Summary of Product Characteristics

1 NAME OF THE MEDICAL PRODUCT

TARLIGE 2.5 mg film-coated tablets

TARLIGE 5 mg film-coated tablets

TARLIGE 10 mg film-coated tablets

TARLIGE 15 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains mirogabalin besilate equivalent to 2.5, 5, 10 and 15 mg of mirogabalin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

TARLIGE 2.5 mg film-coated tablets

Peach, round-shaped film-coated tablets (6.7 mm) printed with “DSC151” and “2.5” on both sides.

TARLIGE 5 mg film-coated tablets

Grayish-red, oblong-shaped film-coated tablets (10.8×5.7 mm) printed with “DSC152” to the left and “5” to the right of the score line on one side and printed with “DSC152” to the left and “5” to the right without score line on the reverse.

TARLIGE 10 mg film-coated tablets

Peach, oblong-shaped film-coated tablets (12.2×6.5 mm) printed with “DSC154” to the left and “10” to the right of the score line on one side and printed with “DSC154” to the left and “10” to the right without score line on the reverse.

TARLIGE 15 mg film-coated tablets

Grayish-red, oblong-shaped film-coated tablets (12.2×6.5 mm) printed with “DSC155” to the left and “15” to the right of the score line on one side and printed with “DSC155” to the left and “15” to the right without score line on the reverse.

The debossed line for scoring is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Neuropathic pain

TARLIGE is indicated for the treatment of neuropathic pain in adult.

4.2 Posology and method of administration

Posology

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.

Renal Impairment

Since mirogabalin concentrations in plasma may increase in patients with reduced renal function, possibly increasing the risk of adverse reactions, careful administration with close monitoring is necessary for these patients. For patients with renal impairment, the dose and dosing intervals should be adjusted, referring to creatinine clearance levels listed in Table 1. Treatment should be started at a low dose, and the dose should be increased in patients who show confirmed tolerability but insufficient effect (see section 5.1 and 5.2).

Table 1: Mirogabalin Dose Adjustment Based on Renal function

		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

Pediatric population

Clinical studies in children have not been conducted.

Elderly population

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 section 5.2).

Elderly patients tend to experience falls resulting in fractures, etc. led by events (e.g., dizziness, somnolence, loss of consciousness) (see section 4.4 and 4.7).

Hepatic Impairment

No dose adjustment is required for patients with hepatic impairment (See section 5.2).

Method of administration

For oral use.

TARLIGE can be taken with or without food (see section 5.2).

4.3 Contraindications

Patients with a history of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Dizziness, somnolence, loss of consciousness

Dizziness, somnolence, and loss of consciousness, which may cause falls and subsequent fractures, etc., may occur. Patients being treated with TARLIGE should be monitored closely; if any abnormalities are noted, appropriate measures, such as discontinuation of treatment or dose reduction, should be taken. (see section 4.2 and 4.7)

Hepatic function disorder

Hepatic function disorder (e.g., AST increased, ALT increased) may occur. Patients being treated with TARLIGE should be monitored closely; if any abnormalities including early symptoms (e.g., general malaise, anorexia) are noted, treatment should be discontinued and appropriate measures should be taken.

Weight gain

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.

Withdrawal symptoms

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.

Ophthalmic disorders

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

Renal impairment

The serious renal impairment is reported post-marketing in patients treated with TARLIGE. If abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

Other Precautions

- 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 the drug should not be used without intention.
- In multinational, placebo-controlled studies conducted in Asian countries, suicide-related adverse events were reported in 5 of 1378 subjects (0.26%; 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.
- 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.

4.5 Interaction with other medicinal products and other forms of interaction

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).

Table 2: Precautions for Co-administration (TARLIGE should be administered with caution when co-administered with the following.)

Drugs	Clinical Symptoms and Measures	Mechanisms and Risk Factors
Probenecid	Co-administration may potentiate the effect 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	Co-administration may potentiate the effect 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	Mechanisms and Risk Factors
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.

