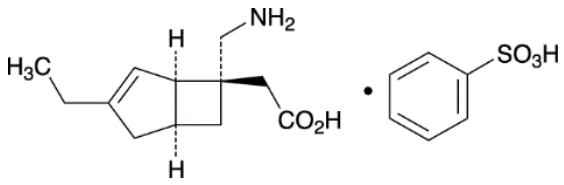
TARLIGE® 2.5 mg
TARLIGE® 5 mg
TARLIGE® 10 mg
TARLIGE® 15 mg
Mirogabalin besilate
Film-coated Tablets

1. COMPOSITION AND DESCRIPTION

1.1 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

1.2 Composition

Brand Name	Active Ingredient(s)	Excipients
TARLIGE 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 5 mg	In 1 tablet 8.78 mg of mirogabalin besilate (equivalent to 5 mg of mirogabalin)	
TARLIGE 10 mg	In 1 tablet 17.56 mg of mirogabalin besilate (equivalent to 10 mg of mirogabalin)	

Brand Name	Active Ingredient(s)	Excipients
TARLIGE 15 mg	In 1 tablet 26.34 mg of mirogabalin besilate (equivalent to 15 mg of mirogabalin)	

1.3 Product Description

Brand Name	Dosage Form	Color	Externals		
			Size (mm)	Thickness (mm)	Weight (mg)
TARLIGE 2.5 mg	Film-coated tablets (round)	Peach	 6.5 (diameter)	 About 3.1	 About 105
TARLIGE 5 mg	Film-coated tablets (oblong / scored)	Grayish red	 10.9 (long diameter) 5.8 (short diameter)	 About 3.8	 About 208
TARLIGE 10 mg	Film-coated tablets (oblong / scored)	Peach	 12.4 (long diameter) 5.8 (short diameter)	 About 4.5	 About 311
TARLIGE 15 mg	Film-coated tablets (oblong / scored)	Grayish red	 12.4 (long diameter) 5.8 (short diameter)	 About 4.5	 About 311

2. PHARMACOKINETICS

2.1 Blood Level

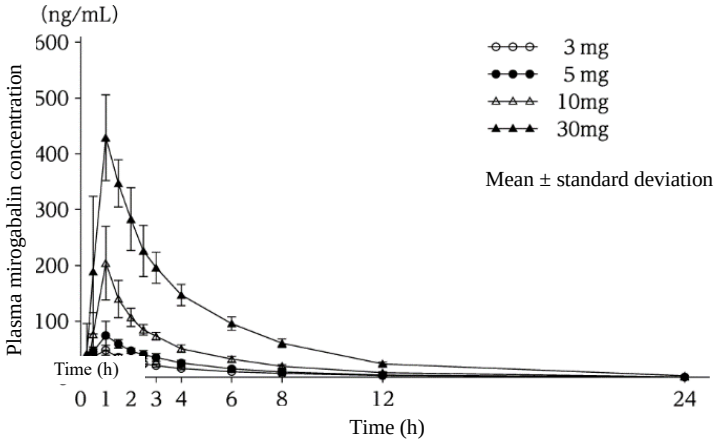
2.1.1 Plasma concentration

(1) Single-dose administration

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

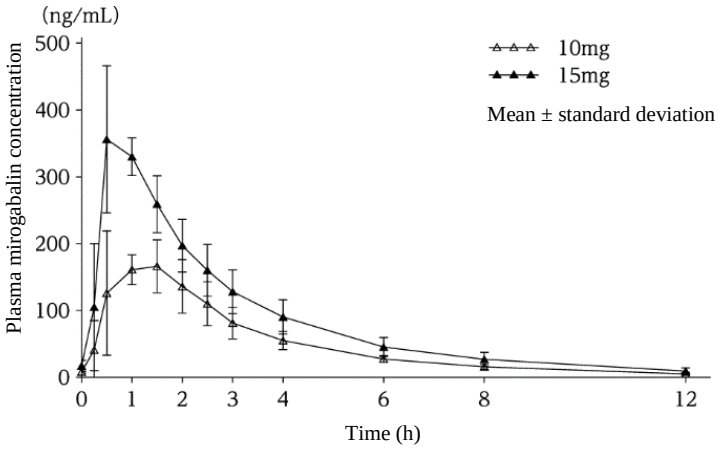
Mean ± standard deviation
Note 1) Median (minimum, maximum)

(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 Japanese 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[1), 2)].

