Valmera™

(Mirogabalin Tablets)

2.5mg, 5mg, 10mg & 15mg Tablets

COMPOSITION

Valmera 2.5mg Tablets
Each film-coated tablet contains:
Mirogabalin Besylate equivalent to
Mirogabalin 2.5mg
(Product complies to innovator specifications)

Valmera 5mg Tablets
Each film-coated tablet contains:
Mirogabalin Besylate equivalent to
Mirogabalin 5mg
(Product complies to innovator specifications)

Valmera 10mg Tablets
Each film-coated tablet contains:
Mirogabalin Besylate equivalent to
Mirogabalin 10mg
(Product complies to innovator specifications)

Valmera 15mg Tablets
Each film-coated tablet contains:
Mirogabalin Besylate equivalent to
Mirogabalin 15mg
(Product complies to innovator specifications)

THERAPEUTIC INDICATIONS

Neuropathic pain:
MIROGABLIN is indicated for the treatment of neuropathic pain in adults.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

For adults, administer mirogablin 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 Mirogablin 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.

Table 1: Mirogablin 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

Mirogablin 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.

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

Hepatic Impairment

No dose adjustment is required for patients with hepatic impairment.

Method of administration

For oral use. Mirogablin can be taken with or without food.

Contraindications

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

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 microgablin should be monitored closely; if any abnormalities are noted, appropriate measures, such as discontinuation of treatment or dose reduction, should be taken.

Hepatic function disorder

Hepatic function disorder (e.g., AST increased, ALT increased) may occur. Patients being treated with microgablin 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 mirogablin 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 mirogablin may cause drug withdrawal symptoms (e.g., insomnia, nausea, diarrhea, decreased appetite). Treatment with mirogablin should be discontinued in a careful manner, such as gradual dose reduction.

Ophthalmic disorders

Treatment with mirogablinmay 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.

Other Precautions

- It should be noted that mirogablin 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 mirogablin 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 mirogablin groups and in none of 869 subjects in the placebo group. 4.5

DRUG INTERACTIONS

Interaction with other medicinal products and other forms of interaction
Mirogablin is predominantly excreted by renal glomerular filtration and tubular secretion. The Transporters involved in the secretion of Mirogablin are organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, H+/organic cation antiporter (MATE) 1, and MATE2-K. Mirogablin is also metabolized by UDP-glucuronosyltransferases (UGTs).

Table 2: Precautions for Co-administration (MIROGABLIN 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 MIROGABLIN.	This is possibly due to the blood mirogablin concentration that increased by the inhibitory effect of probenecid on OAT1, OAT3, and UGT.
Cimetidine	Co-administration may potentiate the effect of MIROGABLIN.	This is possibly due to the blood mirogablin 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.

In vitro study data

- Mirogablin was not metabolized by CYP but was metabolized by UGT1A3, UGT1A4, UGT1A9, UGT2B4, UGT2B7 and UGT2B17.
- Mirogablin was secreted from the kidney and was suggested to be a substrate for OAT1, OAT3, OCT2, MATE1, and MATE2-K.

- Mirogablin 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). Mirogablin 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 mirogablin (15 mg) increased the Cmax and AUClast of mirogablinby 29% and 76%, respectively.
- Co-administration of cimetidine (400 mg) with mirogablin(15 mg) increased the Cmax and AUClast of mirogablinby 17% and 44%, respectively.
- Co-administration of mirogablinwith ethanol or lorazepam had no notable effect on the pharmacokinetics of mirogablinor these drugs. Co-administration of mirogablinin with these drugs decreased attention and balance-function more profoundly than monotherapy withmirogablin.
- Co-administration of mirogablinwith tramadol had no notable effect on the pharmacokinetics of mirogablinor tramadol

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, mirogablinshould be administered only if the expected therapeutic benefits outweigh the possible risks associated with treatment. An animal study (in rats) has shown that mirogablin crossed the placenta.

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 mirogablin transferred to breast milk.

Fertility
There are no clinical data on the effects of mirogablinon female fertility. There was no adverse effect on fertility in an animal study (in rats) .