In vitro study data

- Mirogabalin was not metabolized by CYP but was metabolized by UGT1A3, UGT1A4, UGT1A9, UGT2B4, UGT2B7 and UGT2B17.
- Mirogabalin was secreted from the kidney and was suggested to be a substrate for OAT1, OAT3, OCT2, MATE1, and MATE2-K.
- Mirogabalin did not inhibit or induce major human CYP molecular species, and did not inhibit activities of drug transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K). Mirogabalin also did not inhibit activities of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

In clinical study data

- Co-administration of probenecid (500 mg) with TARLIGE (15 mg) increased the Cmax and AUClast of TARLIGE by 29% and 76%, respectively.
- Co-administration of cimetidine (400 mg) with TARLIGE (15 mg) increased the Cmax and AUClast of TARLIGE by 17% and 44%, respectively.
- Co-administration of TARLIGE with ethanol or lorazepam had no notable effect on the pharmacokinetics of TARLIGE or these drugs. Co-administration of TARLIGE in with these drugs decreased attention and balance-function more profoundly than monotherapy with TARLIGE.
- Co-administration of TARLIGE with tramadol had no notable effect on the pharmacokinetics of TARLIGE or tramadol.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

Pregnancy

For pregnant women and women who may be pregnant, 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 (see section 5.3).

Breast-feeding

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 (see section 5.3).

Fertility

There are no clinical data on the effects of TARLIGE on female fertility. There was no adverse effect on fertility in an animal study (in rats) (see section 5.3).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of TARLIGE is based on three Phase 3 and one Phase 2 studies (854 patients with diabetic peripheral neuropathic pain, 553 patients with postherpetic neuralgia and 306 patients with central neuropathic pain), and from post-authorisation experience.

The most commonly reported adverse reactions associated with TARLIGE treatment in clinical trials are somnolence (16.8%), dizziness (9.7%) and oedema (7.5%).

Tabulated list of adverse reactions

Adverse reactions from TARLIGE in clinical trials, post-authorisation safety studies and spontaneous reporting are summarized in Table 3.

The following terminologies have been used in order to classify the occurrence of adverse reactions: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 3: Mirogabalin Adverse Drug Reactions

MedDRA System Organ Class	**Adverse reactions**	**Frequency**
Metabolism and nutrition disorders	Increased appetite	Uncommon
	Decreased appetite	Uncommon
	Diabetes mellitus (HbA1c increased, Sugar blood level increased)	Uncommon
Psychiatric disorders	Insomnia	Uncommon
	Hallucination	Not known
	Delirium	Not known
Nervous system disorders	Somnolence	Very common
	Dizziness	Common
	Dizziness postural	Uncommon
	Loss of consciousness	Uncommon
	Headache	Uncommon
	Tremor	Uncommon
	Memory impairment	Not known
	Amnesia	Not known
	Dysarthria	Not known
	Hypoaesthesia	Uncommon

MedDRA **System Organ Class**	**Adverse reactions**	**Frequency**
	Taste disorder	Not known
	Dysgeusia	Not known
	Head discomfort	Not known
	Dyskinesia	Not known
	Myoclonus	Not known
Eye disorders	Vision blurred	Uncommon
	Diplopia	Not known
	Visual impairment	Not known
	Visual acuity reduced	Not known
Ear and labyrinth disorders	Vertigo	Uncommon
Vascular disorders	Orthostatic hypotension	Uncommon
	Hypertension	Uncommon
	Palpitations	Not known
	Hot flush	Not known
	Blood pressure decreased	Not known
Gastrointestinal disorders	Constipation	Common
	Abdominal distension	Uncommon
	Dry mouth	Uncommon
	Gastritis	Uncommon
	Vomiting	Uncommon
	Abdominal pain upper	Uncommon
	Gastrooesophageal reflux disease	Uncommon
	Diarrhoea	Not known
	Abdominal discomfort	Not known
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Urticaria	Not known
	Erythema	Not known
	Pruritus	Not known
Musculoskeletal and connective tissue disorders	Muscular weakness	Uncommon
Renal and urinary disorders	Urinary incontinence	Not known
	Pollakiuria	Not known
	Dysuria	Not known
	Urinary retention	Not known
	Renal impairment	Not known
General disorders and administration site conditions	Oedema	Common
	Gait disturbance	Common
	Feeling abnormal	Uncommon
	Thirst	Uncommon
	Face oedema	Uncommon
	Malaise	Uncommon
	Asthenia	Not known
	Eyelid oedema	Uncommon
	Pain	Not known
Investigations	Weight increased	Common
	Hepatic enzyme increased	Common
	Eosinophil count increased	Uncommon
	Blood CK increased	Uncommon

MedDRA System Organ Class	Adverse reactions	Frequency
	Withdrawal syndrome	Uncommon
Injury, poisoning and procedural complications	Fall	Uncommon

4.9 Overdose

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.

