

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Mirogabalin

*A next-generation gabapentinoid developed by Daiichi Sankyo with preferential binding and prolonged dissociation kinetics at the alpha-2-delta-1 subunit of voltage-gated calcium channels, approved in Japan and select Asian jurisdictions for peripheral neuropathic pain and distinguished from pregabalin and gabapentin by subunit selectivity and a potentially wider therapeutic margin.*

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## ABSTRACT

Mirogabalin (DS-5565) is a novel gabapentinoid analgesic that binds with high affinity and selectivity to the  $\alpha$ -2-delta-1 ( $\alpha$ 2delta-1) subunit of voltage-gated calcium channels (VGCCs), developed by Daiichi Sankyo Company and approved in Japan in January 2019 for the treatment of peripheral neuropathic pain associated with diabetic peripheral neuropathy (DPNP) and postherpetic neuralgia (PHN). The compound is marketed as Tarlige in oral tablet formulation and has subsequently received regulatory approval in Taiwan (2020) and Thailand (2022) for peripheral neuropathic pain indications. Unlike the first-generation gabapentinoids gabapentin and pregabalin, which bind nonselectively to both  $\alpha$ 2delta-1 and  $\alpha$ 2delta-2 subunits with comparable affinity and dissociation kinetics, mirogabalin demonstrates preferential binding to the  $\alpha$ 2delta-1 subunit with a dissociation half-life of approximately 11.1 hours at  $\alpha$ 2delta-1 versus 2.4 hours at  $\alpha$ 2delta-2 in human recombinant systems. This kinetic selectivity is hypothesized to confer a favorable ratio of analgesic efficacy (mediated principally through  $\alpha$ 2delta-1 in dorsal root ganglia and spinal cord dorsal horn) to central nervous system adverse effects (mediated in part through  $\alpha$ 2delta-2 in cerebellar Purkinje neurons and other central structures), although this hypothesis has not been formally validated in controlled comparative clinical trials against pregabalin at equipotent analgesic doses.

The clinical development program for mirogabalin comprises two pivotal Phase 3 randomized, double-blind, placebo-controlled trials in Asian patients with DPNP (834 patients) and PHN (765

patients), both of which demonstrated statistically significant reductions in average daily pain scores at week 14 relative to placebo across multiple dose groups (15 mg once daily, 10 mg twice daily, and 15 mg twice daily). A separate Phase 3 program evaluated mirogabalin for central neuropathic pain after spinal cord injury in a multinational Asian trial. In contrast, the global Phase 3 ALDAY program for fibromyalgia pain, consisting of three large randomized trials enrolling more than 3,600 subjects in the United States and Europe, failed to meet the primary efficacy endpoint in all three studies; mirogabalin did not demonstrate statistically significant superiority over placebo for reduction in worst daily pain score at week 13 in fibromyalgia, and the fibromyalgia development program was subsequently discontinued. The compound is not approved by the United States Food and Drug Administration or the European Medicines Agency.

Pharmacokinetically, mirogabalin is rapidly and nearly completely absorbed after oral administration with a time to peak plasma concentration of approximately 1 hour. The compound undergoes limited hepatic metabolism (13 to 20 percent of administered dose) through uridine 5-prime-diphosphoglucuronosyltransferase (UGT) isoforms, with the majority of the dose (61 to 72 percent) excreted unchanged in urine. Renal clearance exceeds glomerular filtration rate, indicating active tubular secretion. Dose adjustment is required in patients with renal impairment. The principal adverse events are somnolence, dizziness, peripheral edema, and weight gain, consistent with the gabapentinoid class but reported at generally lower incidence than pregabalin at comparable analgesic doses in some observational comparisons.

This monograph reviews the chemistry and structural pharmacology of mirogabalin; the  $\alpha 2\delta$  subunit binding characteristics and dissociation kinetics that distinguish the compound from pregabalin and gabapentin; the complete pharmacokinetic record; the preclinical analgesic pharmacology in neuropathic and inflammatory pain models; the clinical evidence base across peripheral neuropathic, central neuropathic, and fibromyalgia indications; sourcing and quality verification considerations; reconstitution and handling; stack interactions; adverse-event signal; and a comparative assessment of five alternative analgesic candidates against mirogabalin on five competency standards.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**International Nonproprietary Name:** Mirogabalin.

**Marketed name:** Tarlige (Daiichi Sankyo; Japan, Taiwan, Thailand).

**Development code:** DS-5565 (Daiichi Sankyo). The development code is the canonical identifier in the preclinical and early clinical pharmacology literature.

**Chemical Abstracts Service registry numbers:** 1138245-13-2 (free base), 1138245-21-2 (besylate salt). The besylate (benzenesulfonate) salt is the formulated pharmaceutical form used in all marketed and clinical trial preparations.

**International Union of Pure and Applied Chemistry name:** (1R,5S,6S)-6-(aminomethyl)-3-ethyl-6-bicyclo[3.2.0]hept-3-enyl acetic acid. The compound is a cyclopentane-fused cyclobutane amino acid derivative bearing structural similarity to the gamma-aminobutyric acid (GABA) analogs gabapentin and pregabalin but with a conformationally constrained bicyclo[3.2.0]heptene scaffold that restricts rotational freedom and confers the subunit-selective binding pharmacology.

## 1.2 Structural class and chemistry

Mirogabalin is a synthetic amino acid analog belonging to the gabapentinoid structural class, a group of compounds that share the pharmacophoric feature of an amino acid moiety (alpha-amino acid or related structure) linked to a lipophilic ring system and that exert their pharmacological activity through binding to the alpha-2-delta auxiliary subunits of voltage-gated calcium channels. The gabapentinoid class includes gabapentin (a cyclohexane amino acid), pregabalin (an isobutyl-substituted GABA analog), and mirogabalin (a bicyclo[3.2.0]heptene amino acid) [1, 2].

**Molecular formula:** C<sub>12</sub>H<sub>19</sub>NO<sub>2</sub> (free base); C<sub>18</sub>H<sub>25</sub>NO<sub>5</sub>S (besylate salt).

**Exact mass:** 209.1416 g/mol (free base, monoisotopic).

**Molecular weight:** 209.28 g/mol (free base); 367.46 g/mol (besylate salt).

**Physical properties:** White to off-white crystalline powder. The besylate salt is freely soluble in water and in common polar organic solvents. The free base is moderately soluble in water. The compound is stable under standard storage conditions (room temperature, dry environment) as both the free base and the besylate salt.

