transporters involved in the secretion of mirogabalin are organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, H^+/organic cation antiporter (MATE) 1, and MATE2-K. Mirogabalin is also metabolized by UDP-glucuronosyltransferases (UGTs) (See Section 12.7.1 Interactions).

Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Clinical Symptoms and Measures	Mechanism and Risk Factors
Probenecid	Co-administration may increase the risk of side effects of Mirogabalin besilate **(**TARLIGE**)**. Monitor individual patient side effects and decrease Mirogabalin dose according to Dosage and Administration (3), when co-administered with OAT or UGT inhibitors such as probenecid.	This is possibly due to the blood mirogabalin concentration that is increased by the inhibitory effect of probenecid on OAT1, OAT3, and UGT.
Cimetidine	Co-administration may increase the risk of side effects of Mirogabalin besilate **(**TARLIGE**)**.	This is possibly due to the blood mirogabalin concentration that is increased by the inhibitory effect of cimetidine on MATE1 and MATE2-K.
Lorazepam Alcohol (drinking)	Co-administration may lead to the decrease in attention and balance-function.	This is possibly due to the interactively potentiated inhibitory effect on the central nervous system.

8. ADVERSE REACTIONS

The following adverse reactions may appear, so observe thoroughly and if abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

8.1 Clinically Significant Adverse Reactions

8.1.1 **Dizziness** (≥ 5%), **somnolence** (≥ 5%), **loss of consciousness** (< 0.1%)

May cause falls and subsequent fractures, etc. If any abnormalities are noted, appropriate measures, such as discontinuation of treatment or dose reduction, should be taken.

8.1.2 **Hepatic function disorder** (frequency unknown)

Hepatic function disorder (e.g., AST increased, ALT increased) may occur. If any abnormalities including early symptoms (e.g., general malaise, anorexia) are noted, treatment should be discontinued, and appropriate measures should be taken.

8.1.3 Renal impairment (frequency unknown)

8.2 Other Adverse Reactions

	≥ 5%	< 5%	Frequency unknown
Neuropsychiatric	Somnolence, dizziness	Dizziness postural, insomnia, loss of consciousness, headache, tremor, hypoaesthesia	Memory impairment, amnesia, dysarthria, hallucination, delirium, taste disorder, dysgeusia, head discomfort, dyskinesia, myoclonus
Ophthalmic		Vision blurred	Diplopia, visual impairment, visual acuity reduced
Hematologic		Eosinophil count increased	

	≥ 5%	< 5%	Frequency unknown
Cardiovascular		Orthostatic hypotension, hypertension	Palpitations, hot flush, blood pressure decreased
Digestive		Constipation, abdominal distension, dry mouth, gastritis, vomiting, increased appetite, decreased appetite, abdominal pain upper, gastrooesophageal reflux disease	Diarrhoea, abdominal discomfort
Hepatic		Hepatic enzyme increased	
Urological			Urinary incontinence, pollakiuria, dysuria, urinary retention
Skin		Rash	Urticaria, erythema, pruritus
Others	Oedema	Weight gain, gait disturbance, feeling abnormal, vertigo, thirst, face oedema, fall, diabetes mellitus (HbA1c increased, sugar blood level increased), malaise, blood CK increased, eyelid oedema, muscular weakness, withdrawal syndrome	Asthenia, pain

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9. OVERDOSAGE

9.1 Symptoms

There have been reports on overdoses of up to 60 mg/day in an overseas clinical study in patients with fibromyalgia[Note)]. Symptoms observed during a mirogabalin overdose included euphoric mood, dysarthria, headache, dysphagia, arthritis, joint swelling, and asthenia.

9.2 Treatment

Hemodialysis is reported to remove 15.3% of mirogabalin.

[Note)] The indication of TARLIGE is neuropathic pain.

10. PRECAUTIONS CONCERNING USE

10.1 Precautions Concerning the Dispensing of the Drug

10.1.1 For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drugs from the package prior to use. If the PTP sheet itself is mistakenly swallowed, the sharp edges of the sheet may be inserted

into and puncture the esophageal mucosa, resulting in serious complications, such as mediastinitis.

