Taiwan Food and Drug Administration

Assessment Report

Trade Name：德力靜® 膜衣錠 15 毫克 /
TARLIGE® F.C. Tablets 15 mg

Active Ingredient：Mirogabalin besilate

License Number：MOHW-PI 027803

Applicant：台灣第一三共股份有限公司

Approval Date：2020/05/06

Indication：1. Diabetic peripheral neuropathic pain.
糖尿病周邊神經病變引起的神經性疼痛
2. Postherpetic neuralgia.
帶狀疱疹後神經痛

1. Background Information

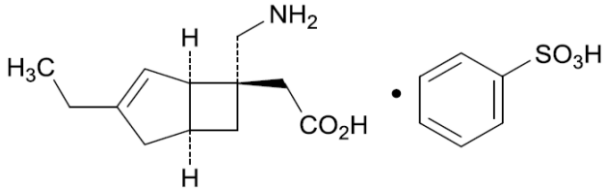
Trade Name	德力靜® 膜衣錠 15 毫克 TARLIGE® F.C. Tablets 15 mg
Active Ingredient(s)	Mirogabalin besilate
Applicant	台灣第一三共股份有限公司
Dosage Form & Strengths	Tablets 15 mg
Indication	1. Diabetic peripheral neuropathic pain. 糖尿病周邊神經病變引起的神經性疼痛 2. Postherpetic neuralgia. 帶狀疱疹後神經痛
Posology	成人的初始口服劑量為 5mg 每日兩次，接著以至少一週的時間將劑量逐漸調升至 10mg 每日兩次。接著可根據個別病人反應和耐受性，再以至少一週的時間將劑量最高調升至 15mg 每日兩次。 The initial oral dose for adults is 5 mg twice daily, and then gradually increases to 10 mg twice daily with an interval of at least 1 week. Based on individual patient response and tolerability, the dose can be increased up to the maximum dose of 15 mg twice daily with an interval of at least 1 week.
Pharmacological Category **ATC Code**	N02BG11 (temporary codes)

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, mirogabalin besilate, is chemically designated as [(1*R*,5*S*,6*S*)-6-(aminomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl]acetic acid monobenzenesulfonate. It has the following structure:



Mirogabalin besilate is a white to pale yellowish-white powder. The molecular formula and the molecular weight are $C_{12}H_{19}NO_2 \cdot C_6H_6O_3S$ and 367.46, respectively. It is non-hygroscopic.

Adequate information of characterization of the drug substance has been provided.

The structure of mirogabalin besilate is confirmed by elemental analysis, IR spectrum, UV spectrum, nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR), mass spectrum, and X-ray crystallography.

The specification of the drug substance includes tests for appearance, identification, impurities, residue on ignition, and assay.

2.1.2 Drug product

Mirogabalin tablets (TARLIGE®) is presented as a film-coated tablets containing 2.5 mg, 5 mg, 10 mg and 15 mg of mirogabalin as mirogabalin besilate and packaged in aluminum blisters. The excipients used in the drug product formulation are well known pharmaceutical ingredients and their quality is compliant with the compendial monographs. A robust process is confirmed by adequate process validation.

Adequate specifications have been presented for the drug product and the test items include description, identification, related substances, uniformity of dosage units, dissolution, and assay. Analytical methods are described well and validated. Stability studies of drug product under long term (30°C/75% RH) and accelerated (40°C/75% RH) condition have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Mirogabalin is a potent and specific ligand of the α2δ subunit of voltage-dependent Ca^{2+} channels. Pharmacology studies demonstrated that mirogabalin inhibited the calcium channel currents of the cultured rat DRG neurons. Mirogabalin had a longer dissociation half-life from α2δ-1 than α2δ-2, in contrast to pregabalin. The binding profile of mirogabalin may contribute to more potent and sustained analgesic effects through α2δ-1 and less central nervous system (CNS) related adverse events through α2δ-2 in comparison with pregabalin. Mirogabalin besylate showed analgesic effects in all the experimental pain models including neuropathic pain models and fibromyalgia models. Mirogabalin besylate inhibited motor coordination at ≥10 mg/kg, induced the CNS depressant symptoms and inhibited spontaneous locomotor activity at ≥30 mg/kg in rats. These changes were considered to be associated with exaggerated pharmacological action of mirogabalin besylate on the CNS. Mirogabalin besylate did not affect the Human Ether-a-go-go Related Gene (hERG) current at up to 300 μM. However, a slight shortening of the Action Potential Duration (APD) was seen at 30 μM *in vitro*, and a decrease in blood pressure was observed at 2000 mg/kg in monkeys. The risk of QT prolongation is considered low. There were no effects on the respiratory in cynomolgus monkeys at up to 2000 mg/kg.