**Stereochemistry:** Mirogabalin contains three stereocenters at positions C1, C5, and C6 of the bicyclo[3.2.0]heptene ring system and is supplied as the single (1R,5S,6S) enantiomer. The stereochemical configuration is critical for binding affinity at the  $\alpha_2\delta$  subunit; the enantiomeric form shows substantially reduced binding. The besylate salt is a 1:1 complex of mirogabalin free base with benzenesulfonic acid. Investigators acquiring research-grade material should confirm enantiomeric purity by chiral high-performance liquid chromatography.

## 1.3 Synthesis

The published synthesis of mirogabalin proceeds through construction of the bicyclo[3.2.0]heptene core via intramolecular [2+2] cycloaddition or ring-closing metathesis strategies, installation of the aminomethyl group, and elaboration of the acetic acid side chain [3]. The stereochemistry is established through asymmetric synthesis or chiral resolution. The besylate salt is prepared by treatment of the free base with one equivalent of benzenesulfonic acid in an appropriate solvent system (typically ethanol or isopropanol) followed by recrystallization. Industrial-scale synthesis by Daiichi Sankyo optimizes yield and stereochemical purity; the marketed product is supplied at greater than 99 percent enantiomeric excess. Detailed synthetic routes are described in patent literature (Daiichi Sankyo patent families WO2009/084682 and related filings) [4].

## 2. Abstract

Mirogabalin (DS-5565) is a selective, high-affinity ligand for the alpha-2-delta-1 subunit of voltage-gated calcium channels developed by Daiichi Sankyo for the treatment of neuropathic pain [1, 2]. The compound belongs to the gabapentinoid structural class alongside gabapentin and pregabalin but is distinguished from these first-generation agents by preferential binding to the alpha2delta-1 subunit over the alpha2delta-2 subunit, with a dissociation half-life ratio of approximately 4.6-fold (11.1 hours at alpha2delta-1 versus 2.4 hours at alpha2delta-2) [5]. This kinetic selectivity profile is the molecular basis for the hypothesized wider therapeutic margin relative to pregabalin and gabapentin, which bind both subunits with comparable affinity and dissociation kinetics.

The compound received its first global regulatory approval in Japan on January 8, 2019, for the treatment of peripheral neuropathic pain, and was launched commercially as Tarlige in April 2019. Subsequent approvals were obtained in Taiwan (2020) and Thailand (2022). The approved indications encompass diabetic peripheral neuropathic pain and postherpetic neuralgia, the two principal peripheral neuropathic pain conditions studied in the pivotal Phase 3 program [6, 7].

Two pivotal Phase 3 randomized, double-blind, placebo-controlled trials conducted in Asian patient populations form the registration evidence base. The DPNP trial (834 patients) demonstrated statistically significant reduction in average daily pain score (ADPS) at week 14 for mirogabalin 10 mg twice daily and 15 mg twice daily versus placebo [7]. The PHN trial (765 patients) demonstrated statistically significant ADPS reduction at week 14 for all three mirogabalin dose groups (15 mg/day, 20 mg/day, and 30 mg/day) versus placebo, with the 30 mg/day group showing the largest treatment difference (least-squares mean difference of negative 0.77 points) [6].

In contrast, the global ALDAY Phase 3 program for fibromyalgia pain, comprising three large randomized controlled trials enrolling more than 3,600 subjects across the United States and Europe, failed to demonstrate superiority of mirogabalin over placebo on the primary endpoint (change in weekly average of worst daily pain score from baseline to week 13) in all three studies [8]. The fibromyalgia development program was subsequently discontinued, and mirogabalin is not approved by

the United States Food and Drug Administration or the European Medicines Agency. The compound remains in clinical development for central neuropathic pain and other neuropathic pain subtypes in Asian jurisdictions.

Pharmacokinetically, mirogabalin is rapidly absorbed (time to peak concentration approximately 1 hour), nearly completely bioavailable, and predominantly renally eliminated as unchanged drug (61 to 72 percent of administered dose) [9, 10]. Hepatic metabolism is minor (13 to 20 percent through UGT-mediated glucuronidation). Dose adjustment is required in renal impairment. The compound does not inhibit or induce cytochrome P450 enzymes at therapeutic concentrations and has a low drug-drug interaction potential.

The principal adverse events at therapeutic doses are somnolence, dizziness, peripheral edema, and weight gain, consistent with the gabapentinoid class [11, 12]. The incidence of somnolence and dizziness appears dose-dependent and is influenced by age, sex, and body weight. Treatment discontinuation rates due to adverse events range from approximately 8 to 14 percent across the pivotal trials.

## 3. Discovery and Development History

### 3.1 Origin

Mirogabalin was discovered at Daiichi Sankyo Company, Limited (Tokyo, Japan) through a structure-activity relationship program aimed at identifying gabapentinoid analogs with improved subunit selectivity at the  $\alpha$ -2- $\delta$  auxiliary subunits of voltage-gated calcium channels [3, 5]. The medicinal chemistry rationale was that first-generation gabapentinoids (gabapentin and pregabalin) bind nonselectively to both the  $\alpha$ 2 $\delta$ -1 and  $\alpha$ 2 $\delta$ -2 subunits, and that central nervous system adverse effects (particularly somnolence, dizziness, and ataxia) may be partially mediated through  $\alpha$ 2 $\delta$ -2, which is expressed at high density in cerebellar Purkinje neurons. A compound with preferential binding to  $\alpha$ 2 $\delta$ -1 (the subunit predominantly expressed in dorsal root ganglia and spinal cord dorsal horn nociceptive circuits) was hypothesized to retain analgesic efficacy while reducing the incidence of central adverse effects.

### 3.2 Preclinical selection

The bicyclo[3.2.0]heptene scaffold of mirogabalin was selected from a series of conformationally constrained amino acid analogs on the basis of high binding affinity at human recombinant  $\alpha$ 2 $\delta$ -1 ( $K_i$  approximately 13.5 nM), moderate binding at  $\alpha$ 2 $\delta$ -2 ( $K_i$  approximately 22.7 nM), and critically, a markedly slower dissociation rate from  $\alpha$ 2 $\delta$ -1 ( $t_{1/2}$  approximately 11.1 hours) than from  $\alpha$ 2 $\delta$ -2 ( $t_{1/2}$  approximately 2.4 hours) [5]. The dissociation kinetic differential was the key differentiator from pregabalin, which shows equal dissociation half-lives of approximately 1.4 hours from both subunits. In preclinical neuropathic pain models (partial sciatic nerve ligation in rats, streptozotocin-induced diabetic neuropathy in rats), mirogabalin produced dose-dependent antiallodynic and antihyperalgesic effects with potency comparable to or greater than pregabalin [5].