11. OTHER PRECAUTIONS

11.1 Information Based on Clinical Use

11.1.1 In multinational, placebo-controlled studies conducted in Asian countries, suicide-related adverse events were reported in 5 of 1378 subjects (0.36%; completed suicide, 1 subject; suicidal ideation, 4 subjects) in the mirogabalin groups and in 4 of 869 subjects (0.46%; suicidal ideation, 4 subjects) in the placebo group.

11.1.2 In multinational, placebo-controlled studies conducted in Asian countries, death cases were reported in 3 of 1378 subjects (0.22%) in the mirogabalin groups and in none of 869 subjects in the placebo group.

11.2 Information Based on Post-marketing

Gabapentinoids such as gabapentin and pregabalin are associated with severe respiratory depression when co-administered with CNS depressants, including opioids, or in the setting of underlying respiratory impairment. In the post-marketing experience, a limited number of serious respiratory depression events were reported with mirogabalin, including in patients with contributory risk factors such as concomitant CNS depressants or underlying respiratory dysfunction.

12. PHARMACOKINETICS

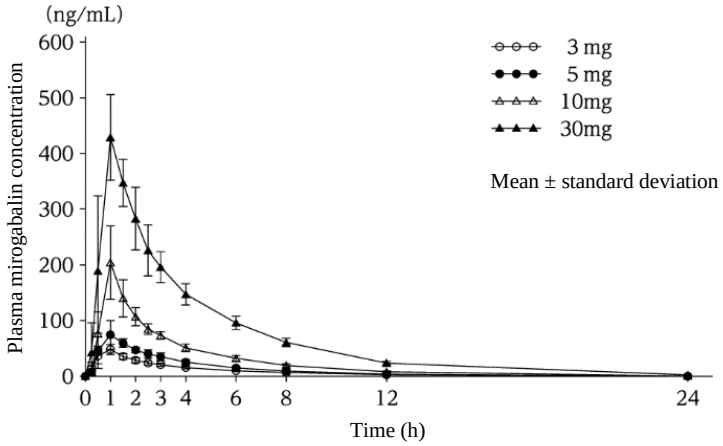
12.1 Blood Level

12.1.1 Single-dose administration

Mirogabalin tablets

Following the administration of mirogabalin at a single oral dose of 3, 5, 10, and 30 mg (6 subjects per dose level) in healthy adults, plasma mirogabalin concentrations reached the maximum concentration (Cmax) at 1 h post-dose, with a half-life ($t_{1/2}$) of 2.96 to 3.37 h. The Cmax and AUCinf of mirogabalin increased in a dose-proportional manner.

Plasma Mirogabalin Concentration-Time Profiles Following a Single Oral Dose



Pharmacokinetic Parameters of Mirogabalin Following a Single Oral Dose

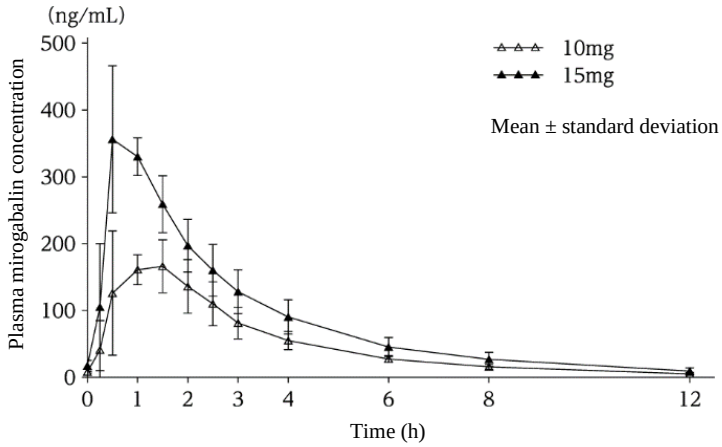
Dose	No. of subjects	Cmax (ng/mL)	Tmax (h)[Note 1)]	AUCinf (ng·h/mL)	$t_{1/2}$ (h)
3 mg	6	48.6 ± 8.47	1.00 (0.50 to 1.00)	184.2 ± 21.75	3.31 ± 0.37
5 mg	6	78.3 ± 18.0	1.00 (0.50 to 2.00)	276.2 ± 26.96	2.96 ± 0.17
10 mg	6	205 ± 64.0	1.00 (1.00 to 1.50)	614.1 ± 84.02	3.32 ± 0.75
30 mg	6	433 ± 67.9	1.00 (1.00 to 1.50)	1682 ± 233.4	3.37 ± 0.26