Treatment: Hemodialysis is reported to remove 15.3% of mirogabalin.

Note) The indication of TARLIGE is neuropathic pain.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic group: ANALGESICS, Other analgesics and antipyretics, ATC Code: N02BF03

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.

Pharmacodynamic effects

- Mirogabalin increased the pain threshold to mechanical stimulation in partial sciatic nerve ligation model rats.
- Mirogabalin increased the pain threshold to mechanical stimulation in streptozotocin-induced diabetic model rats.
- Mirogabalin increased the pain threshold to mechanical stimulation in spinal cord injury model rats.

Clinical efficacy and safety

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.

Table 4: Change in average daily pain score from Baseline at Week 14 in patients with diabetic peripheral neuropathic pain (double-blind phase)

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).

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.

Table 5: Change in average daily pain score from Baseline at Week 14 in patients with postherpetic neuralgia (double-blind phase)

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. 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.

Table 6: Change over Time in visual analog scale in patients with diabetic peripheral neuropathic pain or postherpetic neuralgia (long-term phase)

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).

4. Phase 3 multinational clinical study

In a double-blind controlled study in 299 patients (242 Japanese patients) with central neuropathic pain (central neuropathic pain after spinal cord injury) conducted in Japan and other 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).

Table 7: Change in average daily pain score from Baseline at Week 14 in patients central neuropathic pain (central neuropathic pain after spinal cord injury) (double-blind phase)

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).

5. Phase 3 multinational clinical study (long-term study)

In an open-label, long-term study conducted in Japan and other 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 (200 Japanese 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).

Table 8: Change over Time in visual analog scale in patients with central neuropathic pain (central neuropathic pain after spinal cord injury, central post stroke pain, or central neuropathic pain in Parkinson's disease) (long-term phase)

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).

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.

Table 9: Change in average daily pain score from Baseline at Week 14 in renal impairment patients with diabetic peripheral neuropathic pain or postherpetic neuralgia

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 mg or 15 mg of mirogabalin twice daily for the effective dose.

5.2 Pharmacokinetic properties

Absorption

Mirogabalin was rapidly absorbed in healthy adults. 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. Following the administration of mirogabalin at a single oral dose of 15 mg in the fasted and fed states in 30 healthy adults, 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%. The effect of food on the absorption rate of mirogabalin was limited, therefore mirogabalin can be given under both fasted and fed condition. Following the administration of mirogabalin at multiple oral doses of 10 mg 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.

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.

In an in vitro study, 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. The ^{14}C-mirogabalin human plasma protein binding ratios, determined by ultracentrifugation, were 23.4% to 25.5% at plasma concentrations of 0.1 to 10 μg/mL.

Biotransformation

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.

Elimination

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 with a half-life ($t_{1/2}$) of 2.96 to 3.37 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.

Linearity/non-linearity

The Cmax and AUCinf of mirogabalin increased in a dose-proportional manner following the administration of mirogabalin at a single oral dose of 3, 5, 10, and 30 mg and multiple oral doses of 10 mg and 15 mg in healthy adults.

Elderly

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 years 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 times to 1.24 times of that on Day 1. The pharmacokinetics of mirogabalin in the healthy elderly subjects did not differ significantly from those observed in healthy non-elderly subjects (see section 4.2).

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 4-hour hemodialysis (see section 4.2).

Table 7: Pharmacokinetic Parameters of mirogabalin in Plasma in Japanese subjects with normal renal function or renal impairment

Severity grade of renal impairment (CLcr: mL/min)	No. of subjects	Cmax (ng/mL)	Tmax (h)[Note 1)]	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
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 2)]	6	101 ± 32.9	4.01 (1.92 to 5.00)	1990 ± 916	–

Mean ± standard deviation

Note 1) Median (minimum, maximum)

Note 2) Hemodialysis was performed for 4 h from 24 h post-dose.