### 3.3 Clinical development timeline

Phase 1 studies in healthy volunteers (United States and Japan) characterized the single-dose and multiple-dose pharmacokinetics, tolerability, and pharmacodynamics of mirogabalin besylate at doses ranging from 1 mg to 30 mg [9]. Phase 2 dose-ranging studies in DPNP patients in the United States and Japan established the effective dose range (5 to 15 mg twice daily) and the dose-response relationship [13].

The Phase 3 program bifurcated into two geographic and indication tracks:

**Asian neuropathic pain program:** Two pivotal Phase 3 trials in Asian patients with DPNP (Study 3001) and PHN (Study 3002) were conducted at sites in Japan, Taiwan, South Korea, and other Asian jurisdictions. Both trials met their primary endpoints, supporting the January 2019 Japanese regulatory approval [6, 7].

**Global fibromyalgia program (ALDAY):** Three Phase 3 trials (ALDAY-1, ALDAY-2, ALDAY-3) enrolled more than 3,600 subjects with fibromyalgia at sites in the United States, Europe, and other jurisdictions. All three trials failed to meet the primary efficacy endpoint [8]. The ALDAY program was discontinued, and Daiichi Sankyo withdrew the fibromyalgia indication from its development pipeline.

### 3.4 Regulatory approvals

Japan: January 8, 2019. Indication: peripheral neuropathic pain (encompassing DPNP and PHN). Launched commercially as Tarlige tablets (5 mg, 10 mg, 15 mg) in April 2019.

Taiwan: 2020. Indication: DPNP and PHN.

Thailand: 2022. Indication: peripheral neuropathic pain.

In March 2022, the Japanese Ministry of Health, Labour and Welfare approved a supplemental indication for Tarlige tablets for central neuropathic pain, based on the results of the Phase 3 central neuropathic pain trial conducted across Japan, Korea, and Taiwan [14].

The compound has not been submitted for regulatory approval in the United States, the European Union, or other non-Asian jurisdictions. The US and EU development strategy was predicated on the fibromyalgia indication; with the ALDAY program failure, no Western regulatory submission has been pursued.

## 4. Mechanism of Action

Mirogabalin exerts its pharmacological effects through selective binding to the alpha-2-delta auxiliary subunits of voltage-gated calcium channels (VGCCs). The alpha2delta subunits are accessory proteins that modulate the trafficking, membrane expression, and biophysical properties of the pore-forming alpha-1 subunit of high-voltage-activated calcium channels (principally CaV2.1 P/Q-type, CaV2.2 N-type, and CaV2.3 R-type channels) [1, 2, 15].

### 4.1 Alpha-2-delta subunit pharmacology

The alpha-2-delta subunit family comprises four members (alpha2delta-1 through alpha2delta-4), of which alpha2delta-1 and alpha2delta-2 are the pharmacologically relevant targets for gabapentinoid drugs. The alpha2delta-1 subunit is expressed at high density in dorsal root ganglion neurons, spinal cord dorsal horn laminae I and II, and in multiple brain regions including hippocampus, cortex, and thalamus. The alpha2delta-2 subunit is expressed predominantly in cerebellar Purkinje neurons, in some brainstem nuclei, and in peripheral tissues including heart and skeletal muscle [15].

Gabapentinoid binding to alpha2delta subunits reduces calcium channel trafficking to the presynaptic membrane, decreases calcium influx at nerve terminals, and consequently reduces the release of excitatory neurotransmitters (glutamate, substance P, calcitonin gene-related peptide, norepinephrine) from hyperexcitable presynaptic terminals in neuropathic pain states [1, 16]. The mechanism is state-dependent: gabapentinoid binding preferentially reduces neurotransmitter release from pathologically upregulated alpha2delta-expressing terminals rather than from normally functioning synapses, which contributes to the analgesic selectivity observed in neuropathic versus nociceptive pain conditions.

### 4.2 Binding characteristics of mirogabalin

Mirogabalin binds to both human recombinant alpha2delta-1 and alpha2delta-2 subunits with high affinity. The equilibrium binding affinities ( $K_i$  values) are approximately 13.5 nM at alpha2delta-1 and approximately 22.7 nM at alpha2delta-2

[5]. The absolute binding affinities are therefore broadly similar and are in the same order of magnitude as pregabalin ( $K_d$  approximately 6.0 nM at  $\alpha 2\delta$ -1 and 7.2 nM at  $\alpha 2\delta$ -2).

The critical pharmacological distinction is in the dissociation kinetics. Mirogabalin demonstrates markedly different dissociation half-lives at the two subunits: approximately 11.1 hours at  $\alpha 2\delta$ -1 and approximately 2.4 hours at  $\alpha 2\delta$ -2 in human recombinant binding assays [5]. In contrast, pregabalin shows equal dissociation half-lives of approximately 1.4 hours from both subunits. The dissociation kinetic ratio ( $\alpha 2\delta$ -1 to  $\alpha 2\delta$ -2) for mirogabalin is therefore approximately 4.6, compared to approximately 1.0 for pregabalin.

The functional consequence of this kinetic selectivity is that mirogabalin produces a more sustained reduction in calcium channel activity at  $\alpha 2\delta$ -1-expressing terminals (principally dorsal root ganglion and spinal cord nociceptive circuits) relative to  $\alpha 2\delta$ -2-expressing terminals (principally cerebellar Purkinje neurons). This is hypothesized to translate clinically to maintained analgesic efficacy with a reduced propensity for cerebellar-mediated adverse effects (dizziness, ataxia, gait disturbance) [2, 5].

## 4.3 Downstream analgesic mechanisms

Binding of mirogabalin to  $\alpha 2\delta$ -1 on dorsal root ganglion neurons and presynaptic terminals in the spinal cord dorsal horn reduces calcium influx through CaV2.1 and CaV2.2 channels, decreasing release of glutamate, substance P, and calcitonin gene-related peptide at central nociceptive synapses [16]. In neuropathic pain states,  $\alpha 2\delta$ -1 expression is upregulated in damaged and adjacent sensory neurons, amplifying calcium channel-dependent neurotransmitter release and contributing to central sensitization and allodynia. Mirogabalin binding reverses this pathological upregulation of synaptic transmission.

Additional downstream effects include reduction of spinal wide-dynamic-range neuron excitability, attenuation of wind-up (progressive increase in C-fiber-evoked action potential discharge), and modulation of descending inhibitory pathways from brainstem nuclei. These spinal and supraspinal mechanisms contribute to the reduction of both spontaneous pain and evoked hypersensitivity in neuropathic pain conditions [17].

