Taiwan Food and Drug Administration

Assessment Report

Trade Name : 適秘效膜衣錠 0.2 毫克/ **Symproic Tablets 0.2mg**

Active Ingredient : Naldemedine tosylate

License Number : MOHW-PI 028189

Applicant :台灣塩野義製藥股份有限公司

Approval Date : 2021.10.25

Indication :

治療成人因鴉片類藥物引起之便秘 **(Opioid-induced constipation, OIC)**。

Treatment of Opioid-induced constipation (OIC) in adult patients.

1. Background Information

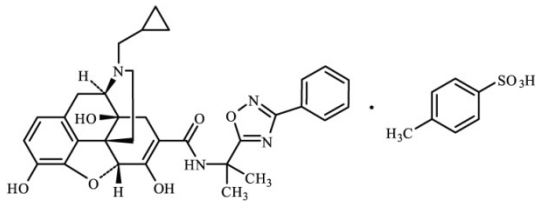
Trade Name	適秘效膜衣錠 0.2 毫克/ Symproic Tablets 0.2mg
Active Ingredient(s)	Naldemedine tosylate
Applicant	台灣塩野義製藥股份有限公司
Dosage Form & Strengths	膜衣錠 0.2mg
Indication	治療成人因鴉片類藥物引起之便秘 (Opioid-induced constipation, OIC)。 Treatment of Opioid-induced constipation (OIC) in adult patients
Posology	詳見仿單
Pharmacological Category **ATC Code**	A06AH05

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, naldemedine tosylate, is chemically designed as 17-(Cyclopropylmethyl)-6,7-didehydro-4,5-epoxy-3,6,14-trihydroxy-N-[2-(3-phenyl-1,2,4-oxadiazol-5-yl) propan-2-yl]morphinan-7-carboxamide 4-methylbenzenesulfonic acid. The molecular formula and the relative molecular mass for naldemedine tosylate are $C_{32}H_{34}N_4O_6 \bullet C_7H_8O_3S$ and 742.84 g/mol, respectively. The chemical structure of naldemedine tosylate is shown below:



It is white to light tan powder. The structure of naldemedine tosylate is confirmed by elemental analysis, IR spectrum, ^{1}H-NMR, ^{13}C-NMR, UV spectrum and mass spectrum. The specification for the drug substance includes tests for description, identity, related substances, residual solvents, water content, residue on ignition, assay and particle size.

2.1.2 Drug Product

The drug product is supplied for oral use as yellow round shaped film-coated tablets containing 0.2mg of naldemedine (equivalent to 0.2604 mg of naldemedine tosylate). All excipients are well known ingredients and suitable for proposed formulation. The specification for the drug product includes description, identity, assay, related substances, water content, uniformity of dosage units and dissolution. Analytical methods were described well and validated. Stability

studies of drug product under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2. Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Naldemedine tosylate is a peripherally-acting μ-opioid receptor antagonist (PAMORA) developed to treat opioid-induced constipation (OIC) in adult patients. Pharmacology data demonstrated that naldemedine acts as a potent μ-opioid receptor antagonist and has potent anti-constipation effects shown as suppressing the opioid-induced inhibition of small intestinal transit. Safety pharmacology studies indicated that naldemedine had no effects on the CNS, cardiovascular and respiratory systems.

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies included a 6-month study in rats and a 9-month study in dogs. The most overt toxicity finding of naldemedine was slight single cell necrosis in hepatocytes with the elevation of ALT and/or ALP activity in dogs, and another main toxicity finding was the suppression of body weight gain in rats. Naldemedine did not present a genotoxic hazard to humans. In addition, two carcinogenicity studies did not evidence any neoplastic induction with maximum tolerated doses achieved.

Reproductive and developmental studies indicated that naldemedine had no teratogenicity potential. However, an abortion, premature delivery, and decreased bodyweight associated with low maternal food consumption were noted in dams receiving naldemedine, and low viability and growth retardation in pups were noted at the dose, which showed maternal toxicity. Naldemedine did not show any primary irritancy to the skin in the rabbit dermal irritation study. Naldemedine showed slight primary irritation potential to the eye in the rabbit ocular irritation study, but it disappeared by washing.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following oral administration, naldemedine is absorbed with the time to achieve peak concentrations (T_{max}) of approximately 0.75 hours in a fasted state. Across the range of doses evaluated, the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in a dose-proportional or almost dose-proportional manner.
Accumulation was minimal following multiple daily doses of naldemedine.