Mean ± standard deviation
Note 1) Median (minimum, maximum)

12.1.2 Multiple-dose administration

Following the administration of mirogabalin at multiple oral doses of 10 and 15 mg (6 subjects per dose level) twice daily in healthy adult subjects for 7 days, steady state was reached by Day 3, with $t_{1/2}$ of 2.43 h for 10-mg dose and 2.83 h for 15-mg dose on Day 7. The Cmax and AUCtau of mirogabalin on Day 7 increased in a dose-proportional manner.

Plasma Mirogabalin Concentration–Time Profiles Following Multiple Oral Doses (Day 7)



Pharmacokinetic Parameters of Mirogabalin Following Multiple Oral Doses (Day 7)

Dose	No. of subjects	Cmax (ng/mL)	Tmax (h)[Note 4)]	AUCtau (ng·h/mL)	$t_{1/2}$ (h)
10 mg per dosing (twice daily)	6	210 ± 39.4	1.50 (0.50 to 2.00)	601.0 ± 63.68	2.43 ± 0.54
15 mg per dosing (twice daily)	6	381 ± 88.0	0.53 (0.50 to 1.53)	1057 ± 142.2	2.83 ± 0.70

Mean ± standard deviation
Note 4) Median (minimum, maximum)

12.2 Absorption

12.2.1 Effect of food

Following the administration of mirogabalin at a single oral dose of 15 mg in the fasted and fed states in 30 healthy adults, the Cmax was 230 and 188 ng/mL, with Tmax of 1.00 and 1.50 h, and the AUClast was 884 and 833 ng·h/mL, respectively. Administration in the fed state resulted in a decrease of Cmax by approximately 18% and a delay of Tmax by 0.5 h, whereas the AUCinf was only reduced by approximately 6%.

12.2.2 Bioavailability

Following the administration of ^{14}C-mirogabalin at a single oral dose of 30 mg (150 μCi) in 6 healthy male adults, over 95% of the total radioactivity administered was excreted in urine. It was considered that more than 95% of orally administered mirogabalin is absorbed.

12.3 Distribution

12.3.1 Volume of distribution

Following the administration of mirogabalin at a single oral dose of 3, 5, 10, and 30 mg (6 subjects per dose level) in healthy adults, the apparent volume of distribution based on the terminal phase (Vz/F) was 78.01 to 87.97 L.

12.3.2 Blood cell transfer rate

Mirogabalin labeled with ^{14}C (abbreviated as ^{14}C-mirogabalin) was distributed into red blood cells, with a ratio of whole blood concentration to plasma concentration of 0.85 to 0.87 in human (*in vitro*).

12.3.3 Plasma protein-binding rate

The ^{14}C-mirogabalin human plasma protein-binding ratio, determined by ultracentrifugation, was 23.4% to 25.5% at plasma concentrations of 0.1 to 10 μg/mL (*in vitro*).

12.4 Metabolism

Following the administration of ^{14}C-mirogabalin at a single oral dose of 30 mg (150 μCi) in 6 healthy male adults, approximately 97% of the radioactivity was recovered in the urine, and approximately 76% of the radioactivity in the urine was recovered as unchanged mirogabalin. The metabolite of mirogabalin found in urine, other than the unchanged mirogabalin, was the lactam form of mirogabalin and accounted for 0.6% of the dose. The *N*-glucuronide conjugate metabolized by UGT was also found.

12.5 Excretion

Following the administration of mirogabalin at a single oral dose of 3, 5, 10, and 30 mg (6 subjects per dose level) in healthy adults, the apparent total body clearance (CL/F) ranged between 16.50 and 18.24 L/h, with a half-life (t1/2) of 2.96 to 3.37 hours. In these subjects, 63.2% to 71.5% of the dose was excreted, unchanged, in the urine, and renal clearance was 10.4 to 12.4 L/h. Following the administration of ^{14}C-mirogabalin at a single oral dose of 30 mg (150 μCi) in 6 healthy male adults, a cumulative excretion rate of total radioactivity up to 168 h post-dose was ≥ 98%; radioactivity recovered in urine and feces was approximately 97% and 1%, respectively.