## 4.4 Selectivity profile

Mirogabalin does not bind to GABA-A or GABA-B receptors and does not interact directly with GABA synthesis, reuptake, or degradation pathways, despite its structural resemblance to GABA [1, 2]. The compound does not bind to opioid receptors, sodium channels, NMDA receptors, or other common analgesic targets at therapeutic concentrations. The pharmacological activity is therefore attributed entirely to the  $\alpha 2\delta$  subunit interaction. This selectivity distinguishes mirogabalin from multimodal analgesics and from the opioid class and is the basis for the absence of abuse potential and physical dependence observed in preclinical and clinical characterization [9].

## 5. Pharmacokinetics and Routes of Administration

### 5.1 Absorption

Mirogabalin besylate is rapidly and nearly completely absorbed after oral administration. Time to maximum plasma concentration (T<sub>max</sub>) is approximately 1 hour in both fasted and fed states [9, 10]. Food does not significantly affect the rate or extent of absorption; the compound may therefore be administered without regard to meals. Oral bioavailability approaches 100 percent, indicating negligible first-pass metabolism. Maximum plasma concentration (C<sub>max</sub>) and area under the plasma concentration-time curve (AUC) increase in an approximately dose-proportional manner across the therapeutic dose range (5 to 15 mg) [9].

### 5.2 Distribution

The volume of distribution of mirogabalin has not been extensively characterized in published human studies but is consistent with moderate tissue distribution based on the pharmacokinetic profile. Plasma protein binding is low (approximately 25 percent or less), which is consistent with the other gabapentinoids and reflects the hydrophilic amino acid character of the compound [10]. The compound penetrates the central nervous system, as evidenced by central pharmacological effects (somnolence, dizziness) at therapeutic doses.

### 5.3 Metabolism

Mirogabalin undergoes limited hepatic metabolism. Approximately 13 to 20 percent of the administered dose is metabolized through uridine 5-prime-diphosphoglucuronosyltransferase (UGT) isoforms [10, 18]. The primary metabolic pathway involves glucuronidation at the carboxylic acid moiety to produce mirogabalin acylglucuronide, which is subsequently converted nonenzymatically to the biologically inactive lactam metabolite A204-4455. Minor metabolites include glucuronidation products of oxidized A204-4455 and mirogabalin N-glucuronide. The compound does not undergo significant cytochrome P450-mediated oxidative metabo-

lism and does not inhibit or induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at therapeutic concentrations [9, 10]. This CYP-independent metabolism is the basis for the low drug-drug interaction potential.

## 5.4 Elimination

Renal excretion is the predominant elimination pathway. In a radiolabeled human mass balance study, 96.85 percent of administered radioactivity was recovered in urine and 1.21 percent in feces [18]. Of the urinary radioactivity, 61 to 72 percent was parent mirogabalin (unchanged drug), with the remainder comprising glucuronide and lactam metabolites. Renal clearance of mirogabalin exceeds the glomerular filtration rate, indicating that active tubular secretion contributes to renal elimination in addition to glomerular filtration [10, 18].

The terminal elimination half-life is approximately 4 to 6 hours after single oral dosing, supporting twice-daily administration for sustained analgesic coverage. No significant accumulation was observed with multiple doses over 14 days at therapeutic dose levels [9].

## 5.5 Routes of administration

Mirogabalin is administered exclusively by the oral route. The marketed formulation (Tarlige) is available as conventional film-coated tablets in 2.5 mg, 5 mg, 10 mg, and 15 mg strengths. An orally disintegrating tablet (ODT) formulation has been developed and shown to be bioequivalent to the conventional tablet in healthy Japanese subjects [19]. No parenteral, transdermal, or topical formulations have been developed or studied.

## 5.6 Special populations

**Renal impairment:** Because renal excretion is the dominant elimination pathway, dose adjustment is required in patients with impaired renal function. The Japanese prescribing information specifies dose reductions for moderate and severe renal impairment and for patients receiving hemodialysis. A dedicated Phase 3 open-label study evaluated mirogabalin safety and efficacy in Japanese patients with renal impairment and peripheral neuropathic pain [20].

**Hepatic impairment:** An open-label single-dose study assessed the effect of mild and moderate hepatic impairment on mirogabalin pharmacokinetics and found no clinically meaningful changes in exposure, consistent with the minor role of hepatic metabolism [21]. No dose adjustment is required for mild or moderate hepatic impairment.

**Elderly:** No specific dose adjustment is mandated for age alone, although elderly patients (65 years and older) may have higher incidence of somnolence and dizziness, likely reflecting age-related decline in renal function and increased central nervous system sensitivity [12].

**Pediatric:** Mirogabalin has not been studied in pediatric populations. No pediatric indications have been approved.

## 6. Preclinical Pharmacology

### 6.1 Neuropathic pain models

Mirogabalin has been evaluated in multiple preclinical neuropathic pain models. In the rat partial sciatic nerve ligation (Seltzer) model, mirogabalin produced dose-dependent reversal of mechanical allodynia with potency comparable to or exceeding pregabalin at equivalent doses [5]. In the streptozotocin-induced diabetic neuropathy model in rats, mirogabalin reversed mechanical hyperalgesia in a dose-dependent manner. In the chronic constriction injury (Bennett) model, the compound produced sustained antiallodynic effects consistent with the prolonged dissociation kinetics at  $\alpha 2\delta 1$  [5, 17].

### 6.2 Inflammatory pain models

Mirogabalin has also been evaluated in inflammatory pain models. In the rat complete Freund's adjuvant (CFA) model of inflammatory pain, mirogabalin produced dose-dependent antihyperalgesic effects [22]. The analgesic effect in inflammatory pain models was observed at higher doses than in neuropathic pain models, consistent with the predominant role of  $\alpha 2\delta 1$  upregulation in neuropathic rather than inflammatory pain states.

### 6.3 Safety pharmacology

Preclinical safety pharmacology studies demonstrated that mirogabalin does not produce clinically significant cardiovascular effects (QT prolongation, hemodynamic changes) at therapeutic exposure multiples. Central nervous system safety pharmacology studies in rats showed dose-dependent sedation and reduced locomotor activity at supratherapeutic doses, consistent with the gabapentinoid class. The compound did not demonstrate abuse potential in preclinical self-administration and conditioned place preference paradigms at doses producing pharmacological effects [9].

## 6.4 Toxicology

Chronic toxicology studies in rats and monkeys at multiples of the human therapeutic exposure did not reveal target-organ toxicity beyond the expected pharmacological effects (sedation, reduced activity). Reproductive toxicology studies did not demonstrate teratogenicity at exposures up to the studied multiples of the human dose. Genotoxicity and carcinogenicity assessments were completed as part of the regulatory submission package; no positive findings have been reported in the published literature.