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 2)]	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 2) Median (minimum, maximum)

2.2 Absorption

2.2.1 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%.

2.3 Distribution

2.3.1 Volume of distribution

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

2.3.2 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*).

2.3.3 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*).

2.4 Metabolism

Following the administration of ^{14}C-mirogabalin at a single oral dose of 30 mg (150 μCi) in healthy male adults (6 subjects), 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

2.5 Excretion

Following the administration of mirogabalin at a single oral dose of 3, 5, 10, and 30 mg in 6 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 healthy male adults (6 subjects), a cumulative excretion rate of radioactivity up to 168 h post-dose was ≥ 98%; radioactivity recovered in urine and feces was approximately 97% and 1%, respectively.

2.6 Patients with Specific Backgrounds

2.6.1 Pharmacokinetics in patients with renal impairment

Following the administration of mirogabalin at a single oral dose of 5 mg in 30 Japanese 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[3), 4)]. [see 8.1, 8.3.1, and 8.6.2]

Severity grade of renal impairment (CLcr: mL/min)	No. of subjects	Cmax (ng/mL)	Tmax (h)[Note 3)]	AUClast (ng·h/mL)	CLcr (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
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 4)]	6	101 ± 32.9	4.01 (1.92 to 5.00)	1990 ± 916	–

Mean ± standard deviation
Note 3) Median (minimum, maximum)
Note 4) Hemodialysis was performed for 4 h from 24 h post-dose.

2.6.2 Pharmacokinetics in 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.

2.6.3 Pharmacokinetics in 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[5)]. [see 8.3.5.1]

2.7 Drug-Drug Interactions

2.7.1 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 TARLIGE (15 mg) increased the Cmax and AUClast of TARLIGE by 29% and 76%, respectively[6)]. [see 8.4.1]

(2) Co-administration of cimetidine (400 mg) with TARLIGE (15 mg) increased the Cmax and AUClast of TARLIGE by 17% and 44%, respectively[6)]. [see 8.4.1]

(3) Co-administration of TARLIGE with ethanol or lorazepam had no notable effect on the pharmacokinetics of TARLIGE or these drugs. Co-administration of TARLIGE with these drugs decreased attention and balance-function more profoundly than monotherapy with TARLIGE[7), 8)]. [see 8.4.1]

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

3. CLINICAL STUDIES

3.1.Clinical Studies for Efficacy and Safety

3.1.1 Phase 3 multinational clinical study

In a double-blind controlled study in 824 patients with diabetic peripheral neuropathic pain, 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[9)].

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).

3.1.2 Phase 3 multinational clinical study

In a double-blind controlled study in 763 patients with postherpetic neuralgia, 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[10)].

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).

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

In Phase 3, open-label, long-term studies conducted in Asia, 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[11), 12)].

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).

3.1.4 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[13]. [see 8.1 and 8.3.1]

Treatment group (CLcr: mL/min)	Week	No. of subjects evaluated	Pain score[Note 12), Note 13)]	Change from baseline at Week 14[Note 14)]
Moderate renal impairment (59 ≥ CLcr ≥ 30)[Note 15)]	Baseline	30	5.65 ± 1.049	−1.79 ± 0.335
	Week 14	26	3.81 ± 1.834	
Severe renal impairment (29 ≥ CLcr ≥ 15)[Note 16)]	Baseline	5	5.97 ± 1.275	−2.07 ± 0.871
	Week 14	4	3.83 ± 3.082	

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) Least squares mean ± standard error
Note 15) The maintenance dose was 15 mg/day.
Note 16) 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.

