Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Mitar 10mg

2. Qualitative and quantitative composition

Each film-coated tablet contains mirogabalin besylate equivalent to 10 mg of mirogabalin.
Excipient with known effect: each film-coated tablet contains lactose monohydrate.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Yellow to light yellow colored round shaped biconvex film coated tablets plain on both sides

4. Clinical particulars

4.1 Therapeutic indications

Mirogabalin is indicated for the treatment of diabetic peripheral neuropathic pain and postherpetic neuralgia.

4.2 Posology and method of administration

Posology

The initial oral dose for adults is 5 mg twice daily, increased gradually to 10 mg twice daily at intervals of at least 1 week. Based on individual patient response and tolerability, the dose may be increased up to a maximum of 15 mg twice daily, at intervals of at least 1 week.

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	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

Paediatric population

Clinical studies in children have not been conducted.

Elderly population

Mitar 5 mg tablets should be administered with care, and dose and dosing-interval adjustment based on creatinine clearance is required, as elderly patients often have reduced renal function (see section 5.2). Elderly patients tend to experience falls resulting in fractures and similar

injuries as a consequence of events such as dizziness, somnolence and loss of consciousness (see sections 4.4 and 4.7).

Hepatic impairment

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

Method of administration

Orally with a glass of water.

4.3 Contraindications

Mirogabalin is contraindicated in: patients with hypersensitive to Mirogabalin. Patients with mild to moderate Hepatic and Renal impairment

4.4 Special warnings and precautions for use

This medicinal product may cause dizziness, somnolence or loss of consciousness. Patients should avoid operating potentially dangerous machinery, including driving a car. Particular attention should be paid in elderly patients. This medicinal product may cause weight gain, blurred vision and double vision.

Dizziness, somnolence and loss of consciousness

Dizziness, somnolence and loss of consciousness, which may lead to falls and subsequent fractures, may occur. Patients should be monitored closely; if any abnormality is noted, appropriate measures such as discontinuation of treatment or dose reduction should be taken.

Hepatic function disorder

Hepatic function disorder (e.g. increased AST, increased ALT) may occur. Patients should be monitored closely; if any abnormality, including early symptoms such as general malaise or anorexia, is noted, treatment should be discontinued and appropriate measures taken.

Weight gain

Treatment may cause weight gain. Caution should be exercised regarding the potential occurrence of obesity. If signs of obesity are noted, appropriate measures such as diet and/or exercise therapy should be taken. As weight gain may be associated with dose increase or long-term use, body weight should be measured regularly.

Withdrawal symptoms

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

Ophthalmic disorders

Treatment may cause ophthalmic disorders (e.g. amblyopia, abnormal vision, blurred vision and diplopia). Caution should be exercised regarding their potential occurrence, including careful history taking at medical examinations.

Other precautions

- It should be noted that Mirogabalin 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

Mitar 5mg Tablets may interact with drugs that are metabolized by the same hepatic enzymes, such as CYP3A4 and CYP2D6 inhibitors or inducers. These interactions can affect the plasma concentrations and efficacy of Mirogabalin or co-administered drugs. Co-administration with OAT1, OAT3, OCT2, MATE1, MATE2-K or UGT inhibitors may increase Mirogabalin exposure, should be used with caution.

Table 2

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

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

Medicinal product	Clinical symptoms and measures	Mechanism and risk factors
Probenecid	Co-administration may potentiate the effect of Mitar.	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 Mitar.	This is possibly due to the blood mirogabalin concentration that increased by the inhibitory effect of cimetidine on MATE1, and MATE2-K
Lorazepam; alcohol (drinking)	Co-administration may potentiate the effect of Mitar.	This is possibly due to the interactively potentiated inhibitory effect on the central nervous system.

4.6 Pregnancy and Lactation

Women of childbearing potential / contraception in males and females

Fertility: There are no specific studies evaluating the effects of Mirogabalin on fertility in humans.

Animal studies may provide some insights, but their relevance to humans is limited. If fertility is a concern, patients should discuss this with their healthcare provider.

Pregnancy: Mirogabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies have shown some adverse effects on embryo-fetal development at high doses. Therefore, Mirogabalin should be avoided during pregnancy unless the benefits outweigh the risks.

Lactation: It is not known whether Mirogabalin is excreted in human breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Mirogabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Women who are pregnant, planning to become pregnant, or breastfeeding should consult their healthcare provider before taking Mirogabalin. Healthcare providers can provide individualized guidance based on the patient's medical history and the specific circumstances of their pregnancy or lactation. In some cases,

Alternative treatment options may be considered that have a better-established safety profile during pregnancy and lactation.

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4.7 Effects on ability to drive and use machines

Effects on ability to drive and use machines: Mirogabalin may cause event(s) (e.g., dizziness, somnolence, loss of consciousness).

Patients being treated with Mirogabalin must be warned not to operate potentially dangerous machinery, such as driving a car

4.8 Undesirable effects

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

Tabulated list of adverse reactions

The following terminology has been used 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 reaction	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
	Hypoaesthesia	Uncommon
	Memory impairment, amnesia, dysarthria	Not known
	Taste disorder, dysgeusia, head discomfort	Not known