2.2.2 Toxicological Studies

Repeated-dose toxicity studies were conducted in rat and monkey up to 26-week and 39-week, respectively. In both species, the dose-limiting toxicity was considered to be abnormal clinical signs associated with CNS depression, resulting from exaggerated pharmacological action. In the higher dose levels, target organs were the stomach, heart, and kidney in rats and the stomach and heart in monkeys, respectively. Histopathological changes in the squamous epithelium of the stomach have been reported for other drugs or chemicals that irritate the stomach lining. The findings in the stomach were possibly considered due to local irritation of besylate. Mirogabalin besylate is not mutagenic *in vitro* or *in vivo*. No treatment-related tumors or proliferative lesions were noted in a 2-year mice carcinogenicity study up to 100 mg/kg/day. In rats, a statistically significant increase in the incidence of transitional cell papilloma in the urinary bladder was noted in males receiving 100 mg/kg/day with low incidence (3/60 male only). However, neither cytotoxicity nor proliferative activity in the urinary bladder urothelium was noted in the mechanistic studies for urinary bladder tumors in male rats. The finding of urinary bladder tumors was not considered to reflect a relevant risk to humans. Persistent proestrus and estrus were noted in rat fertility and early embryonic development (FEED) study at 100 mg/kg/day. Mirogabalin besylate did not show any evidence of teratogenic potential in rats or rabbits. In the rat pre-and postnatal development (PPND) study, prolongation of the pregnancy period was noted at 100 mg/kg/day. A low live birth index was noted in the F_1 animals at ≥30 mg/kg/day. Therefore, mirogabalin may only be used if the expected therapeutic benefits outweigh the possible risks associated with treatment.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The recommend initial dose of mirogabalin is 5 mg BID taken orally for adult patients and then increases the dose gradually to 10 mg BID over at least 1 week. The dose may then be increased up to 15 mg BID, based on individual patient response and tolerability.

The dose exposure of mirogabalin was approximately increased in dose proportional manner at the dose range 3 mg to 75 mg. Following the administration of mirogabalin at multiple oral doses of 10 and 15 mg BID in Japanese healthy subjects for 7 days, steady state was reached by Day 3, with $t_{1/2}$ of 2.43 hours for 10 mg dose and 2.83 hours for 15 mg dose on Day 7. For 10 mg dose, mean±SD mirogabalin for $C_{max,ss}$ was 210±39.4 ng/mL and $AUC_{tau,ss}$ was 601±63.68 ng•h/mL. For 15 mg dose, $C_{max,ss}$ was 381±88 ng/mL and $AUC_{tau,ss}$ was 1057±142.2 ng•h/mL. The PK parameters were no significant difference between healthy subject and target population.

The AUC of mirogabalin was similar (reduced 6%) and the C_{max} was reduced by 18% after oral administration to healthy subjects taken with a high-fat meal compared to the fasted state.

The apparent volume of distribution (V_z/F) of mirogabalin was 78 to 88 L in healthy non-Japanese subjects following oral 3 to 30 mg. The protein binding rate was 23.4% to 25.5% at plasma concentrations of 0.1 μg/ml to 10 μg/ml and blood to plasma ratio was about 0.85 to 0.87.

Mirogabalin was metabolized by UGT. Following the administration of ^{14}C-mirogabalin at a single oral dose of 30 mg (150 μCi) in healthy male adults, a cumulative excretion rate of radioactivity up to 168 hours post-dose was ≥98%; radioactivity recovered in urine and feces was approximately 97% (76% as unchanged mirogabalin) and 1% , respectively.