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 (see section 4.2).

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

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

5.3 Preclinical safety data

- In safety pharmacology studies in rats and monkeys, mirogabalin besilate was well-tolerated at clinically relevant doses.
- In repeated dose toxicity studies in rats and monkeys, the dose-limiting toxicity of mirogabalin besilate was abnormal clinical signs (i.e. prone position, hypoactivity, staggering gait, ataxia) associated with depression of the central nervous system resulting from exaggerated pharmacological action. The mean $AUC_{0\text{-}24h}$ value at the NOAEL (10 mg/kg/day) in rats, the most sensitive species, was 4.7 times higher than that at the maximum recommended clinical dose of 15 mg twice daily.
- Mirogabalin besilate was not teratogenic in rats or rabbits, and did not show reproductive toxicity in males or disturbance in fertility and early embryonic development. But, prolonged proestrus and estrus were observed in the female at the dose of 100 mg/kg/day. In pre- and postnatal development studies including maternal function in rats, prolongation of the pregnancy period was noted at 100 mg/kg/day. In the F1 animals, a low live birth index was noted at 30 mg/kg/day or more. The mean $AUC_{0\text{-}24h}$ value at the NOAEL (10 mg/kg/day) for the next generation was 5.2 times higher than that at the maximum recommended clinical dose of 15 mg twice daily.
- Mirogabalin besilate did not show genotoxic potential in the bacterial reverse mutation study, chromosomal aberration study, or single dose rat bone marrow micronucleus study up to at 2000 mg/kg.
- Two-year carcinogenicity studies with mirogabalin besilate were conducted in mice and rats. No tumors were observed in mice at exposures up to 13.5 times the mean human exposure at the maximum recommended clinical dose (15 mg twice daily). In rats, an increased incidence of transitional cell papilloma in the urinary bladder was observed only in males at 100 mg/kg/day. However, the incidence of hyperplasia in the urinary bladder did not increase significantly in any group and mirogabalin besilate did not increase the labeling index of Ki-67-positive cells in the urinary bladder up to at 100 mg/kg/day in the 4-, 13-, 26- or 104-week repeated dose studies. At the dose (30 mg/kg/day) which the $AUC_{0\text{-}24h}$ value was 22.1 times higher than the maximum recommended clinical dose (15 mg twice daily), statistically significant increase of incidence of transitional cell papilloma

was not observed. Taken together, the tumorigenic potential of mirogabalin besilate was considered to be very low. There is no evidence to suggest an associated risk to humans.

Environmental Risk Assessment (ERA)

The environmental risk assessment of mirogabalin besilate has been conducted in accordance to European guidelines on ERA. No environmental impact is anticipated from the clinical use of mirogabalin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

D-mannitol

Microcrystalline cellulose

Carmellose calcium

Tocopherol

Magnesium aluminometasilicate

Citric acid hydrate

Magnesium stearate

Tablet coating:

Hypromellose

Titanium oxide

Talc

Yellow ferric oxide

Red ferric oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to packaging.

6.4 Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

TARLIGE are packed in a carton of 6 sheets in units of desiccant embedded aluminum/aluminum (Al/Al) blisters containing 10 film-coated tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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.

7 MARKETING AUTHORISATION HOLDER

DAIICHI SANKYO (THAILAND) LTD.

24th Fl., United Center Bldg., 323, Silom Rd., Silom, Bangrak, Bangkok, 10500, Thailand

8 MARKETING AUTHORISATION NUMBER

TARLIGE 2.5 mg film-coated tablets	Reg. No. 1C 17/65 (NC)
TARLIGE 5 mg film-coated tablets	Reg. No. 1C 18/65 (NC)
TARLIGE 10 mg film-coated tablets	Reg. No. 1C 19/65 (NC)
TARLIGE 15 mg film-coated tablets	Reg. No. 1C 20/65 (NC)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 27 September 2022
Date of last renewal: NA

10 DATE OF REVISION OF THE TEXT

April 2025