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Mirogablinmay cause event(s) (e.g., dizziness, somnolence, loss of consciousness). Patients being treated with mirogablinmust be warned not to operate potentially dangerous machinery, such as driving a car.

ADVERSE DRUG REACTIONS

Summary of the safety profile
The safety profile of mirogablinis 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 mirogablintreatment in clinical trials are somnolence (16.8%), dizziness (9.7%) and oedema (7.5%).

Tabulated list of adverse reactions Adverse reactions from MIROGABLIN 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: Mirogablin Adverse Drug Reactions

MedDRA System Organ Class	**Adverse reactions**	**Frequency**
Metabolism and nutrition disorders	Increased appetite	Uncommon
	Decreased appetite	Uncommon
	Diabetes mellitus	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
	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
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
Investigations	Weight increased	Common
	Hepatic enzyme increased	Common
	Eosinophil count increased	Uncommon
	Blood CK increased	Uncommon
	Withdrawal syndrome	Uncommon
Injury, poisoning and procedural complications	Fall	Uncommon

REPORTING OF SUSPECTED ADVERSE REACTIONS
Reporting suspected adverse reactions via: pv@searlecompany.com

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 Mirogablin overdose included euphoric mood, dysarthria, headache, dysphagia, arthritis, joint swelling, and asthenia.
Treatment: Hemodialysis is reported to remove 15.3% of Mirogablin.
Note) The indication of mirogablinis neuropathic pain.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties

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

Mechanism of action
Mirogablin is considered to exhibit its analgesic effect by reducing calcium current via binding to the α2δ subunit, which plays an auxiliary role in functions of voltage-gated calcium channels in the nervous system. The analgesic effect of Mirogablin is also suggested to involve activation of the noradrenergic pathway in the descending pain inhibitory system.

Pharmacodynamic effects
- Mirogablin increased the pain threshold to mechanical stimulation in partial sciatic nerve ligation model rats.
- Mirogablin increased the pain threshold to mechanical stimulation in streptozotocin- induced diabetic model rats.
- Mirogablin 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 mirogablin 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 mirogablin 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 withdiabetic 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 possiblepain])

Note 2) Mean ± standard deviation

Note 3) Missing values were imputed using the multiple imputation method based on a model assuming missing not at randommechanism. 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/daygroup 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 Mirogablin 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 Mirogablin 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 withpostherpetic 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 possiblepain])

Note 7) Mean ± standard deviation

Note 8) Missing values were imputed using the multiple imputation method based on a model assuming missing not at randommechanism. 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/daygroup 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 gainin 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 patientswith diabetic peripheral neuropathic pain or 237 patients with postherpetic neuralgia, the meanpain intensity is shown in the table below.

Table 6: Change over Time in visual analog scale in patients with diabetic peripheralneuropathic 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 centralneuropathic pain (central neuropathic pain after spinal cord injury) conducted in Japan and other Asian countries, each patient received 14-week treatment with mirogablin (10 mg/day for 1 week, 20 mg/day for 1 week, and then 30 mg/day or 20 mg/day, depending on safety, for12 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 mirogablin group showed statistically significant improvement in pain scores atweek 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			
Mirogablin	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 possiblepain].)

Note 13) Mean ± standard deviation

Note 14) Missing values were imputed using the multiple imputation method based on a model assuming missing not at randommechanism. 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'srule.

Note 15) Least squares mean ± standard error

The frequency of adverse reactions in the mirogablin 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, orcentral neuropathic pain in Parkinson's disease), the mean pain intensity is shown in the tablebelow).

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 mirogablin is 5 mg of mirogablin twice daily for the initial dose, and 10 mg or 15 mg of mirogablin twice daily for the effective dose.

PHARMACOKINETIC PROPERTIES

Absorption

Mirogablin was rapidly absorbed in healthy adults. Following the administration of mirogablin at a single oral dose of 3, 5, 10, and 30 mg (6 subjects per dose level) in healthy adults, plasma mirogablin concentrations reached the maximum

concentration (Cmax) at 1 hpost-dose. Following the administration of mirogablin 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 decreaseof Cmax by approximately 18% and a delay of Tmax by 0.5 h, whereas the AUCinf was onlyreduced by approximately 6%. The effect of food on the absorption rate of mirogablin was limited, therefore mirogablin can be given under both fasted and fed condition. Following theadministration of mirogablin at multiple oral doses of 10 mg and 15 mg (6 subjects per doselevel) twice daily in Japanese healthy adult subjects for 7 days, steady state was reached by Day 3.

