Minrova™
(Mirogabalin)

1. NAME OF THE PRODUCT

Minrova™ (Mirogabalin) 2.5mg Tablet
Minrova™ (Mirogabalin) 5mg Tablet
Minrova™ (Mirogabalin) 10mg Tablet
Minrova™ (Mirogabalin) 15mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Minrova™ 2.5mg Tablet
Each film coated tablet contains:
Mirogabalin Besylate Eq. to Mirogabalin.....2.5mg

Minrova™ 5mg Tablet
Each film coated tablet contains:
Mirogabalin Besylate Eq. to Mirogabalin.....5mg

Minrova™ 10mg Tablet
Each film coated tablet contains:
Mirogabalin Besylate Eq. to Mirogabalin.....10mg

Minrova™ 15mg Tablet
Each film coated tablet contains:
Mirogabalin Besylate Eq. to Mirogabalin.....15mg

3. PHARMACEUTICAL FORM

Film coated tablet

Appearance:
Minrova™ 2.5mg Tablet: Light blue color tablet, round shape plain on both sides.
Minrova™ 5mg Tablet: Light purple to purple color tablet, oval shape plain on one side and break line on other side.
Minrova™ 10mg Tablet: Dark pink color film coated tablet, round shape tablet with break line on one side and plain on other side.
Minrova™ 15mg Tablet: Chocolate brown color tablet, round shape tablet with break line on one side and plain from other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Neuropathic pain:

Minrova™ is indicated for the treatment of neuropathic pain in adult.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

For adults, administer **Minrova**™ at an initial oral dose of 5mg twice daily, and then increase the dose by 5mg per dosing with an interval of at least 1 week up to 15mg twice daily. The dose may be increased or decreased appropriately in the range between 10mg and 15mg twice daily, based on individual patient age or symptoms.

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

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		10mg to 30mg	5mg to 15mg	2.5mg to 7.5mg
Initial Dose		5mg twice daily	2.5mg twice daily	2.5mg once daily
Effective Dose	Minimum dose	10mg twice daily	5mg twice daily	5mg once daily
	Recommended dose	15mg twice daily	7.5mg twice daily	7.5mg once daily

Paediatric population: Clinical studies in children have not been conducted.

Elderly population: Minrova™ 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.

Minrova™ can be taken with or without food.

4.3. CONTRAINDICATIONS:

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

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Dizziness, somnolence, loss of consciousness: Dizziness, somnolence, and loss of consciousness, which may cause falls and subsequent fractures, etc., may occur. Patients being treated with mirogabalin 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 mirogabalin 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 mirogabalin 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 mirogabalin may cause drug withdrawal symptoms (e.g., insomnia, nausea, diarrhoea, decreased appetite). Treatment with mirogabalin should be discontinued in a careful manner, such as 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.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Mirogabalin is predominantly excreted by renal glomerular filtration and tubular secretion. The transporter involved in the secretion of mirogabalin are organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, H^+/organic cation antiporter (MATE) 1, and MATE2-K.

Precautions for Co-administration (mirogabalin 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 mirogabalin.	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 mirogabalin.	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 facilitate the decrease in attention and balance-function.	This is possibly due to the interactively potentiated inhibitory effect on the central nervous system.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: As the potential risk for humans is unknown, effective contraception must be used in women of childbearing potential. There are no clinical data on the effects of mirogabalin on female fertility.

Pregnancy: For pregnant women and women who may be pregnant, mirogabalin should be administered only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

Breast-feeding: The continuation or discontinuation of breast-feeding should be considered while taking account of the expected therapeutic benefits and the benefits of maternal feeding.

4.7. 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 adverse reactions ranked under headings of system organ class and frequency using the following convention: 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).

Metabolism and nutrition disorders:

Uncommon: Increased appetite, decreased appetite, diabetes mellitus

Psychiatric disorders:
Uncommon: Insomnia
Not known: Hallucination, delirium
Nervous system disorders:
Very Common: Somnolence
Common: Dizziness
Uncommon: Dizziness postural, loss of consciousness, headache, tremor, hypoaesthesia
Not Known: Memory impairment, amnesia, dysarthria, taste disorder, dysgeusia, head discomfort, dyskinesia, myoclonus
Eye disorders:
Uncommon: Vision blurred
Not Known: Diplopia, visual impairment, visual acuity reduced
Ear and labyrinth disorders:
Uncommon: Vertigo
Vascular disorders:
Uncommon: Orthostatic hypotension, hypertension
Not known: Palpitations, hot flush, blood pressure decreased
Gastrointestinal disorders:
Common: Constipation
Uncommon: Abdominal distension, dry mouth, gastritis, vomiting, abdominal pain upper, gastro-oesophageal reflux disease
Not known: Diarrhoea, abdominal discomfort
Skin and subcutaneous tissues disorders:
Uncommon: Rash
Not known: Urticaria, pruritus, erythema
Musculoskeletal and connective tissue disorders:
Uncommon: Muscular weakness
Renal and urinary disorders:
Not Known: Urinary incontinence, pollakiuria, dysuria, urinary retention
General disorders and administration site conditions:
Common: Oedema, gait disturbance
Uncommon: Feeling abnormal, thirst, face oedema, malaise, eyelid oedema
Not Known: Asthenia
Investigations:
Common: Weight increased, hepatic enzyme increased
Uncommon: Eosinophil count increased, blood CK increased, withdrawal syndrome
Injury, poisoning and procedural complications:
Uncommon: Fall

4.9. OVERDOSE:

Symptoms: There have been reports on overdoses of up to 60mg/day in an overseas clinical study in patients with fibromyalgia*. Symptoms observed during a mirogabalin overdose included euphoric mood, dysarthria, headache, dysphagia, arthritis, joint swelling, and asthenia.

