Tarlyca™

(Mirogabalin)

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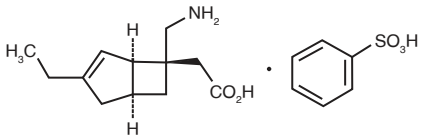
Film-coated Tablets
2.5mg, 5mg, 10mg & 15mg

DESCRIPTION

Tarlyca (Mirogabalin) contains Mirogabalin Besylate, a voltage gated calcium channel $\alpha_2\delta$ subunit ligand. The chemical name of Mirogabalin is 2-[(1R,5S,6S)-6-(aminomethyl)-3-ethyl-6-bicyclo[3.2.0]hept-3-enyl] acetic acid;benzenesulfonic acid. Its molecular formula is $C_{12}H_{19}NO_2 \cdot C_6H_6O_3S$ and the structural formula is:



Mirogabalin Besylate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tarlyca (Mirogabalin) is available for oral administration as:

Tarlyca Tablets 2.5mg
Each film-coated tablet contains:
Mirogabalin Besylate equivalent to Mirogabalin…2.5mg

Tarlyca Tablets 5mg
Each film-coated tablet contains:
Mirogabalin Besylate equivalent to Mirogabalin…5mg

Tarlyca Tablets 10mg
Each film-coated tablet contains:
Mirogabalin Besylate equivalent to Mirogabalin…10mg

Tarlyca Tablets 15mg
Each film-coated tablet contains:
Mirogabalin Besylate equivalent to Mirogabalin…15mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Mirogabalin plays an auxiliary role in the function of voltage-gated calcium channels in the nervous system α2. It is thought to exert analgesic effects by suppressing calcium currents through binding to δ subunits. In addition, the analgesic effect of Mirogabalin is also involved in the activation of the noradrenaline pathway of the descending pain inhibitory system.

Pharmacokinetics

Absorption

When a single oral dose of 3mg, 5mg, 10mg and 30mg (6 doses each) were administered orally to healthy adults, C_{max} was reached 1 hour after administration, and $t_{1/2}$ was 2.96 to 3.37 hours. C_{max} and AUC_{inf} increased in proportion to the dose.
When 10mg and 15mg (6 doses each) were administered orally to healthy adults twice daily for 7 days, steady state was reached by day 3, and the $t_{1/2}$ on day 7 was 2.43 and 2.83 hours. C_{max} and AUC_{tau} on day 7 increased in proportion to the dose.

Effects of Diet

When a single oral dose of 15mg as Mirogabalin was administered to healthy adults, the C_{max} was 230 and 188 ng/mL fasting and postprandial at 1.00 and 1.50 hours, and the AUC_{last} was 884 and 833 ng.hr/mL, respectively. Postprandial administration reduced C_{max} by about 18% and prolonged T_{max} by 0.5 hours, while AUC_{inf} decreased by about 6%.

Distribution

The apparent terminal phase volume of distribution (Vz/F) when administered orally as 3mg, 5mg, 10mg, and 30 mg (6 doses each) to healthy adults was 78.01 to 87.97 L.

Metabolism

After a single oral dose of 30mg (150 μCi) of ^{14}C-labeled form in six healthy adult males, approximately 97% of the administered radioactivity was recovered in the urine, of which approximately 76% was unchanged. Urinary metabolites other than unchanged forms were lactam forms, and 0.6% of the administered dose was recovered. In addition, N-glucuronate conjugates metabolized by UGTs were also detected.

Excretion

The CL/F of a single oral dose of 3mg, 5mg, 10mg, and 30mg (6 doses each) as Mirogabalin in healthy adults was 16.50 to 18.24L/hr. The urinary excretion rate of the unchanged body was 63.2 to 71.5%, and the renal clearance was 10.4 to 12.4L/hr. When a single oral dose of 30mg ^{14}C labeled form (150 μCi) was administered orally to healthy adult males, the cumulative excretion rate of total radioactivity reached more than 98% by 168 hours after administration, with approximately 97% excreted in urine and approximately 1% excreted in feces.

Special Population

Patients with Renal Impairment

When patients with normal renal function and renal dysfunction were administered 5mg orally as a single dose of Mirogabalin, an increase in AUC_{last} was observed with a decrease in CLcr. In patients with end-stage renal failure requiring hemodialysis, 15.3% of the Mirogabalin administered by 4-hour hemodialysis was recovered in the hemodialysis fluid.

Degree of renal impairment (CLcr: mL/min)	Number of examples	C_{max} (ng/mL)	T_{max} (hr)#	AUC_{last} (ng・hr/mL)	CLr (L/hr)
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)	1,350±259	1.92±0.463
End-stage renal failure dialysis*	6	101±32.9	4.01 (1.92～5.00)	1,990±916	–

Mean ± standard deviation
Median (min~max)
* Hemodialysis was performed for 4 hours 24 hours after administration.