12.6 Patients with Specific Backgrounds

12.6.1 Patients with renal impairment

Following the administration of mirogabalin at a single oral dose of 5 mg in 30 subjects with normal renal function or renal impairment, AUClast increased in association with decreased creatinine clearance (CLcr). In patients with end-stage renal disease requiring hemodialysis, 15.3% of dosed mirogabalin was removed from blood during a 4-hour hemodialysis.

Severity grade of renal impairment (CLcr: mL/min)	No. of subjects	Cmax (ng/mL)	Tmax (h)[Note 5)]	AUClast (ng·h/mL)	CLr (L/h)
CLcr ≥ 90	4	71.2 ± 25.6	1.25 (0.98 to 2.00)	321 ± 52.5	10.9 ± 1.52
60 ≤ CLcr < 90 (mild)	6	81.4 ± 29.0	1.74 (0.97 to 4.00)	422 ± 85.1	7.83 ± 1.61
30 ≤ CLcr < 60 (moderate)	9	76.9 ± 13.3	1.95 (1.03 to 5.00)	655 ± 144	4.48 ± 1.87
CLcr < 30 (severe)	5	118 ± 25.8	2.00 (1.47 to 5.00)	1350 ± 259	1.92 ± 0.463
End-stage renal disease requiring hemodialysis[Note 6)]	6	101 ± 32.9	4.01 (1.92 to 5.00)	1990 ± 916	–

Mean ± standard deviation

Note 5) Median (minimum, maximum)

Note 6) Hemodialysis was performed for 4 h from 24 h post-dose.

12.6.2 Patients with hepatic impairment

Following the administration of mirogabalin at a single oral dose of 15 mg in 16 subjects with mild or moderate hepatic impairment, Cmax in subjects with mild and moderate hepatic impairment was 1.0 and 0.8 times that in healthy subjects, respectively, and AUCinf in subjects with mild and moderate hepatic impairment was 0.9 and 1.1 times that in healthy subjects, respectively. The pharmacokinetics of mirogabalin was not studied in patients with severe hepatic impairment.

12.6.3 Elderly subjects

Following the administration of mirogabalin at multiple oral doses of 5, 10, and 15 mg (6 subjects per dose level, including 13 subjects younger than 65 years) twice daily in healthy elderly subjects between 55 and 75 years of age for 14 days, steady state was reached by Day 3, with $t_{1/2}$ of 3.58 to 4.55 h on Day 14. The $AUC_{0\text{-}12h}$ on Day 14 was 1.13 to 1.24 times to that on Day 1. The pharmacokinetics of mirogabalin in healthy elderly subjects did not differ significantly from those observed in healthy non-elderly subjects.

12.7 Drug-Drug Interactions

12.7.1 Interactions

Mirogabalin did not inhibit or induce major human CYP molecular species and did not inhibit the activities of drug transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K). Mirogabalin also did not inhibit the activities of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP). Mirogabalin was secreted from the kidney and was suggested to be a substrate for OAT1, OAT3, OCT2, MATE1, and MATE2-K. Mirogabalin was also metabolized by UGTs (*in vitro*).

(1) Co-administration of probenecid 500 mg with mirogabalin 15 mg increased the Cmax and AUClast of mirogabalin by 29% and 76%, respectively (Non-Japanese data).

(2) Co-administration of cimetidine 400 mg with mirogabalin 15 mg increased the Cmax and AUClast of mirogabalin by 17% and 44%, respectively (Non-Japanese data).

(3) Co-administration of mirogabalin with ethanol or lorazepam had no notable effect on the pharmacokinetics of mirogabalin or these drugs. Co-administration of mirogabalin with these drugs decreased attention and balance-function more profoundly than monotherapy with mirogabalin.

(4) Co-administration of mirogabalin with tramadol had no notable effect on the pharmacokinetics of mirogabalin or tramadol.

Note) The approved dose of TARLIGE is 5 mg of mirogabalin twice daily for the initial dose, and 10 or 15 mg of mirogabalin twice daily for the effective dose.