4. PHARMACOLOGY

4.1 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[14), 15)]. The analgesic effect of mirogabalin is also suggested to involve activation of the noradrenergic pathway in the descending pain inhibitory system[16)].

4.2 Analgesic Effect

4.2.1 Mirogabalin increased the pain threshold to mechanical stimulation in partial sciatic nerve ligation model rats[14)].

4.2.2 Mirogabalin increased the pain threshold to mechanical stimulation in streptozotocin-induced diabetic model rats[14)].

4.2.3 Mirogabalin increased the pain threshold to mechanical stimulation in spinal cord injury model rats[17)].

5. INDICATIONS

Peripheral neuropathic pain.

6. 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.

7. CONTRAINDICATIONS

TARLIGE is contraindicated for use in the following patients:
Patients with a history of hypersensitivity to any ingredients of TARLIGE

8. PRECAUTIONS

8.1 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. [see 2.6.1, 3.1.4, 8.3.1, and 8.3.5.1]

		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

8.2 Important Precautions

8.2.1 TARLIGE may cause event(s) (e.g., dizziness, somnolence, loss of consciousness). Patients being treated with TARLIGE must be warned not to operate potentially dangerous machinery, such as driving a car. [see 8.5.1.1]

8.2.2 Treatment with 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.

8.2.3 It should be noted that 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 TARLIGE should not be used without intention.

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

8.2.5 Treatment with 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.

8.3 Precautions Concerning Patients with Specific Backgrounds

8.3.1 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. [see 2.6.16, 3.1.4, 8.1, and 8.3.5.1]

8.3.2 Pregnant Women

There are no adequate data on the use of Tarlige (mirogabalin) in pregnant women. An animal study (in rats) has shown that mirogabalin crossed the placenta (see section Preclinical safety data). However, the potential risk to humans is unknown. Therefore, Tarlige should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Effective contraception must be used in women of childbearing potential.

8.3.3 Breastfeeding Women

An animal study (in rats) has shown that mirogabalin is transferred to breast milk. As the safety of mirogabalin in infants is not known, breast-feeding is not recommended during treatment with mirogabalin. A decision must be made whether to discontinue breast-feeding or to discontinue from mirogabalin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

8.3.4 Pediatric Use

Clinical studies in children have not been conducted.

8.3.5 Geriatric Use

8.3.5.1 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. [see 2.6.3, 8.1, and 8.3.1]

8.3.5.2 Elderly patients tend to experience falls resulting in fractures, etc. led by events (e.g., dizziness, somnolence, loss of consciousness). [see 8.5.1.1]

8.4 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).

8.4.1 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 [see 2.7.1]	Co-administration may potentiate the effects of TARLIGE.	This is possibly due to the blood mirogabalin concentration that increased by the inhibitory effect of probenecid on OAT1, OAT3, and UGT.
Cimetidine [see 2.7.1]	Co-administration may potentiate the effects of TARLIGE.	This is possibly due to the blood mirogabalin concentration that increased by the inhibitory effect of cimetidine on MATE1 and MATE2-K.

Drugs	Clinical Symptoms and Measures	Mechanism and Risk Factors
Lorazepam Alcohol (drinking) [see 2.7.1]	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.

8.5 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.

8.5.1 Clinically Significant Adverse Reactions

8.5.1.1 **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. [see 8.2.1 and 8.3.5.2]

8.5.1.2 **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.

8.5.2 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

8.5.3 Reporting of suspected side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

Pusat Farmakovigilans/ MESO Nasional

Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan

Jl. Percetakan Negara No.23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id.

Phone: +62-21-4244691 Ext. 1079

Website: https://e-meso.pom.go.id/ADR

8.6 Overdosage

8.6.1 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.

8.6.2 Treatment

Hemodialysis is reported to remove 15.3% of mirogabalin. [see 2.6.1]

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

8.7 Precautions Concerning Use

8.7.1 Precautions Concerning the Dispensing of the Drug

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.

8.8 Other Precautions

8.8.1 Information Based on Clinical Use

8.8.1.1 In multinational, placebo-controlled studies conducted in Japan and other 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.