Patients with Hepatic Impairment

The C_{max} of a single oral dose of 15mg as Mirogabalin in patients with mild and moderate hepatic dysfunction was 1.0 and 0.8 times, respectively, compared to healthy adults, and the AUC_{inf} was 0.9 and 1.1 times, respectively.

Elderly

When 5mg, 10mg, and 15mg (including 6 patients at each dose and 13 cases under 65 years of age) were administered orally twice a day for 14 days as Mirogabalin to healthy elderly people aged 55 to 75 years, steady state was reached by day 3, and the $t_{1/2}$ on day 14 was 3.58 to 4.55 hours. The $AUC_{0\text{-}12hr}$ on day 14 was 1.13 to 1.24 times that of day 1. No significant differences in pharmacokinetics were observed compared to healthy non-elderly people.

THERAPEUTIC INDICATIONS

Tarlyca (Mirogabalin) is indicated for the treatment of neuropathic pain in adults.

DOSAGE AND ADMINISTRATION

For adults, administer Tarlyca (Mirogabalin) 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.

Special Population

Patients with Renal Impairment

When administering to patients with renal dysfunction, the dosage and administration interval should be adjusted by referring to the creatinine clearance values shown in the following table. Start with a low dose and increase if tolerability is confirmed and inadequate.

		Degree of renal dysfunction (CLcr: mL/min)		
		Mild (90>CLcr≥60)	Moderate (60>CLcr≥30)	Severe (including hemodialysis patients) (30>CLcr)
Daily dose		10 to 30mg	5 to 15mg	2.5 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

ADVERSE REACTIONS

Following adverse reactions have been reported with the use of Mirogabalin:

Somnolence, floating dizziness, postural dizziness, insomnia, loss of consciousness, headache, tremor, hypoesthesia, memory impairment, amnesia, articulation disorder, hallucinations, delirium, dysgeusia, dysgeusia, head discomfort, dyskinesia, myoclonus, blurred vision, double vision, vision impairment, vision loss, increased eosinophil count, orthostatic hypotension, hypertension, palpitations, hot flashes, low blood pressure, constipation, bloating, dry mouth, gastritis, vomiting, increased appetite, decreased appetite, upper abdominal pain, gastroesophageal reflux disease, diarrhea, abdominal discomfort, elevated liver enzymes, urinary incontinence, frequent urination, difficulty urinating, urinary retention, rash, urticaria, erythema, pruritus, edema, weight gain, gait disturbances, abnormal sensation, rotational vertigo, dry mouth, facial edema, falls, diabetes mellitus (elevated HbA1c, elevated blood glucose levels), fatigue, elevated blood CK, eyelid edema, muscle weakness, withdrawal syndrome, asthenia and pain.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

Mirogabalin is contraindicated in patients with hypersensitivity to the active substance or to any of the excipient of the product.

PRECAUTIONS

Dizziness, somnolence, loss of consciousness

Dizziness, somnolence and loss of consciousness, which may cause fall and subsequent fracture, etc., may occur. Patient 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.

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 measure regularly.

Withdrawal symptoms

Abrupt discontinuation of treatment with Mirogabalin may cause drug withdrawal symptoms (e.g., insomnia, nausea, diarrhea, decrease 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, blurred vision, and diplopia). Caution should be exercised for potential occurrence of ophthalmic disorders in medical examination including careful history taking.

Hepatic Impairment

Hepatic dysfunction such as elevated AST and ALT may occur. If any abnormalities, including initial symptoms such as general malaise and loss of appetite, are observed, discontinue administration and take appropriate measures.

Elderly

Administer carefully by adjusting the dosage and dosage interval with reference to the creatinine clearance value. Elderly patients often have reduced renal function. In elderly, there is a risk of falling and fractures due to dizziness, somnolence, loss of consciousness, etc., in elderly.

Other Precautions

It should be noted that Mirogabalin for neuropathic pain is not a casual 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.

Pregnancy

Pregnant women or women who may be pregnant should be given Mirogabalin only when the therapeutic benefit is judged to outweigh the risks.

Nursing Mothers

Considering the therapeutic benefits and the benefits of breastfeeding, consider continuing or discontinuing breastfeeding.

DRUG INTERACTIONS

Drug Name	Clinical Symptoms and Measures	Mechanism and Risk Factors
Probenecid	Coadministration 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	Coadministration 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)	Coadministration may facilitate the decrease in attention and balance function.	This is possibly due to the interactively potentiated inhibitory effect on the central nervous system.

OVERDOSAGE

Symptoms

Symptoms observed at the time of overdose were euphoria, dysphasia, headache, dysphagia, arthritis, joint swelling, and asthenia.

Treatment

In cases of overdose, standard supportive measures should be adopted as required. This drug is removed by hemodialysis 15.3%.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Tarlyca (Mirogabalin) Tablets 2.5mg are available in blister pack of 10's.
Tarlyca (Mirogabalin) Tablets 5mg are available in blister pack of 10's.
Tarlyca (Mirogabalin) Tablets 10mg are available in blister pack of 10's.
Tarlyca (Mirogabalin) Tablets 15mg are available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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