Note) AUCinf: Area under the plasma concentration–time curve up to infinity
AUClast: Area under the plasma concentration–time curve up to the last quantifiable time
AUCtau: Area under the plasma concentration–time curve during dosing interval

13. CLINICAL STUDIES

Therapeutic group: ANALGESICS, Other analgesics and antipyretics, Gabapentinoids

ATC Code: N02BF03

13.1 Clinical Studies for Efficacy and Safety

13.1.1 Phase 3 multinational clinical study in diabetic peripheral neuropathic pain

In a double-blind controlled study in 824 patients with diabetic peripheral neuropathic pain in Asian countries, each patient received 14-week treatment with mirogabalin 15 mg (5 mg/day for 1 week, 10 mg/day for 1 week, and then 15 mg/day for 12 weeks: total 14-week treatment), 20 mg (5 mg twice daily for 1 week and then 10 mg twice daily for 13 weeks: total 14-week treatment), or 30 mg (5 mg twice daily for 1 week, 10 mg twice daily for 1 week, and then 15 mg twice daily for 12 weeks: total 14-week treatment)[Note)] or placebo.

The mirogabalin 30-mg/day group showed statistically significant improvement in pain scores at Week 14 compared with the placebo group.

Treatment group	**Week**	**No. of subjects evaluated**	**Pain score[Note 1), Note 2)]**	**Change from baseline at Week 14[Note 3), Note 4)]**	**Difference from placebo [95% confidence interval][Note 3)]**	***P* value[Note 5)]**
Placebo	Baseline	330	5.59 ± 1.012	−1.31 ± 0.095	–	–
	Week 14	310	4.22 ± 1.820			
20 mg/day	Baseline	165	5.57 ± 0.899	−1.47 ± 0.135	−0.15 [−0.48, 0.17]	0.3494
	Week 14	151	4.14 ± 1.685			

Treatment group	Week	No. of subjects evaluated	Pain score[Note 1), Note 2)]	Change from baseline at Week 14[Note 3), Note 4)]	Difference from placebo [95% confidence interval][Note 3)]	*P* value[Note 5)]
30 mg/day	Baseline	165	5.55 ± 0.967	−1.81 ± 0.136	−0.50 [−0.82, −0.17]	0.0027
	Week 14	142	3.73 ± 1.845			

Note 1) Weekly mean pain score (pain scores were assessed on an 11-point rating scale from 0 [no pain] to 10 [worst possible pain].)

Note 2) Mean ± standard deviation

Note 3) Missing values were imputed using the multiple imputation method based on a model assuming missing not at random mechanism. After imputation, the data sets were analyzed using a linear mixed-effects model with treatment groups, weeks, and interactions between treatment groups and weeks as fixed effects, weeks as repetition effect, and weekly mean pain scores at baseline as covariate, and the results were combined according to Rubin's rule.

Note 4) Least squares mean ± standard error

Note 5) The 20-mg/day and 30-mg/day groups were, respectively, compared with the placebo group at a significance level of 0.025 (two-sided). If both groups were statistically significant, the 15-mg/day group was supposed to be compared with the placebo group at a significance level of 0.05. If no statistical significances were demonstrated in both groups, the 15-mg/day group was not supposed to be compared with the placebo group. If either the 20-mg/day group or the 30-mg/day group was statistically significant, the 15-mg/day group was supposed to be compared with the placebo group at a significance level of 0.025.

The frequencies of adverse reactions were 18.8% (31/165 patients) in the 20-mg/day group and 36.4% (60/165) in the 30-mg/day group. Common adverse reactions in the 20-mg/day group included somnolence in 9.7% (16/165), dizziness in 7.9% (13/165), oedema peripheral in 1.8% (3/165), and weight gain in 1.8% (3/165); those in the 30-mg/day group included somnolence in 14.5% (24/165), dizziness in 9.1% (15/165), oedema peripheral in 5.5% (9/165), and weight gain in 5.5% (9/165).