## 7. Clinical Evidence Base

### 7.1 Diabetic peripheral neuropathic pain

The pivotal Phase 3 study in DPNP (Study 3001) was a multicenter, randomized, double-blind, placebo-controlled trial conducted at sites in Japan, Taiwan, South Korea, and other Asian jurisdictions [7]. A total of 834 patients with painful diabetic peripheral neuropathy were randomized to placebo (n=330), mirogabalin 15 mg once daily (n=164), mirogabalin 10 mg twice daily (n=165), or mirogabalin 15 mg twice daily (n=165) for up to 15 weeks including a 1 to 2 week titration period. The primary endpoint was change in average daily pain score (ADPS) from baseline to week 14.

Both the 10 mg twice daily and 15 mg twice daily groups demonstrated statistically significant improvement in ADPS versus placebo. The 15 mg once daily group showed numerical improvement that did not reach statistical significance in all analyses, supporting the twice-daily dosing regimen for optimal analgesic coverage. Onset of analgesic effect was observed as early as 2 days after initiation of treatment. The study completion rate was 90.5 percent (755 of 834 randomized patients) [7].

Treatment-emergent adverse events were dose-dependent. Somnolence occurred in 3.8 percent (placebo), 10.8 percent (15 mg QD), 14.5 percent (10 mg BID), and 19.1 percent (15 mg BID) of patients. Dizziness occurred in 2.7 percent, 5.7 percent, 9.1 percent, and 13.1 percent, respectively [7].

### 7.2 Postherpetic neuralgia

The pivotal Phase 3 study in PHN (Study 3002) was a multicenter, randomized, double-blind, placebo-controlled trial conducted in Asian patients aged 20 years and older with postherpetic neuralgia [6]. A total of 765 patients were randomized 2:1:1:1 to placebo (n=303), mirogabalin 15 mg/day (n=152), mirogabalin 20 mg/day (n=153), or mirogabalin 30 mg/day (n=155) for up to 14 weeks. The primary endpoint was change in ADPS from baseline to week 14.

All three mirogabalin dose groups demonstrated statistically significant improvement in ADPS versus placebo. The least-squares mean differences versus placebo were negative 0.41 (15 mg/day), negative 0.47 (20 mg/day), and negative 0.77 (30 mg/day), showing a dose-dependent response [6]. The most common treatment-emergent adverse events were somnolence, nasopharyngitis, dizziness, weight increase, and edema, and all were mild or moderate in severity.

## 7.3 Pooled analysis of pivotal trials

A pooled analysis of the two pivotal Phase 3 studies confirmed the efficacy and safety findings of the individual trials [23]. The pooled population demonstrated that mirogabalin produced statistically significant pain relief from as early as 2 days after administration, with effect sustained through the 14-week treatment period. The pooled safety analysis confirmed that the most common adverse events (somnolence, dizziness, peripheral edema, weight gain) were dose-dependent, generally mild to moderate, and consistent with the gabapentinoid class profile.

## 7.4 Central neuropathic pain

A Phase 3, multinational, randomized, double-blind, placebo-controlled trial evaluated mirogabalin for central neuropathic pain after spinal cord injury, conducted at 120 sites in Japan, Korea, and Taiwan [14, 24]. This trial formed the basis for the March 2022 supplemental approval in Japan for central neuropathic pain. A subsequent 52-week open-label extension study demonstrated long-term safety and sustained efficacy in Asian patients with central neuropathic pain [25].

## 7.5 Fibromyalgia (ALDAY program)

The ALDAY program comprised three Phase 3 randomized, double-blind, placebo-controlled and active-controlled (pregabalin) 13-week trials evaluating mirogabalin for fibromyalgia pain in global populations (predominantly United States and Europe), enrolling more than 3,600 subjects total (more than 1,200 per study) [8]. The primary endpoint in each trial was change in weekly average of worst daily pain score from baseline to week 13.

None of the three ALDAY trials met the primary efficacy endpoint. Mirogabalin did not demonstrate statistically significant superiority over placebo in any of the three studies, and the active comparator (pregabalin) also did not separate from

placebo in these trials [8]. The failure of both mirogabalin and the active comparator to separate from placebo raised questions about trial design, placebo response rates, and the broader challenge of demonstrating gabapentinoid efficacy in fibromyalgia populations in global trials with high placebo response. The fibromyalgia development program was subsequently discontinued.

## 7.6 Other indications under investigation

Additional clinical studies have evaluated mirogabalin as add-on therapy for peripheral neuropathic pain after thoracic surgery (the ADMIT-NeP study), for neuropathic pain associated with lumbar spinal stenosis, and for chemotherapy-induced peripheral neuropathy [26, 27, 28]. These studies have generally reported positive efficacy signals in their respective populations, though they are smaller in scale and not pivotal registration trials.

The MIROP study, a multi-center, prospective, open-label study, evaluated switching from pregabalin to mirogabalin in patients with peripheral neuropathic pain and reported maintained or improved pain control with generally lower incidence of somnolence and dizziness following the switch [29].

## 8. Sourcing and Quality Verification

Pharmaceutical-grade mirogabalin besylate (Tarlige brand, Daiichi Sankyo) is the highest quality source for research applications where clinical-grade material is required. The pharmaceutical-grade material is supplied as conventional film-coated tablets in 2.5 mg, 5 mg, 10 mg, and 15 mg strengths and as orally disintegrating tablets. Pharmaceutical sourcing is feasible in Japan, Taiwan, and Thailand where the compound is marketed.

Research-grade mirogabalin besylate is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Selleckchem, Cayman Chemical, BOC Sciences, MedKoo Biosciences, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the besylate salt; the free base is available from some suppliers but is less commonly stocked. Pricing varies by supplier and quantity; typical research-grade pricing is in the range of \$100 to \$500 per 100 mg at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (210.15 plus or minus 0.01 for the protonated free base  $[M+H]^+$ ; 368.15 plus or minus 0.01 for the besylate salt)
- Chiral HPLC confirmation of enantiomeric purity (greater than 99 percent enantiomeric excess of the (1R,5S,6S) form)
- Nuclear magnetic resonance spectroscopy (proton and carbon-13) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories provide independent verification of vendor certificates of analysis. The research-grade mirogabalin market is smaller than that for pregabalin or gabapentin, and lot-to-lot variability from some suppliers has been

observed; on-receipt analytical confirmation is appropriate for any investigation where dose-response precision is required.

