**Summary of Product Characteristics for Pharmaceutical Products**

## 1. Name of the medicinal product:

Mitar 2.5 mg

## 2. Qualitative and quantitative composition

Each film-coated tablet contains mirogabalin besylate equivalent to 2.5 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 coloured, round shaped, biconvex film-coated tablets, plain on both sides. No score line is present; the tablet cannot be divided into equal doses.

## 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**

Plasma mirogabalin concentrations may increase in patients with reduced renal function, possibly increasing the risk of adverse reactions; careful administration with close monitoring is necessary in these patients. The dose and dosing interval should be adjusted according to creatinine clearance as shown in Table 1. Treatment should be started at a low dose and increased in patients who show confirmed tolerability but insufficient effect (see sections 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 haemodialysis (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 |

| | | Severity grade of renal impairment (creatinine clearance [CLcr]: mL/min) | | |
|---|---|---|---|---|
| | **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 2.5 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**
For oral use. To be taken 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 with Mirogabalin 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

**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 1,378 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

This medicinal product may interact with medicinal products metabolised by the same hepatic enzymes, such as CYP3A4 and CYP2D6 inhibitors or inducers. Such interactions may affect the plasma concentrations and efficacy of mirogabalin or of the co-administered medicinal product. Co-administration with inhibitors of OAT1, OAT3, OCT2, MATE1, MATE2-K or UGT may increase mirogabalin exposure and should be used with caution.

**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 |

| Medicinal product | Clinical symptoms and measures | Mechanism and risk factors |
|---|---|---|
| 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**

As the potential risk to humans is unknown, effective contraception must be used by women of childbearing potential.

**Pregnancy**

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

**Breast-feeding**

It is not known whether mirogabalin is excreted in human breast milk. Because many medicinal products are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue breast-feeding or to discontinue the medicinal product, taking into account the importance of the treatment 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.

## 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 drug reactions, Mirogabalin-treated patients, 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**

Adverse reactions from Mirogabalin in clinical trials, post-authorization 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 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 |
| | 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 |

| MedDRA System Organ Class | Adverse reaction | Frequency |
|---|---|---|
| | 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**

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

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 analog of the neurotransmitter, gamma-aminobutyric acid (GABA). It is a potent and specific ligand of the α2δ subunit of voltage-dependent Ca2+channels, which reduces calcium (Ca2+) influx and neurotransmission in dorsal root ganglia

(DRGs), inhibiting neurotransmitter release in presynaptic neuron endings. Mirogabalin acts as a ligand for α2δ subunits of voltage-gated calcium channels (VGCCs). These channels are 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.
Mirogabalin 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 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**

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 scoreNote 1), Note 2)** | **Change from baseline at Week** | **Difference from placebo [95%** | ***P* valueNote** |
|---|---|---|---|---|---|---|
| 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).

**1. 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 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).

1. **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)

**2. 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).

**2. 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).

### 3. 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 is rapidly absorbed (time to maximum concentration approximately 1 hour) and eliminated unchanged in the urine (61–72% urinary excretion). Exposure increases in a dose-proportional manner after single or multiple 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 4: 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)* | AUClast (ng·h/mL) | CLr (L/h) |
|---|---|---|---|---|---|
| CLcr ≥ 90 | 4 | 71.2 ± 25.6 | 1.25 (0.98–2.00) | 321 ± 52.5 | 10.9 ± 1.52 |
| 90 > CLcr ≥ 60 (mild) | 6 | 81.4 ± 29.0 | 1.74 (0.97–4.00) | 422 ± 85.1 | 7.83 ± 1.61 |
| 60 > CLcr ≥ 30 (moderate) | 9 | 76.9 ± 13.3 | 1.95 (1.03–5.00) | 655 ± 144 | 4.48 ± 1.87 |
| 30 > CLcr (severe) | 5 | 118 ± 25.8 | 2.00 (1.47–5.00) | 1350 ± 259 | 1.92 ± 0.463 |
| End-stage renal disease requiring haemodialysis | 6 | 101 ± 32.9 | 4.01 (1.92–5.00) | 1990 ± 916 | – |

Values are mean ± standard deviation. *Median (minimum, maximum). Haemodialysis

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 AUC0-24h 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.

birth index was noted at 30 mg/kg/day or more. The mean AUC0-24h 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 AUC0-24h 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.

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
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/CTD12726/27007

**9. Date of first authorization/renewal of the authorization**

2026 June 12

**10. Date of revision of the text**

2026 June 12