MedDRA System Organ Class	Adverse reaction	Frequency
	Dyskinesia, myoclonus	Not known
Eye disorders	Vision blurred	Uncommon
	Diplopia, visual impairment, visual acuity reduced	Not known
Ear and labyrinth disorders	Vertigo	Uncommon
Vascular disorders	Orthostatic hypotension	Uncommon
	Hypertension	Uncommon
	Palpitations, hot flush, blood pressure decreased	Not known
Gastrointestinal disorders	Constipation	Common
	Abdominal distension, dry mouth, gastritis	Uncommon
	Vomiting, abdominal pain upper, gastro-oesophageal reflux disease	Uncommon
	Diarrhoea, abdominal discomfort	Not known
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Urticaria, erythema, pruritus	Not known
Musculoskeletal and connective tissue disorders	Muscular weakness	Uncommon
Renal and urinary disorders	Urinary incontinence, pollakiuria, dysuria, urinary retention	Not known
General disorders and administration site conditions	Oedema	Common
	Gait disturbance	Common
	Feeling abnormal, thirst, face oedema, malaise, eyelid oedema	Uncommon
	Asthenia	Not known
Investigations	Weight increased	Common
	Hepatic enzyme increased	Common
	Eosinophil count increased, blood CK increased	Uncommon
	Withdrawal syndrome	Uncommon
Injury, poisoning and procedural complications	Fall	Uncommon

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms

Overdoses of up to 60 mg/day have been reported in an overseas clinical study in patients with fibromyalgia. Symptoms observed during mirogabalin overdose included euphoric mood, dysarthria, headache, dysphagia, arthritis, joint swelling and asthenia.

Treatment

Haemodialysis is reported to remove 15.3% of mirogabalin. If an overdose is suspected, immediate medical attention should be sought.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, gabapentinoids. ATC code: N02BF03.

Mechanism of action

Mirogabalin is an analogue of the neurotransmitter gamma-aminobutyric acid (GABA). It is a potent and specific ligand of the α2δ subunit of voltage-dependent calcium channels, reducing calcium influx and neurotransmission in dorsal root ganglia and inhibiting neurotransmitter release at presynaptic neuron endings. These channels are present in the central nervous system and play a crucial role in transmitting pain signals from peripheral nerves to the spinal cord and brain. By binding to the α2δ subunits, mirogabalin inhibits the influx of calcium ions into neurons, thereby reducing the release of neurotransmitters involved in pain transmission. The analgesic effect 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, in streptozotocin-induced diabetic model rats, and 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 evaluate	Pain score[Note 1), Note 2)]	Change from baseline at Week	Difference from placebo [95%	*P* value[Note 5)]
Placebo	Baseline	330	5.59 ± 1.012	-1.31 ± 0.095	–	–
	Week	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	151	4.14 ± 1.685			
30 mg/day	Baseline	165	5.55 ± 0.967	-1.81 ± 0 136	-0.50 [-0.82, -	0.0027
	Week	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 scoreNote 6), Note 7)	Change from baseline at Week 14Note 8), Note 9)	Difference from placebo [95% confidence interval]Note 8)	*P* valueNote 10)
Placebo	Baseline	303	5.75 ± 1.130	-1.20 ± 0.099	–	–
	Week	263	4.40 ± 2.115			
20 mg/day	Baseline	153	5.70 ± 1.015	-1.68 ± 0.141	-0.47 [-0.81, -	0.0058
	Week	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 wasstatistically 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		Postherpetic neuralgia	
	No. of subjects	**Pain intensity**	**No. of subjects**	**Pain intensity**
Pre-	214	42.1 ± 20.41	237	43.5 ± 21.38
Week	200	35.7 ± 20.30	219	34.7 ± 21.80
Week	186	34.4 ± 20.89	203	32.7 ± 21.81
Week	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)],	Change from baseline at Week 14[Note]	Difference from placebo [95% confidence 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	No. of subjects	Pain intensity
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:	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]	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 Mirogabalin 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

After oral administration, mirogabalin was rapidly absorbed (time to maximum concentration,~1 hour) and eliminated through urine unchanged (61%-72% urinary excretion).

Exposure increased in a dose-proportional manner after single or multiple Mirogabalin doses. 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 14C (abbreviated as 14C-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 14C-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 14C-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 (t1/2) 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 14C-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 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 mirogabalin in the healthy elderly subjects did not differ significantly from those observed in healthy non-elderly subjects .

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.

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 Note	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 .

Note

The approved dose of Mitar 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 besylate was well- tolerated at clinically relevant doses.

Repeated Dose Toxicity: studies in rats and monkeys, the dose-limiting toxicity of mirogabalin 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_{0-24h} 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.

Teratogenic: Mirogabalin 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_{0-24h} 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.

Genotoxic: Mirogabalin 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.

Carcinogenicity: Two-year carcinogenicity studies with mirogabalin besylate 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 besylate 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_{0-24h} 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 besylate was considered to be very low. There is no evidence to suggest an associated risk to humans

6. Pharmaceutical Particulars

6.1 List of Excipients

Tablet core

Microcrystalline cellulose (PH 101)
Microcrystalline cellulose (PH 102)
Mannitol
Lactose monohydrate
Pregelatinised starch
Sodium lauryl sulfate
Colloidal anhydrous silica
Talc
Magnesium stearate
Purified water
Readycoat Film AQ Yellow (AY-517)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 months from the date of manufacture.

6.4 Special Precautions for storage

Do not store above 30°C. Protect from direct sunlight. Keep all medicines out of the reach of children.

6.5 Nature and Content of container

Alu-Alu blister pack of 3 × 10 tablets, packed in a printed unit carton with literature insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Dawa Limited
Plot No. 7879/8, Baba Dogo Road, Ruaraka
P.O. Box 16633-00620, Nairobi, Kenya.

Manufacturer

Cubit Lifesciences LLP
Plot No. 39-40, Ozone Industrial Park, At. & Post: Kerala-Bhayla, Near Kerala G.I.D.C., Taluka: Bavla, Dist. Ahmedabad – 382220, Gujarat, India.

Legal category

Prescription only medicine (POM).

8. Marketing Authorization Number

H2026/CTD12725/26893]

9. Date of first authorization/renewal of the authorization

2026 June 12

10. Date of revision of the text

2026 June 12