13.1.2 Phase 3 multinational clinical study in post herpetic neuralgia

In a double-blind controlled study in 763 patients with postherpetic neuralgia in Asian countries, each patient received 14-week treatment with mirogabalin 15 mg (5 mg/day for 1 week, 10 mg/day for 1 week, and then 15 mg/day for 12 weeks: total 14-week treatment), 20 mg (5 mg twice daily for 1 week and then 10 mg twice daily for 13 weeks: total 14-week treatment), or 30 mg (5 mg twice daily for 1 week, 10 mg twice daily for 1 week, and then 15 mg twice daily for 12 weeks: total 14-week treatment)[Note)] or placebo.

The mirogabalin 20- and 30-mg/day groups showed statistically significant improvement in pain scores at Week 14 compared with the placebo group.

Treatment group	Week	No. of subjects evaluated	Pain score[Note 6), Note 7)]	Change from baseline at Week 14[Note 8), Note 9)]	Difference from placebo [95% confidence interval][Note 8)]	*P* value[Note 10)]
Placebo	Baseline	303	5.75 ± 1.130	−1.20 ± 0.099	–	–
	Week 14	263	4.40 ± 2.115			
20 mg/day	Baseline	153	5.70 ± 1.015	−1.68 ± 0.141	−0.47 [−0.81, −0.14]	0.0058
	Week 14	129	3.99 ± 1.839			
30 mg/day	Baseline	155	5.65 ± 1.025	−1.97 ± 0.137	−0.77 [−1.10, −0.44]	< 0.0001
	Week 14	139	3.71 ± 1.797			

Note 6) Weekly mean pain score (pain scores were assessed on an 11-point rating scale from 0 [no pain] to 10 [worst possible pain].)

Note 7) Mean ± standard deviation

Note 8) Missing values were imputed using the multiple imputation method based on a model assuming missing not at random mechanism. After imputation, the data sets were analyzed using a linear mixed-effects model with treatment groups, weeks, and interactions between treatment groups and weeks as fixed effects, weeks as repetition effect, and weekly mean pain scores at baseline as covariate, and the results were combined according to Rubin's rule.

Note 9) Least squares mean ± standard error

Note 10) The 20-mg/day and 30-mg/day groups were, respectively, compared with the placebo group at a significance level of 0.025 (two-sided). If both groups were statistically significant, the 15-mg/day group was supposed to be compared with the placebo group at a significance level of 0.05. If no statistical significances were demonstrated in both groups, the 15-mg/day group was not supposed to be compared with the placebo group. If either the 20-mg/day group or the 30-mg/day group was statistically significant, the 15-mg/day group was supposed to be compared with the placebo group at a significance level of 0.025.

The frequencies of adverse reactions were 35.3% (54/153 patients) in the 20-mg/day group and 44.5% (69/155) in the 30-mg/day group. Common adverse reactions in the 20-mg/day group included somnolence in 17.0% (26/153), dizziness in 8.5% (13/153), and weight gain in 4.6% (7/153); those in the 30-mg/day group included somnolence in 22.6% (35/155), dizziness in 14.2% (22/155), and oedema in 7.1% (11/155).

13.1.3 Phase 3 multinational clinical studies (long-term studies)

In open-label, long-term studies conducted in Asian countries, which had a 52-week treatment period (a titration period of 4 weeks and a dose-adjustment period of 48 weeks, during which the dose of mirogabalin was administered as 10 mg twice daily or 15 mg twice daily), in 214 patients with diabetic peripheral neuropathic pain or 237 patients with postherpetic neuralgia, the mean pain intensity is shown in the table below.

Assessment time point	Diabetic peripheral neuropathic pain		Postherpetic neuralgia	
	No. of subjects evaluated	Pain intensity (mm)[Note 11)]	No. of subjects evaluated	Pain intensity (mm)[Note 11)]
Pre-dose	214	42.1 ± 20.41	237	43.5 ± 21.38
Week 12	200	35.7 ± 20.30	219	34.7 ± 21.80
Week 24	186	34.4 ± 20.89	203	32.7 ± 21.81
Week 52	169	31.1 ± 20.70	184	28.6 ± 22.16

Note 11) Mean ± standard deviation; assessed on a visual analog scale (VAS) from 0 to 100 mm.