8.8.1.2 In multinational, placebo-controlled studies conducted in Japan and other 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.

8.9 Precautions for Handling

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

9. STORAGE

Do not store above 30° C.

10. SHELF LIFE

Please refer to outer carton, pillow or blister package.

ON DOCTOR PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

11. PACKAGING

TARLIGE 2.5 mg	: Box, 1 pillow pack @ 10 blisters with dessicant @ 10 film-coated tablets
TARLIGE 5 mg	: Box, 1 pillow pack @ 10 blisters with dessicant @ 10 film-coated tablets
TARLIGE 10 mg	: Box, 1 pillow pack @ 10 blisters with dessicant @ 10 film-coated tablets
TARLIGE 15 mg	: Box, 1 pillow pack @ 10 blisters with dessicant @ 10 film-coated tablets

Reg. No:

Under license by:
Daiichi Sankyo Co., Ltd.
3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan

Manufactured by:
TAIYO Pharma Tech Co., Ltd.
4-38, Aketacho, Takatsuki, Osaka, Japan

Packaged and released by:
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

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Date of Package Insert
March 2025 (Version 0.0)

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Leaflet: Informasi Produk Untuk Pasien
TARLIGE® 2.5 mg
TARLIGE® 5 mg
TARLIGE® 10 mg
TARLIGE® 15 mg
Mirogabalin besilate
Tablet Salut Selaput

Mohon leaflet ini dibaca baik-baik sebelum Anda mulai mengonsumsi obat ini karena mengandung informasi penting untuk Anda.

- Simpan leaflet ini setelah Anda baca. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau tenaga kesehatan lainnya.
- Jika Anda mengalami efek samping, konsultasikan kepada dokter atau tenaga kesehatan lainnya. Termasuk kemungkinan efek samping yang tidak tercantum di leaflet ini. Lihat Bagian 4.

Apa yang ada dalam leaflet ini

1. Apa itu TARLIGE dan apa kegunaannya

TARLIGE mengandung zat aktif mirogabalin besilate.
Obat ini digunakan untuk nyeri neuropati perifer, yaitu nyeri karena terdapat kerusakan saraf perifer atau saraf tepi.

2. Apa yang perlu Anda tahu sebelum menggunakan TARLIGE

Jangan menggunakan TARLIGE:

Jika Anda pasien dengan riwayat alergi atau hipersensitif terhadap bahan atau komposisi produk ini (Lihat Bagian 6).

Peringatan dan Perhatian:

- TARLIGE dapat menyebabkan pusing, mengantuk, kehilangan kesadaran. Pasien yang menggunakan TARLIGE harus diperingatkan untuk tidak mengoperasikan mesin yang berpotensi bahaya, seperti mengendarai mobil.
- TARLIGE dapat menyebabkan penambahan berat badan.
- TARLIGE digunakan untuk terapi pendukung nyeri neuropatik dan tidak boleh digunakan tanpa tujuan.
- Penghentian penggunaan TARLIGE secara tiba-tiba dapat menyebabkan gejala putus obat (misalnya insomnia, mual, diare, nafsu makan menurun). Penggunaan TARLIGE harus dihentikan dengan hati-hati, seperti pengurangan dosis secara bertahap.
- Penggunaan TARLIGE dapat menyebabkan gangguan pada mata (misalnya, penglihatan abnormal, penglihatan kabur).

Sebelum menggunakan obat ini, ceritakan pada dokter atau tenaga kesehatan lain:

- Jika Anda pasien dengan gangguan ginjal.

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Jika hal-hal di atas berlaku untuk Anda, jangan gunakan TARLIGE dan beri tahu dokter atau tenaga kesehatan lainnya. Jika Anda tidak yakin, konsultasikanlah dengan dokter atau tenaga kesahatan lain sebelum menggunakan TARLIGE.