2.3.2 Interaction Studies

Mirogabalin is OAT1, OAT3, OCT2, MATE1, MATE2-K and UGT substrate. Mirogabalin did not inhibit or induce major human CYP molecular species, and did not inhibit activities of drug transporters (including OAT1, OAT3, organic cation transporter [OCT] 1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp and BCRP).

Co-administrated with OAT1, OAT3, OCT2, MATE1, MATE2-K or UGT inhibitor may increase mirogabalin exposure, so used with caution.

2.3.3 Special Populations

Age (adult and elderly) did not significantly affect the PK of mirogabalin based on the Study A-U104.

Following oral administration of a single 5 mg dose of mirogabalin in subjects with different grade of renal impairment, mirogabalin AUC_t was approximately 1.33-fold, 1.90-fold, 3.64-fold and 5.25-fold in subjects with mild, moderate, severe renal impairment and end stage renal disease (ESRD), respectively, relative to healthy controls. C_{max} increased with increasing severity of renal impairment, the degree of increase was less than that of AUC_t. 15.3% of dosed mirogabalin was removed from blood during 4-hour hemodialysis in ESRD patients. No dose adjustment is recommended in mild renal impairment. Reduce the 50% dose in moderate renal impairment. Reduce the 75% dose in severe renal impairment and ESRD patient.

C_{max} was approximately 1.04-, and 0.85-fold and AUC_{inf} was approximately 0.88-, and 1.10-fold in subjects with mild and moderate hepatic impairment, respectively, relative to healthy controls after single oral 15 mg. No dose adjustment is recommended in mild or moderate hepatic impairment. No PK data of mirogabalin are available for severe hepatic impairment subject.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The sponsor provided two phase III studies targeting the two representative populations of peripheral neuropathic pain: “diabetic peripheral neuropathic pain (DPNP)”and “postherpetic neuralgia (PHN)”. Both studies were conducted in Asia.

Study J303 was for DPNP patients, and study J304 was for PHN patients. These two studies were multinational, randomized, double-blind, placebo-controlled, parallel-group studies. Study J303 enrolled adult subjects with type 1 or 2 diabetes mellitus (DM), and study J304 enrolled subjects with pain more than 3 months after herpes zoster skin rash. Subjects must have visual analog scale (VAS) pain ≥ 40 mmin Short-Form McGill Pain Questionnaire (SF-MPQ), and average daily pain score (ADPS) ≥ 4 over past 7 days on the 11-point numerical rating scale (NRS) to be enrolled in both studies. Eligible subjects were randomized (2:1:1:1) to placebo or one of 3 different doses of mirogabalin: 15 mg QD group, 10 mg BID group, or 15 mg BID group. The double blinded treatment period was 14 weeks, including a 1-2 weeks titration period. Subjects who completed administration in the 14-week double-blind phase entered the long term 52-week extension phase with flexible mirogabalin 10 or 15 mg BID.

The primary efficacy endpoint was change in ADPS from baseline to Week 14 using 11-point point NRS. Multiple test procedures were applied as: first tested 10 mg BID group and the 15 mg BID group against placebo (significance level 0.025 respectively), and then 15 mg QD group if any or both the BID group were statistically significant.

There were 834 subjects randomized in study J303, and 765 subjects randomized in study J304. In general, subject demographics and baseline characteristics were balanced among the treatment groups. All the subjects were Asian.

Study J303 in subjects with DPNP showed that 15 mg BID group was superior to placebo group in the primary endpoint of change from baseline in ADPS at Week 14 (imputed LS mean change (SE): -1.81 (0.136) vs. -1.31 (0.095); difference (95% CI): -0.50 (-0.82, -0.17); p-value = 0.0027). The other two doses did not demonstrate statistical significance in the primary endpoint (10 mg BID and 15 mg QD, respectively; imputed LS mean change (SE): -1.47 (0.135) and -1.34 (0.136); difference vs. placebo (95% CI): -0.15 (-0.48, 0.17) and -0.03 (-0.35, 0.30); p-value=0.3494 and 0.8773).