## 9. Reconstitution and Handling

Mirogabalin besylate is freely soluble in water as the besylate salt. For in vitro research applications, the compound is supplied as a crystalline powder and is reconstituted in aqueous media (water, phosphate-buffered saline, cell culture medium) at concentrations up to 10 to 50 mM. For applications requiring higher stock concentrations or where aqueous solubility limits are approached, dimethyl sulfoxide (DMSO) may be used as the primary stock solvent at concentrations up to 100 mM, with subsequent dilution into aqueous experimental media.

Storage of the solid compound at room temperature (15 to 25 degrees Celsius) in a dry, light-protected environment is adequate for long-term stability. Refrigerated storage (2 to 8 degrees Celsius) is recommended for extended storage periods (greater than 6 months). Aqueous stock solutions should be prepared fresh or stored refrigerated for no more than 7 to 14 days. DMSO stock solutions may be stored at negative 20 degrees Celsius for up to 6 months with minimal degradation. Aliquoting of stock solutions for single-use is recommended to minimize freeze-thaw cycles.

For in vivo research applications in animal models, mirogabalin is typically prepared as an oral suspension or solution in 0.5 percent methylcellulose, distilled water, or normal saline at concentrations appropriate for the target dose and administration volume. Oral gavage is the standard route of administration in rodent studies, consistent with the clinical oral administration route.

## 10. Stack Interactions and Combinations

Mirogabalin has a low drug-drug interaction potential owing to its predominantly renal elimination, minimal CYP-mediated metabolism, and lack of CYP inhibition or induction at therapeutic concentrations [9, 10]. Investigators conducting research with mirogabalin in combination with other compounds should consider the following interaction categories:

**Renal elimination interactions:** Compounds that compete for active tubular secretion may alter mirogabalin renal clearance. The specific renal transporter(s) involved in mirogabalin tubular secretion have not been fully characterized in published literature; investigators using combinations with known renal tubular secretion substrates (metformin, cimetidine, trimethoprim) should monitor for pharmacokinetic interactions.

**Other gabapentinoids:** Concurrent use with gabapentin or pregabalin is pharmacologically redundant, as all three compounds act on the same  $\alpha_2\delta$  binding site. The combination produces no additional efficacy beyond that achievable with either agent alone and increases the risk of dose-dependent adverse effects (somnolence, dizziness, edema). Switching studies (pregabalin to mirogabalin) have been conducted clinically but concurrent administration is not recommended [29].

**Central nervous system depressants:** Concurrent administration with opioids, benzodiazepines, sedating antihistamines, alcohol, or other central nervous system depressants may produce additive sedation and respiratory depression risk. This interaction is a class effect of the gabapentinoids and has been the subject of regulatory warnings for pregabalin and gabapentin; the same caution applies to mirogabalin.

**Antidiabetic agents:** Given the DPNP indication, many patients receiving mirogabalin are concurrently treated with insulin, metformin, sulfonylureas, or other antidiabetic agents. No specific pharmacokinetic interactions have been characterized between mirogabalin and antidiabetic agents. The combination is used routinely in the approved clinical setting without specific precautions beyond standard glycemic monitoring.

**Antihypertensive agents:** No specific interactions have been characterized. Additive blood pressure lowering or orthostatic effects are theoretically possible with centrally acting antihypertensives or alpha-blockers but have not been reported as clinically significant.

**Analgesic combinations:** Mirogabalin has been studied as add-on therapy to nonsteroidal anti-inflammatory drugs (NSAIDs) in lumbar spinal stenosis with neuropathic pain and as add-on to conventional pain therapy after thoracic surgery [26, 27]. These combination approaches have shown additive analgesic benefit without unexpected pharmacokinetic or pharmacodynamic interactions.

# 11. Adverse Events and Safety

## 11.1 Common adverse events

The principal adverse events observed in the pivotal Phase 3 trials and in post-marketing surveillance are consistent with the gabapentinoid class:

- Somnolence (10 to 27 percent depending on dose, the most frequently reported adverse event; dose-dependent, generally mild to moderate)
- Dizziness (6 to 13 percent, dose-dependent)
- Peripheral edema (3 to 6 percent)
- Weight gain (approximately 2 to 5 percent at higher doses)
- Nasopharyngitis (reported in Asian trial populations at rates similar to placebo)
- Headache (2 to 4 percent)

These adverse events are similar in character to those observed with pregabalin and gabapentin. Some observational studies and the MIROP switching study have suggested that the incidence of somnolence and dizziness may be lower with mirogabalin than with pregabalin at comparable analgesic doses, although this observation has not been confirmed in a prospective randomized head-to-head comparison trial [29, 30].

## 11.2 Dose-dependent adverse event profile

The incidence of somnolence and dizziness increases with mirogabalin dose in a consistent pattern across the pivotal trials. In the DPNP trial, somnolence rates ranged from 10.8 percent (15 mg QD) to 19.1 percent (15 mg BID), and dizziness rates ranged from 5.7 percent to 13.1 percent over the same dose range [7]. The dose titration schedule (starting at lower doses and increasing over 1 to 2 weeks) was implemented in the pivotal trials to mitigate the initial onset of these adverse effects.

## 11.3 Risk factors for adverse events

Post-marketing analyses and retrospective studies have identified several risk factors for increased incidence of somnolence and dizziness during mirogabalin treatment: female sex, age 65 years or older, baseline body weight below 60 kg, and concurrent opioid therapy [12, 30]. These factors had no notable impact on analgesic efficacy. Dose adjustment based on these risk factors is at the clinician's discretion; the prescribing information does not mandate sex-based or weight-based dosing.

## 11.4 Treatment discontinuation

Treatment-emergent adverse events led to discontinuation of mirogabalin in 7.7 to 13.9 percent of patients across the pivotal trials, compared to 3.9 to 11.0 percent in placebo groups [23]. The most common reasons for discontinuation were somnolence and dizziness. Most discontinuations occurred during the titration period.

## 11.5 Long-term safety

Open-label extension studies of up to 52 weeks in duration have demonstrated acceptable long-term safety with no new safety signals emerging beyond those observed in the shorter pivotal trials [25, 31]. Weight gain was observed to be progressive with long-term administration, consistent with the gabapentinoid class.

## 11.6 Abuse potential

Mirogabalin has not been classified as a controlled substance in Japan or in other jurisdictions where it is approved. Pregabalin, in contrast, is classified as a Schedule V controlled substance in the United States. Preclinical studies did not demonstrate significant abuse potential for mirogabalin, and the clinical development program did not identify signals of misuse or dependence [9]. The absence of controlled-substance scheduling is a practical advantage for clinical use and for research procurement.