Interaksi Obat TARLIGE
Ceritakan kepada dokter Anda jika Anda sedang menggunakan atau baru saja menggunakan obat lain.
Termasuk obat-obatan yang Anda beli tanpa resep dan obat-obatan herbal.
Secara khusus, beritahukan kepada dokter Anda jika Anda mengonsumsi obat-obatan ,makanan atau minuman berikut ini:

- Probenesid
- Simetidin
- Lorazepam
- Minuman Alkohol

Kehamilan dan Menyusui
Tarlige tidak boleh diminum selama kehamilan atau masa menyusui, kecuali atas anjuran dokter. Jika Anda hamil, menyusui, menduga diri hamil, atau merencanakan kehamilan, mintalah saran dari dokter atau apoteker Anda sebelum meminum obat ini.

Penggunaan TARLIGE pada usia lanjut

- TARLIGE harus diberikan dengan hati-hati dan diperlukan penyesuaian dosis dan interval dosis berdasarkan hasil pemeriksaan fungsi ginjal (tingkat klirens kreatinin). Pasien usia lanjut sering mengalami penurunan fungsi ginjal.
- Pasien usia lanjut cenderung dapat mengalami jatuh dikarenakan efek samping seperti pusing, mengantuk dan kehilangan kesadaran.

Penggunaan TARLIGE pada Pediatrik
Efektivitas dan keamanan pada pasien anak belum ditetapkan.

3. Bagaimana cara penggunaan TARLIGE
Pada pasien dewasa, TARLIGE digunakan secara oral, diberikan dengan dosis awal 5 mg dua kali sehari, kemudian ditingkatkan dosis sebesar 5 mg per dosis dengan interval minimal 1 minggu hingga 15 mg dua kali sehari.

Dosis dapat ditingkatkan atau diturunkan dengan tepat dalam kisaran antara 10 mg dan 15 mg dua kali sekali, berdasarkan usia atau gejala masing-masing pasien.

Jangan menggunakan TARLIGE dalam dosis ganda untuk menggantikan dosis yang terlewat.

Jika Anda menggunakan TARLIGE melebihi dosis yang dianjurkan dan merasakan gejala seperti suasana hati gembira, gangguan bicara, sakit kepala, kesulitan menelan, radang sendi, pembengkakan sendi, serta lemas dan lelah berlebihan, segera informasikan kepada dokter Anda.

4. Kemungkinan efek samping
Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping meskipun tidak semua orang mengalaminya.
Efek samping berikut dapat terjadi. Jika terjadi, informasikanlah kepada dokter Anda sehingga Anda akan diberi perawatan yang tepat.

Jika Anda mengalami salah satu efek samping, atau jika Anda melihat efek samping yang tidak tercantum dalam leaflet ini, silakan beri tahu dokter Anda atau tenaga kesehatan lainnya.

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Efek samping yang signifikan

- Pusing
- Mengantuk
- Kehilangan kesadaran
- Gangguan fungsi hati

Efek samping lain

- Pusing postural (pusing atau rasa berputar saat berdiri)
- Insomnia
- Sakit kepala
- Tremor
- Hipoestesia (hilangnya sebagian atau seluruh sensasi di bagian tubuh)
- Gangguan ingatan
- Amnesia
- Disartria (gangguan bicara akibat kelemahan pada fungsi otot yang digunakan untuk berbicara)
- Halusinasi
- Delirium (kondisi penurunan kesadaran dan mengalami kebingungan parah)
- Gangguan pengecapan
- Ketidaknyamanan di kepala
- Dyskinesia (gerakan tidak terkendali pada bagian wajah atau tubuh tertentu)
- Mioklonus (kedutan atau sentakan otot)
- Penglihatan kabur
- Diplopia (penglihatan ganda)
- Gangguan penglihatan
- Ketajaman penglihatan menurun
- Jumlah eosinofil meningkat
- Hipotensi ortostatik (tekanan darah rendah yang dipicu oleh perubahan posisi tubuh saat hendak berdiri)
- Hipertensi
- Jantung berdebar
- Sensasi panas
- Tekanan darah menurun
- Konstipasi atau sembelit
- Perut kembung
- Mulut kering
- Gastritis atau iritasi lambung
- Muntah
- Nafsu makan meningkat atau menurun
- Sakit perut bagian atas
- *Gastroesophageal Reflux Disease* (GERD) (penyakit asam lambung yang ditandai dengan nyeri pada ulu hati atau sensasi terbakar di dada akibat naiknya asam lambung menuju esofagus (kerongkongan))
- Diare
- Perut tidak nyaman
- Enzim hati meningkat
- Inkontinensia urin (kondisi hilangnya kontrol kandung kemih)
- Pollakiuria (gangguan sering buang air kecil)