Study J304 in subjects with PHN showed that all three dose groups each was superior to placebo group in the primary endpoint of change from baseline in ADPS at Week 14(15 mg BID, 10 mg BID, and 15 mg QD vs. placebo, respectively; imputed LS mean change (SE): -1.97 (0.137), -1.68 (0.141), and -1.61 (0.138) vs. -1.20 (0.099); difference (95% CI): -0.77 (-1.10, -0.44), -0.47 (-0.81, -0.14), and -0.41

(-0.74, -0.07); p-value: <0.0001, =0.0058, and =0.0170).

In both studies, dose-response relationship was noted. In the long-term study phase, the treatment effect was evaluated by SF-MPQ VAS score at week 66, and it showed maintenance of treatment effect after long term treatment.

2.4.2 Safety Results

In two phase III studies, the most common treatment-emergent adverse events (TEAEs) for mirogabalin treatment were nasopharyngitis, somnolence, dizziness, oedema peripheral and weight increased.The incidence of TEAE was highest in the 15 mg BID group than placebo (73-78% vs. 52-61%).The mirogabalin groups showed higher incidence of TEAE leading to discontinuation compared with the placebo group, and the incidence increased with dosing. The highest discontinuation rate was in the pooled mirogabalin 15 mg BID group (8.8%) versus 3.9% in the pooled placebo group during the double-blind phase. TEAEs to discontinuation were of diverse causes. The most common causes of discontinuation were dizziness, somnolence and oedema peripheral.

In two phase III studies, there were a total of 4 death-TEAEs in mirogabalin groups, and all in the mirogabalin groups. Among these events, there was one drowning event to death (15 mg BID group in the long term phase) reported as “study drug-related” by the investigator. Other 3 deaths were drowing, complete suicide, and death, but all these events were judged as not related to study drug. The incidence was very low and was consistent with the known risk of antiepileptic drugs (AEDs), including the gabapentinoids.

CNS side effects (dizziness, somnolence) were significant in the phase III studies. Around 13% subjects had TEAEs of dizziness and 19% subjects had TEAEs of somnolence in the mirogabalin 15 mg BID group. However, there were only 0.9% and 1.9% of subjects discontinued mirogabalin 15 mg BID due to somnolence and dizziness, respectively. The incidence of falls, accidents and injuries was 20.6% in the long term phase of study J303, and 8.4% in the long term phase of study J304. The TEAEs relating to drug abuse were 0.6-8.6% across studies, and all events were feeling abnormal. However, other drug abuse potential studies showed there was no significant difference from mirogabalin under therapeutic dosing range to placebo in drug abuse potential.

2.5 Bridging Study Evaluation

After multiple dosing (15 mg QD, 10 mg BID and 15 mg BID), the mirogabalin $AUC_{tau,ss}$ and $C_{max,ss}$ in Asian targeted population was about 22% and 71% higher than in non-Asian targeted population due to the difference in distribution of baseline body weight between Asian patients and non-Asian patients. The inter-subject

variation of mirogabalin C_{max} or AUC in food effect study was about 17 to 23%.

Although the C_{max} in Asian targeted population was slight higher than in non-Asian "targeted population" after considering the inter-subject variation, this C_{max} difference in 2 ethnic groups did not be observed the significant safety difference in clinical. Therefore, mirogabalin is none to ethnically sensitive from PK aspect. Moreover, most of phase II and phase III trials of mirogabalin were conducted in Asia.

The two phase III pivotal trials (study J303 and J304) were conducted in East Asian. The number of Taiwanese subjects was 98. There was no significant ethnic difference. Since the main evidence of efficacy and safety were came from Asian study, the bridging study could be waived.

2.6 Conclusion

Generally, the overall benefit-risk assessment of mirogabalin was favorable for DPNP and PHN. Based on the evidences from the clinical trials, CDE suggests approving mirogabalin for the treatment of “diabetic peripheral neuropathic pain” and “postherpetic neuralgia”

3. Post-Marketing Requirements

No special post-marketing requirement.