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

2. INDICATIONS

Neuropathic pain

3. DOSAGE AND ADMINISTRATION

Usually, for adults, 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 (90 > CLcr ≥ 60)	Moderate (60 > CLcr ≥ 30)	Severe (including patients on hemodialysis) (30 > CLcr)
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 PRECAUTIONS

5.1 Mirogabalin besilate (TARLIGE) may cause event(s) (e.g., dizziness, somnolence, loss of consciousness). 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 It should be noted that Mirogabalin besilate (TARLIGE) for neuropathic pain is not a causal therapy but a supportive therapy. Therefore, the underlying disease of the pain should be diagnosed and treated concurrently, and Mirogabalin besilate (TARLIGE) should not be used without intention.

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.

6. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

6.1 Patients with Renal Impairment

The dose and dosing intervals should be adjusted, referring 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.

6.3 Breastfeeding Women

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).

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 potentiate the effects of Mirogabalin besilate (TARLIGE).	This is possibly due to the blood mirogabalin concentration that increased by the inhibitory effect of probenecid on OAT1, OAT3, and UGT.
Cimetidine	Co-administration may potentiate the effects of Mirogabalin besilate (TARLIGE).	This is possibly due to the blood mirogabalin concentration that increased by the inhibitory effect of cimetidine on MATE1 and MATE2-K.
Lorazepam Alcohol (drinking)	Co-administration may facilitate 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** (frequency unknown), **somnolence** (frequency unknown), **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	
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.

12. PHARMACOKINETICS

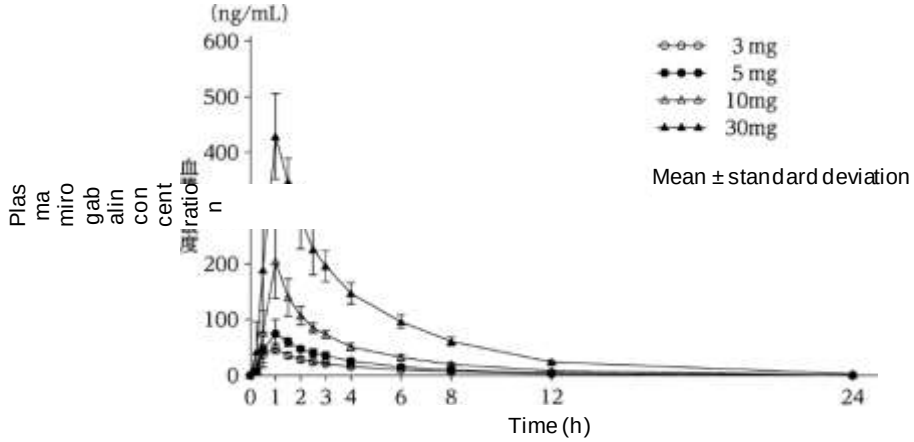
12.1 Blood Level

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

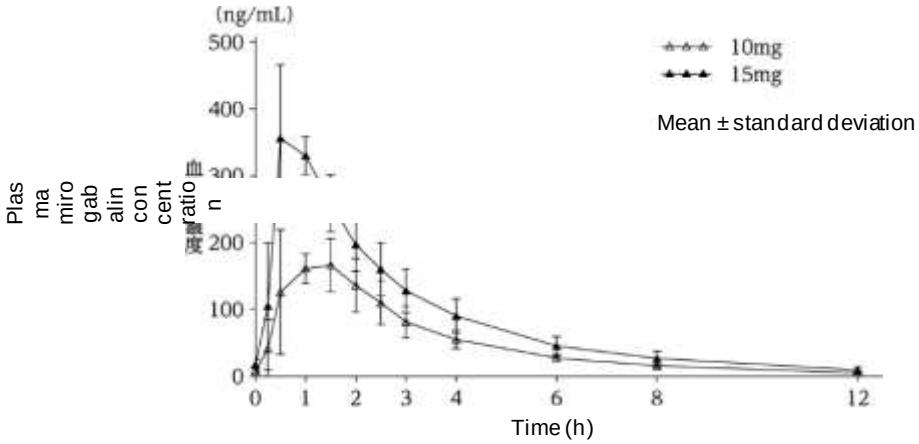
Dose	No. of subjects	Cmax (ng/mL)	Tmax (h)[Note 1)]	AUCinf (ng·h/mL)	$t_{1/2}$ (h)
3 mg	6	48.6 ± 8.47	1.00 (0.50 to 1.00)	184.2 ± 21.75	3.31 ± 0.37
5 mg	6	78.3 ± 18.0	1.00 (0.50 to 2.00)	276.2 ± 26.96	2.96 ± 0.17
10 mg	6	205 ± 64.0	1.00 (1.00 to 1.50)	614.1 ± 84.02	3.32 ± 0.75
30 mg	6	433 ± 67.9	1.00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

12.3 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. 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
90 > CLcr ≥ 60 (mild)	6	81.4 ± 29.0	1.74 (0.97 to 4.00)	422 ± 85.1	7.83 ± 1.61

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)
60 > CLcr ≥ 30 (moderate)	9	76.9 ± 13.3	1.95 (1.03 to 5.00)	655 ± 144	4.48 ± 1.87
30 > CLcr (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, respectively, higher than that in healthy subjects, and AUCinf in subjects with mild and moderate hepatic impairment was 0.9 and 1.1 times, respectively, greater than that in healthy subjects.

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 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 (10 mg/day for 1 week and then 20 mg/day for 13 weeks: total 14-week treatment), or 30 mg (10 mg/day for 1 week, 20 mg/day for 1 week, and then 30 mg/day 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			
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 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 (10 mg/day for 1 week and then 20 mg/day for 13 weeks: total 14-week treatment), or 30 mg (10 mg/day for 1 week, 20 mg/day for 1 week, and then 30 mg/day 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), 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 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 (10 mg/day for 1 week, 20 mg/day for 1 week, and then 30 mg/day or 20 mg/day, depending on safety, for 12 weeks for subjects with CLcr ≥ 60 mL/min at screening, and 5 mg/day for 1 week, 10 mg/day for 1 week, and then 15 mg/day or 10 mg/day, 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.

14.2 Analgesic Effect

14.2.1 Mirogabalin increased the pain threshold to mechanical stimulation in partial sciatic nerve ligation model rats.

14.2.2 Mirogabalin increased the pain threshold to mechanical stimulation in streptozotocin-induced diabetic model rats.

14.2.3 Mirogabalin increased the pain threshold to mechanical stimulation in spinal cord injury model rats.

15. PHYSICOCHEMICAL PROPERTIES

Non-proprietary Name: Mirogabalin besilate

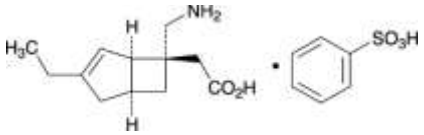
Chemical Name: [(1*R*,5*S*,6*S*)-6-(Aminomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl]acetic acid monobenzenesulfonate

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

Microscopic holes due to moisture absorption may appear on the surface of tablets after opening.

Store below 30°C.

18. PACKAGING

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

(Al/Al blister: with desiccant) 14, 140 tablets (14 tablets per blister)

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

(Al/Al blister: with desiccant) 14, 140 tablets (14 tablets per blister)

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

(Al/Al blister: with desiccant) 14, 140 tablets (14 tablets per blister)

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

(Al/Al blister: with desiccant) 14, 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

20 June 2025