## 11.7 Pregnancy and lactation

Human pregnancy data for mirogabalin are not available. Animal reproductive toxicology studies did not demonstrate teratogenicity at the studied exposure multiples. The Japanese prescribing information advises against use during pregnancy

unless the potential benefit justifies the potential risk. Data on excretion into human breast milk are not available; the prescribing information advises caution during lactation.

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative analgesic candidates against mirogabalin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal alpha2delta ligands and related gabapentinoid or neuropathic pain analgesic candidates with substantive clinical pharmacology programs.

### 12.1 Pregabalin (Lyrica)

**Mechanism:** Nonselective alpha2delta ligand binding both alpha2delta-1 and alpha2delta-2 subunits with high affinity ( $K_d$  approximately 6.0 nM and 7.2 nM, respectively) and equal dissociation kinetics ( $t_{1/2}$  approximately 1.4 hours from both subunits) [15, 32].

**Development trajectory:** Developed by Pfizer (originally Warner-Lambert/Parke-Davis), pregabalin received FDA approval in 2004 for neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia, with subsequent approvals for fibromyalgia (2007), neuropathic pain associated with spinal cord injury (2012), and as adjunctive therapy for partial-onset seizures. The compound has been approved in more than 100 jurisdictions worldwide and is the most extensively used gabapentinoid globally. Generic pregabalin is available following patent expiration.

**Novelty:** Low. Pregabalin is a well-established, first-generation gabapentinoid with more than 20 years of clinical use.

**Effect size:** Moderate. In neuropathic pain indications, pregabalin produces number-needed-to-treat (NNT) values of approximately 4 to 8 for 50 percent pain reduction, depending on the population studied [32]. Effect sizes in fibromyalgia are smaller (NNT approximately 8 to 12). The analgesic effect is modest but consistent across multiple neuropathic pain subtypes.

**Promising potential:** Stable. The compound is mature and fully registered; no further expansion of indications is anticipated. Generic availability has expanded access globally.

**Side-effect profile:** The principal adverse events are somnolence, dizziness, peripheral edema, weight gain, and blurred vision. The incidence of somnolence (15 to 25 percent) and dizziness (10 to 30 percent) at therapeutic doses is consistently reported across registration trials. Pregabalin is classified as Schedule V in the United States due to a modest abuse and dependence potential identified during development.

**Overall validation:** High. Pregabalin is the most extensively validated alpha2delta ligand with the broadest range of approved indications and the largest clinical evidence base.

**Comparison to mirogabalin:** Pregabalin lacks the subunit-selective dissociation kinetics of mirogabalin and binds alpha2delta-1 and alpha2delta-2 with equal persistence. The broader approval base, extensive safety database, and controlled-substance scheduling (reflecting demonstrated abuse potential) distinguish pregabalin from mirogabalin. Mirogabalin's advantages are the preferential alpha2delta-1 kinetics, absence of controlled-substance scheduling, and potentially lower incidence of central adverse effects, though these advantages have not been confirmed in prospective head-to-head trials.

## 12.2 Gabapentin (Neurontin)

**Mechanism:** Alpha2delta ligand with moderate affinity ( $K_d$  approximately 59 nM at alpha2delta-1) and modest selectivity for alpha2delta-1 over alpha2delta-2 ( $K_d$  approximately 153 nM at alpha2delta-2) in equilibrium binding assays [15, 33].

**Development trajectory:** Developed by Parke-Davis (now Pfizer), gabapentin was originally approved as an antiepileptic in 1993 and subsequently received FDA approval for postherpetic neuralgia in 2002. The compound is used off-label for multiple neuropathic pain conditions, fibromyalgia, restless legs syndrome, and anxiety disorders. Generic gabapentin is widely available and inexpensive.

**Novelty:** Low. Gabapentin is the oldest marketed gabapentinoid with more than 30 years of clinical use.

**Effect size:** Moderate. Analgesic effect sizes in neuropathic pain are broadly similar to pregabalin, though direct comparison is complicated by the nonlinear (saturable) absorption pharmacokinetics of gabapentin that produce variable bioavailability at higher doses [33]. NNT for 50 percent pain reduction is approximately 5 to 8 in postherpetic neuralgia.

**Promising potential:** Stable. The compound is mature, fully generic, and widely prescribed. Extended-release formulations (gabapentin enacarbil, Horizant; gastroretentive gabapentin, Gralise) have been developed to improve the absorption pharmacokinetics.

**Side-effect profile:** Similar to pregabalin: somnolence, dizziness, peripheral edema, weight gain, ataxia. Gabapentin is generally considered to have a somewhat lower abuse potential than pregabalin and is not federally scheduled as a controlled substance in the United States, though some states have enacted individual scheduling.

**Overall validation:** High. Extensive clinical use, large evidence base, well-characterized safety profile.

**Comparison to mirogabalin:** Gabapentin has lower binding affinity than mirogabalin at both  $\alpha 2\delta$  subunits, saturable absorption kinetics that limit dose proportionality, and a shorter duration of effect requiring three-times-daily dosing. Mirogabalin's advantages include higher potency, subunit-selective kinetics, linear pharmacokinetics, and twice-daily dosing. Gabapentin's advantages include extensive safety data, low cost, and broad availability.

## 12.3 Gabapentin enacarbil (Horizant)

**Mechanism:** Prodrug of gabapentin that is actively transported by MCT-1 and other intestinal transporters, converting the saturable absorption pharmacokinetics of gabapentin to linear, dose-proportional absorption [34]. Following absorption, gabapentin enacarbil is rapidly hydrolyzed to gabapentin, which then acts as an  $\alpha 2\delta$  ligand identical to gabapentin.

**Development trajectory:** Developed by XenoPort (now Arbor Pharmaceuticals) and approved by the FDA in 2011 for moderate-to-severe restless legs syndrome and in 2012 for postherpetic neuralgia. The prodrug approach addresses the princi-

pal pharmacokinetic limitation of gabapentin (saturable intestinal absorption via the large neutral amino acid transporter LAT1) while maintaining the same pharmacological mechanism.

**Novelty:** Low to moderate. The novelty is pharmacokinetic (prodrug strategy) rather than pharmacological.

**Effect size:** Comparable to gabapentin at equivalent systemic exposures, with the advantage of dose-proportional exposure across the therapeutic range.

**Promising potential:** Low. The compound occupies a narrow niche (gabapentin prodrug with improved PK) and has not expanded beyond restless legs syndrome and PHN indications. Market penetration is limited compared to generic gabapentin.

**Side-effect profile:** Identical to gabapentin once converted to the active moiety. Somnolence, dizziness, and headache are the principal adverse events.

**Overall validation:** Moderate. The compound is FDA-approved and clinically validated but has limited clinical adoption.