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

* The indication of mirogabalin is neuropathic pain.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Analgesics, Other analgesics and antipyretics.

ATC Code: N02BF03

Mechanism of action: Mirogabalin is considered to exhibit its analgesic effect by reducing calcium current via binding to the $\alpha_2\delta$ subunit, which plays an auxiliary role in functions of voltage-gated calcium channels in the nervous system. The analgesic effect of mirogabalin is also suggested to involve activation of the noradrenergic pathway in the descending pain inhibitory system.

5.2. PHARMACOKINETICS PROPERTIES:

Absorption: Following the administration of mirogabalin at a single oral dose, the effect of food on the absorption rate of mirogabalin was limited, therefore mirogabalin can be given under both fasted and fed condition.

Distribution: Following the administration of mirogabalin at a single oral dose the apparent volume of distribution based on the terminal phase (Vz/F) was 78.01 to 87.97 L.

Metabolism: 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 30mg, 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.

5.3. PRECLINICAL SAFETY DATA:

In safety pharmacology studies in rats and monkeys, Mirogabalin besylate was well-tolerated at clinically relevant doses.

In repeated dose toxicity studies in rats and monkeys, the dose-limiting toxicity of mirogabalin besylate was abnormal clinical signs (i.e., prone position, hypoactivity, staggering gait, ataxia) associated with depression of the central nervous system resulting from exaggerated pharmacological action. The mean $AUC_{0\text{-}24h}$ value at the NOAEL (10mg/kg/day) in rats, the most sensitive species,

was 4.7 times higher than that at the maximum recommended clinical dose of 15mg twice daily.

Mirogabalin besylate 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 100mg/kg/day. In pre- and postnatal development studies including maternal function in rats, prolongation of the pregnancy period was noted at 100mg/kg/day. In the F1 animals, a low live birth index was noted at 30mg/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 15mg twice daily.

Mirogabalin besylate 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 2000mg/kg.

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 (15mg twice daily). In rats, an increased incidence of transitional cell papilloma in the urinary bladder was observed only in males at 100mg/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 100mg/kg/day in the 4-, 13-, 26- or 104-week repeated dose studies. At the dose (30mg/kg/day) which the $AUC_{0\text{-}24h}$ 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 mirogabalin besylate was considered to be very low. There is no evidence to suggest an associated risk to humans.

Environmental Risk Assessment (ERA): The environmental risk assessment of mirogabalin besylate has been conducted in accordance to European guidelines on ERA. No environmental impact is anticipated from the clinical use of mirogabalin.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Minrova™ 2.5mg Tablet:

- Microcrystalline Cellulose
- Mannitol
- Carboxymethyl Cellulose Calcium
- Tocopherol
- Citric Acid Monohydrate
- Magnesium Aluminometa Silicate

- Magnesium Stearate
- Hypromellose
- Titanium Dioxide
- Talcum Powder
- Lake Blue FCF
- Lake Indigo Carmine

Minrova™ 5mg Tablet:

- Microcrystalline Cellulose
- Mannitol
- Carboxymethyl Cellulose Calcium
- Tocopherol
- Citric Acid Monohydrate
- Magnesium Aluminometa Silicate
- Magnesium Stearate
- Hypromellose
- Titanium Dioxide
- Talcum Powder
- Amaranth Lake Color

Minrova™ 10mg Tablet:

- Microcrystalline Cellulose
- Mannitol
- Carboxymethyl Cellulose Calcium
- Tocopherol
- Citric Acid Monohydrate
- Magnesium Aluminometa Silicate
- Magnesium Stearate
- Hypromellose
- Titanium Dioxide
- Talcum Powder
- Ponceau 4R Lake Color

Minrova™ 15mg Tablet:

- Microcrystalline Cellulose
- Mannitol
- Carboxymethyl Cellulose Calcium
- Tocopherol
- Citric Acid Monohydrate
- Magnesium Aluminometa Silicate
- Magnesium Stearate

- Hypromellose
- Titanium Dioxide
- Talcum Powder
- Chocolate Brown HT Color

6.2. INCOMPATIBILITIES:
Not applicable

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Do not store over 30°C and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.
Keep out of the reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
Minrova™ 2.5mg Tablet: Alu/Alu Blister, pack size is 14's.
Minrova™ 5mg Tablet: Alu/Alu Blister, pack size is 14's.
Minrova™ 10mg Tablet: Alu/Alu Blister, pack size is 10's.
Minrova™ 15mg Tablet: Alu/Alu Blister, pack size is 10's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposed of in accordance to local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
Minrova™ 2.5mg Tablet: Innovator's Specs.
Minrova™ 5mg Tablet: Innovator's Specs.
Minrova™ 10mg Tablet: Innovator's Specs.
Minrova™ 15mg Tablet: Innovator's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

Minrova™ 2.5mg Tablet: 131027
Minrova™ 5mg Tablet: 131026
Minrova™ 10mg Tablet: 131025
Minrova™ 15mg Tablet: 131028

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Minrova™ 2.5mg Tablet: 24th November, 2025
Minrova™ 5mg Tablet: 24th November, 2025
Minrova™ 10mg Tablet: 24th November, 2025
Minrova™ 15mg Tablet: 24th November, 2025

10. DATE OF REVISION OF THE TEXT

منروواTM ٹیبلٹ
(میروگیبالِن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