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- Disuria (rasa nyeri, tidak nyaman, atau panas saat buang air kecil)
- Retensi urin (gangguan susah buang air kecil)
- Ruam
- Urtikaria (biduran)
- Eritema (munculnya bercak kemerahan pada kulit)
- Pruritus (rasa gatal)
- Edema
- Peningkatan berat badan
- Gangguan gaya berjalan
- Perasaan tidak normal
- Vertigo
- Haus
- Edema wajah
- Jatuh
- Diabetes melitus (HbA1c meningkat, kadar gula darah meningkat)
- Malaise (rasa lelah, tidak enak badan dan tidak nyaman)
- Kreatinin kinase darah meningkat
- Edema kelopak mata
- Kelemahan otot
- Sindrom putus obat
- Asthenia (kelemahan fisik atau kekurangan energi)

Pelaporan efek samping
Jika Anda mengalami efek samping, bicarakan dengan dokter, apoteker atau perawat Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini.
Anda juga dapat melaporkan efek samping atau kondisi yang tidak nyaman langsung kepada Industri Farmasi melalui situs web kami www.mt-pharma-id.com pada *Section* Farmakovigilans.
Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Bagaimana cara penyimpanan TARLIGE

- Jangan menyimpan obat ini pada suhu diatas 30˚ C.
- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan TARLIGE setelah tanggal kedaluwarsa yang tercantum pada kemasan karton, *pillow* atau blister.

6. Isi kemasan dan informasi lainnya
Apa kandungan TARLIGE
Zat aktifnya adalah mirogabalin besilate setara dengan mirogabalin 2.5 mg, 5 mg, 10 mg dan 15 mg dalam setiap tablet.
Bahan lainnya adalah D-mannitol, microcrystalline cellulose, carmellose calcium, tocopherol, citric acid hydrate, magnesium aluminometasilicate, magnesium stearate, hypromellose, titanium oxide, talc, yellow ferric oxide dan red ferric oxide.

Seperti apa TARLIGE dan isi kemasannya

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TARLIGE 2.5 mg adalah tablet salut selaput berbentuk bulat berwarna persik dalam kemasan dus, 1 pillow pack @ 10 blister dengan desikan @ 10 tablet salut selaput
TARLIGE 5 mg adalah tablet salut selaput berbentuk lonjong dengan garis cetakan berwarna merah keabuan dalam kemasan dus, 1 pillow pack @ 10 blister dengan desikan @ 10 tablet salut selaput
TARLIGE 10 mg adalah tablet salut selaput berbentuk lonjong dengan garis cetakan berwarna persik dalam kemasan dus, 1 pillow pack @ 10 blister dengan desikan @ 10 tablet salut selaput
TARLIGE 15 mg adalah tablet salut selaput berbentuk lonjong dengan garis cetakan berwarna merah keabuan dalam kemasan dus, 1 pillow pack @ 10 blister dengan desikan @ 10 tablet salut selaput

7. Nomor Izin Edar
Reg. No:

8. Peringatan khusus
HARUS DENGAN RESEP DOKTER

Dibawah lisensi oleh:
Daiichi Sankyo Co., Ltd.
3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan

Dibuat oleh:
TAIYO Pharma Tech Co., Ltd
4-38, Aketacho, Takatsuki, Osaka, Japan

Dikemas dan dirilis oleh:
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

Leaflet ini direvisi terakhir pada Maret 2025

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