The frequencies of adverse reactions were 27.6% (59/214 patients) in patients with diabetic peripheral neuropathic pain and 39.7% (94/237) in patients with postherpetic neuralgia. Common adverse reactions in patients with diabetic peripheral neuropathic pain included somnolence in 7.9% (17/214), dizziness in 6.1% (13/214), and oedema peripheral in 4.7% (10/214); those in patients with postherpetic neuralgia included somnolence in 13.5% (32/237), dizziness in 10.1% (24/237), and weight gain in 7.2% (17/237).

13.1.4 Phase 3 multinational clinical study in central neuropathic pain

In a double-blind controlled study in 299 patients with central neuropathic pain (central neuropathic pain after spinal cord injury) conducted in Asian countries, each patient received 14-week treatment with mirogabalin (5 mg twice daily for 1 week, 10 mg twice

daily for 1 week, and then 15 mg twice daily or 10 mg twice daily, depending on safety, for 12 weeks for subjects with CLcr ≥ 60 mL/min at screening, and 2.5 mg twice daily for 1 week, 5 mg twice daily for 1 week, and then 7.5 mg twice daily or 5 mg twice daily, depending on safety, for 12 weeks for subjects with CLcr 30 mL/min to < 60 mL/min at screening: total 14-week treatment) or placebo.

The mirogabalin group showed statistically significant improvement in pain scores at Week 14 compared with the placebo group.

Treatment group	Week	No. of subjects evaluated	Pain score[Note 12), Note 13)]	Change from baseline at Week 14[Note 14), Note 15)]	Difference from placebo [95% confidence interval][Note 14)]	*P* value
Placebo	Baseline	149	6.09 ± 1.270	−0.52 ± 0.132	–	–
	Week 14	135	5.50 ± 1.932			
Mirogabalin	Baseline	150	6.04 ± 1.309	−1.23 ± 0.132	−0.71 [−1.08, −0.34]	0.0001
	Week 14	132	4.70 ± 1.863			

Note 12) Weekly mean pain score (pain scores were assessed on an 11-point rating scale from 0 [no pain] to 10 [worst possible pain].)

Note 13) Mean ± standard deviation

Note 14) Missing values were imputed using the multiple imputation method based on a model assuming missing not at random mechanism. After imputation, the data sets were analyzed by an analysis of covariance with treatment groups as a fixed effect and weekly mean pain score at baseline as a covariate, and the results were combined according to Rubin's rule.

Note 15) Least squares mean ± standard error

The frequency of adverse reactions in the mirogabalin group was 41.1% (62/151 patients). Common adverse reactions included somnolence in 25.8% (39/151), dizziness in 6.6% (10/151), and weight gain in 4.6% (7/151).

13.1.5 Phase 3 multinational clinical study (long-term study)

In an open-label, long-term study conducted in Asian countries, which had a 52-week treatment period (a titration period of 4 weeks, a dose-adjustment period of 47 weeks, and a tapering period of 1 week), in 210 patients with central neuropathic pain (central neuropathic pain after spinal cord injury, central post stroke pain, or central neuropathic pain in Parkinson's disease), the mean pain intensity is shown in the table below.

Assessment time point	No. of subjects evaluated	Pain intensity (mm)[Note 16)]
Pre-dose	210	61.4 ± 20.42
Week 12	182	49.3 ± 24.16
Week 24	170	46.3 ± 25.30
Week 48	167	45.2 ± 25.74
Week 52	170	49.7 ± 25.79

Note 16) Mean ± standard deviation; assessed on a visual analog scale (VAS) from 0 to 100 mm.

The frequency of adverse reactions was 40.0% (84/210 patients). Common adverse reactions included somnolence in 15.2% (32/210), oedema peripheral in 9.0% (19/210), and dizziness in 7.1% (15/210).

13.1.6 Japanese Phase 3 clinical study

In a Phase 3 open-label study, which had a 14-week treatment period (a titration period of 2 weeks and a fixed-dose period of 12 weeks), in patients with diabetic peripheral neuropathic pain or postherpetic neuralgia and with renal impairment, the pain scores at Week 14 are shown in the table below.