**Comparison to mirogabalin:** Gabapentin enacarbil addresses the pharmacokinetic limitations of gabapentin but not the pharmacological limitations (nonselective  $\alpha_2\delta$  binding). Mirogabalin offers both pharmacokinetic advantages (linear absorption, twice-daily dosing) and pharmacological advantages (subunit-selective dissociation kinetics).

## 12.4 Duloxetine (Cymbalta)

**Mechanism:** Serotonin-norepinephrine reuptake inhibitor (SNRI) that enhances descending inhibitory pain pathways from brainstem nuclei through augmentation of serotonergic and noradrenergic neurotransmission in the spinal cord dorsal horn [35]. The mechanism is fundamentally different from the  $\alpha_2\delta$  ligand mechanism and targets a distinct component of the neuropathic pain processing circuit.

**Development trajectory:** Developed by Eli Lilly and approved by the FDA for diabetic peripheral neuropathic pain (2004), fibromyalgia (2008), and chronic musculoskeletal pain (2010), in addition to major depressive disorder and generalized anx-

xiety disorder indications. Duloxetine is the most widely used non-gabapentinoid first-line pharmacotherapy for neuropathic pain and fibromyalgia in the United States.

**Novelty:** Low. The SNRI mechanism for pain is well established.

**Effect size:** Moderate. NNT for 50 percent pain reduction in DPNP is approximately 5 to 6, broadly comparable to pregabalin [35]. Effect sizes in fibromyalgia are similar. The combination of duloxetine with pregabalin or gabapentin is a common clinical practice and has been studied in controlled trials.

**Promising potential:** Stable. The compound is fully generic and widely prescribed; no further indication expansion is anticipated.

**Side-effect profile:** Nausea (the most common adverse event at initiation, typically transient), somnolence, dizziness, constipation, dry mouth, decreased appetite. The side-effect profile is distinct from the gabapentinoid class and in some patients complementary (allowing combination therapy without overlapping adverse effects). Cardiovascular effects include modest blood pressure elevation. Abrupt discontinuation can produce a discontinuation syndrome.

**Overall validation:** High. Extensively validated for neuropathic pain and fibromyalgia with a large evidence base.

**Comparison to mirogabalin:** Duloxetine operates through a fundamentally different mechanism (monoamine reuptake inhibition versus  $\alpha 2\delta$  channel modulation) and is therefore a complement rather than a direct competitor. The two mechanisms target different components of the neuropathic pain circuit, and combination therapy is a rational clinical approach. Mirogabalin has the advantage of an  $\alpha 2\delta$ -selective mechanism with low CYP interaction potential; duloxetine is a moderate CYP2D6 inhibitor and has broader drug-drug interaction considerations.

## 12.5 Capsaicin 8% patch (Qutenza)

**Mechanism:** Topical agonist of the transient receptor potential vanilloid 1 (TRPV1) channel on nociceptive C-fiber terminals. High-concentration application produces initial nociceptor activation followed by prolonged defunctionalization of cuta-

neous nociceptive fibers through calcium-mediated neurotoxicity and retraction of epidermal nerve fibers [36]. The mechanism is local and peripheral, fundamentally different from the systemic central mechanisms of gabapentinoids and SNRIs.

**Development trajectory:** Developed by NeurogesX (now Averitas Pharma/Gruenenthal) and approved by the FDA in 2009 for PHN and by the EMA for peripheral neuropathic pain. The 8% capsaicin patch (Qutenza) is applied by a healthcare professional in a single 30-minute or 60-minute application, with analgesic effect lasting approximately 3 months per application.

**Novelty:** Moderate to high. The topical defunctionalization mechanism is distinct from all systemic neuropathic pain pharmacotherapies.

**Effect size:** Moderate. NNT for 30 percent pain reduction in PHN is approximately 7 to 10. Effect is localized to the area of application [36]. The intermittent dosing (single application every 3 months) is a practical advantage for adherence.

**Promising potential:** Moderate. The compound occupies a niche for patients with localized neuropathic pain who cannot tolerate or have not responded to systemic therapies. Market penetration is limited by the requirement for healthcare professional application and procedural pain during application.

**Side-effect profile:** Application-site pain and erythema are the principal adverse effects. No systemic adverse events at meaningful incidence. The absence of systemic central nervous system effects (somnolence, dizziness) is a significant differentiator from gabapentinoids.

**Overall validation:** Moderate. FDA and EMA approved with a modest clinical evidence base.

**Comparison to mirogabalin:** Capsaicin 8% patch and mirogabalin operate through entirely different mechanisms (peripheral TRPV1 defunctionalization versus central  $\alpha 2\delta$  modulation) and target different patient populations. The patch is suited for localized neuropathic pain with a requirement for absence of systemic adverse effects; mirogabalin is suited for generalized peripheral neuropathic pain requiring systemic treatment. The two approaches are complementary and could theoretically be combined.

## 12.6 Comparator summary

The five comparator compounds occupy distinct positions in the neuropathic pain pharmacotherapy landscape. **Pregabalin** is the closest pharmacological comparator to mirogabalin, sharing the  $\alpha 2\delta$  ligand mechanism but lacking subunit selectivity and carrying controlled-substance scheduling. **Gabapentin** is the oldest and most widely used gabapentinoid, limited by nonlinear pharmacokinetics. **Gabapentin enacarbil** addresses gabapentin's pharmacokinetic limitations without pharmacological advancement. **Duloxetine** operates through a complementary SNRI mechanism and is the principal non-gabapentinoid first-line neuropathic pain pharmacotherapy. **Capsaicin 8% patch** provides a topical, non-systemic alternative for localized pain.

Mirogabalin occupies a position in this landscape as a next-generation gabapentinoid with improved subunit selectivity and dissociation kinetics relative to pregabalin and gabapentin, linear pharmacokinetics relative to gabapentin, and absence of controlled-substance scheduling relative to pregabalin. The principal limitations are the geographic restriction of regulatory approvals (Japan, Taiwan, Thailand), the absence of US and EU approval, the failed fibromyalgia program, and the limited head-to-head clinical comparison data against pregabalin that would be required to confirm the hypothesized therapeutic margin advantage. The clinical evidence base, while positive in the approved Asian neuropathic pain indications, is smaller in scale and geographic scope than the pregabalin and gabapentin evidence bases.

Investigators considering mirogabalin for neuropathic pain research should expect analgesic effect sizes in the range observed with other gabapentinoids (modest but consistent in neuropathic pain populations), should consider the renal elimination pathway for dose adjustment in impaired renal function, and should evaluate the compound in the context of the comparator landscape as a pharmacologically refined but geographically restricted alternative to the established first-generation gabapentinoids.

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