Distribution

Following the administration of mirogablin at a single oral dose of 3, 5, 10, and 30 mg in 6healthy 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, mirogablin labeled with ^{14}C (abbreviated as ^{14}C-Mirogablin) 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-Mirogablin human plasma protein binding ratios, determined by ultracentrifugation, were 23.4% to 25.5% at plasma concentrations of 0.1to 10 μg/mL.

Biotransformation

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

Elimination

Following the administration of mirogablin 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-Mirogablin 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 mirogablin increased in a dose-proportional manner following the administration of mirogablin 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 mirogablin 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 t1/2 of 3.58 to 4.55 h on Day 14. The AUC0-12h on Day 14 was 1.13 times to 1.24 times of that on Day 1. The pharmacokinetics of mirogablin in the healthy elderly subjects did not differ significantly from those observed in healthy non-elderly subjects.

Renal impairment

Following the administration of mirogablin 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 mirogablin was removed from blood during 4-hour hemodialysis.

Table 7: Pharmacokinetic Parameters of mirogablin 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 mirogablin 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.

Note) The approved dose of MIROGABLIN is 5 mg of mirogablin twice daily for the initial dose, and 10 mg or 15 mg of mirogablin 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

PRECLINICAL SAFETY DATA

- In safety pharmacology studies in rats and monkeys, mirogablin besilate was well- tolerated at clinically relevant doses.
- In repeated dose toxicity studies in rats and monkeys, the dose-limiting toxicity of mirogablin besilate was abnormal clinical signs (i.e. prone position, hypoactivity, staggering gait, ataxia) associated with depression of the central nervous system resultingfrom 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.
- Mirogablin besilate was not teratogenic in rats or rabbits and did not show reproductivetoxicity in males or disturbance in fertility and early embryonic development. Butprolonged 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, prolongationof 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.
- Mirogablin besilate did not show genotoxic potential in the bacterial reverse mutation study, chromosomal aberration study, or single dose rat bone marrow micronucleus studyup to at 2000 mg/kg.

Two-year carcinogenicity studies with mirogablin besilate were conducted in mice and rats. No tumors were observed n 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 onlyin males at 100 mg/kg/day. However, the incidence of hyperplasia in the urinary bladder did not increase significantly in any group and mirogablin besilate did not increase the labeling index of Ki-67-positive cells in the urinary bladder up to at 100 mg/kg/day

in the4-, 13-, 26- or 104-week repeated dose studies. At the dose (30 mg/kg/day) which the AUC_{0-24h} value was 22.1 times higher than the maximum recommended clinical dose (15mg twice daily), statistically significant increase of incidence of transitional cell papilloma was not observed. Taken together, the tumorigenic potential of mirogablin 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 mirogablin besilate has been conducted in accordance to European guidelines on ERA. No environmental impact is anticipated from the clinical use of mirogablin.

PRESENTATION
Valmera 2.5mg Tablets are available in Alu-Alu blister in a pack of 30's (3x10's) tablets.
Valmera 5mg Tablets are available in Alu-Alu blister in a pack of 30's (3x10's) tablets.
Valmera 10mg Tablets are available in Alu-Alu blister in a pack of 30's (3x10's) tablets.
Valmera 15mg Tablets are available in Alu-Alu blister in a pack of 30's (3x10's) tablets.

INSTRUCTIONS
To be sold on the prescription of a registered medical practitioner only.
Protect from sunlight, moisture and heat.
Do not store and transport above 30°C.
Keep all medicines out of sight & reach of children.

REGISTRATION NUMBER

Valmera 2.5mg Tablets	:	128173
Valmera 5mg Tablets	:	128170
Valmera 10mg Tablets	:	128171
Valmera 15mg Tablets	:	128172

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