Treatment group (CLcr: mL/min)	Week	No. of subjects evaluated	Pain score[Note 17), Note 18)]	Change from baseline at Week 14[Note 19)]
Moderate renal impairment (59 ≥ CLcr ≥ 30)[Note 20)]	Baseline	30	5.65 ± 1.049	−1.79 ± 0.335
	Week 14	26	3.81 ± 1.834	
Severe renal impairment (29 ≥ CLcr ≥ 15)[Note 21)]	Baseline	5	5.97 ± 1.275	−2.07 ± 0.871
	Week 14	4	3.83 ± 3.082	

Note 17) Weekly mean pain score (pain scores were assessed on an 11-point rating scale from 0 [no pain] to 10 [worst possible pain].)
Note 18) Mean ± standard deviation
Note 19) Least squares mean ± standard error
Note 20) The maintenance dose was 15 mg/day.
Note 21) The maintenance dose was 7.5 mg/day.

The frequencies of adverse reactions were 30.0% (9/30 patients) in patients with moderate renal impairment and 0% (0/5) in patients with severe renal impairment. Common adverse reactions in patients with moderate renal impairment included somnolence in 13.3% (4/30) and dizziness in 6.7% (2/30).

Note) The approved dose of TARLIGE is 5 mg of mirogabalin twice daily for the initial dose, and 10 or 15 mg of mirogabalin twice daily for the effective dose.

14. PHARMACOLOGY

14.1 Mechanism of Action

Mirogabalin is considered to exhibit its analgesic effect by reducing calcium current via binding to the $\alpha_2\delta$ subunit, which plays an auxiliary role in functions of voltage-gated calcium channels in the nervous system. The analgesic effect of mirogabalin is also suggested to involve activation of the noradrenergic pathway in the descending pain inhibitory system.

15. PHYSICOCHEMICAL PROPERTIES

Non-proprietary Name: Mirogabalin besilate

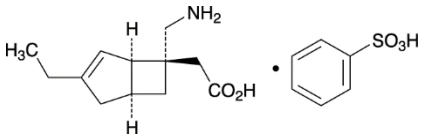
Chemical Name: [(1*R*,5*S*,6*S*)-6-(Aminomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl]acetic acid monobenzenesulfonate

Molecular Formula: $C_{12}H_{19}NO_2 \cdot C_6H_6O_3S$

Molecular Weight: 367.46

Description: Mirogabalin besilate is a white to pale yellowish-white powder.

Structural Formula:



Melting Point: 169°C

Partition Coefficient: 1-octanol/Britton-Robinson buffer (pH3.0): −0.59
1-octanol/Britton-Robinson buffer (pH7.5): −0.05
1-octanol/Britton-Robinson buffer (pH12.0): −1.10

16. CONTRAINDICATIONS

Patients with a history of hypersensitivity to any ingredients of TARLIGE

17. PRECAUTIONS FOR HANDLING AND STORAGE CONDITIONS

Store in original packaging to protect tablets from moisture.

Store below 30°C.

18. PACKAGING

< Mirogabalin besilate (TARLIGE) Film-coated Tablets 2.5 mg>

Alu/Alu blister, embedded with desiccant. 140 tablets (14 tablets per blister)

< Mirogabalin besilate (TARLIGE) Film-coated Tablets 5 mg>

Alu/Alu blister, embedded with desiccant. 140 tablets (14 tablets per blister)

< Mirogabalin besilate (TARLIGE) Film-coated Tablets 10 mg>

Alu/Alu blister, embedded with desiccant. 140 tablets (14 tablets per blister)

< Mirogabalin besilate (TARLIGE) Film-coated Tablets 15 mg>

Alu/Alu blister, embedded with desiccant. 140 tablets (14 tablets per blister)

19. SHELF LIFE

The expiry date is stated on the packaging.

20. PRODUCT REGISTRATION HOLDER:

20.1 Malaysia
A. Menarini Singapore Pte. Ltd.,
B-18-2, Level 18, The Ascent Paradigm,
No.1 Jalan SS7/26A, Kelana Jaya,
47301 Selangor Darul Ehsan,
Malaysia

20.2 Singapore
A. Menarini Singapore Pte. Ltd.
30 Pasir Panjang Road
#08-32 Mapletree Business City
Singapore 117440

21. DATE OF REVISION OF TEXT

30 June 2026