A high-fat meal decreased the rate, but not the extent of naldemedine absorption. The Cmax was decreased by approximately 35% and time to achieve Cmax was delayed from 0.75 hours in the fasted state to 2.5 hours in the fed state, whereas there was no meaningful change in the AUC

in the fed state.

Plasma protein binding of naldemedine in humans is 93% to 94%. The mean apparent volume of distribution during the terminal phase (Vz/F) is 155 L. The terminal elimination half-life of naldemedine is 11 hours.

Naldemedine is primarily metabolized by CYP3A to nor-naldemedine, with minor contribution from UGT1A3 to form naldemedine 3-G. Nor-naldemedine and naldemedine 3-G have been shown to have antagonistic activity for opioid receptors, with less potent effect than naldemedine. Following oral administration of [^{14}C]-labeled naldemedine, the primary metabolite in plasma was nor-naldemedine, with a relative exposure compared to naldemedine of approximately 9% to 13%. Naldemedine 3-G was a minor metabolite in plasma, with a relative exposure to naldemedine of less than 3%. Naldemedine also undergoes cleavage in the GI tract to form benzamidine and naldemedine carboxylic acid.

Following oral administration of [^{14}C]-labeled naldemedine, the total amount of radioactivity excreted in the urine and feces was 57% and 35% of the administered dose of naldemedine, respectively. The amount of naldemedine excreted unchanged in the urine was approximately 16% to 18% of the administered dose. Benzamidine was the most predominant metabolite excreted in the urine and feces, representing approximately 32% and 20% of the administered dose of naldemedine, respectively. The percentage of unchanged drug in feces has not been estimated.

2.3.2 Interaction Studies

In in vitro studies at clinically relevant concentrations, naldemedine did not inhibit the major CYP enzymes (including CYP1A2, CYP2A6, CYP2B6, CYP2C& CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A11 isozymes) and is not an inhibitor of transporters (including OATP1B1, OATP1B3, OCTI, OCT2, OAT1, OAT3, BCRP, or P-gp). Naldemedine did not cause significant induction of CYP1A2, CYP2B6, CYP3A4, UGT1A2, UGT1A6, or UGT2B7 isozymes.

Naldemedine is primarily metabolized by CYP3A4 enzyme with minor contribution from UGT1A3. Naldemedine is a substrate of P-gp. Concomitant use of itraconazole, a strong CYP3A inhibitor, increased exposure to naldemedine 2.9 fold that may result in an increased risk of adverse reactions. Concomitant use of moderate CYP3A inhibitors such as fluconazole, may increase the plasma concentration of naldemedine. Concomitant use of rifampicin, a strong CYP3 A inducer, significantly decreased exposure to naldemedine by 83%. Concomitant use of P-gp inhibitors such as cyclosporine may increase plasma concentrations of naldemedine.

2.3.3 Special Populations

A population pharmacokinetic analysis from clinical studies with naldemedine did not identify a clinically meaningful effect of age, sex, or race on the pharmacokinetics of naldemedine.

The pharmacokinetics of naldemedine after administration of a 0.2 mg single oral dose of naldemedine was studied in 8 subjects with mild (n=8, estimated glomerular filtration rate [eGFR] of 60 to 89 mL/min/1.73 m^2), moderate (n=8, eGFR 30 to 59 mL/min/1.73 m^2), and severe (n=6, eGFR less than 30 mL/min/1.73 m^2) renal impairment, and subjects with end-stage renal disease (ESRD) requiring hemodialysis (n=8), and compared to healthy subjects with normal renal function (n=8, estimated creatinine clearance of at least 90 mL/min). The pharmacokinetics of naldemedine between subjects in all groups were similar. Plasma concentrations of naldemedine in subjects with ESRD requiring hemodialysis were similar when naldemedine was administered either pre-or post-hemodialysis, indicating that naldemedine was not removed from the blood by hemodialysis.

The effect of hepatic impairment on the pharmacokinetics of a 0.2 mg single oral dose of naldemedine was studied in subjects with hepatic impairment classified as mild (n=8, Child-Pugh Class A) or moderate (n=8, Child-Pugh Class B) and compared with healthy subjects with normal hepatic function (n=8). The pharmacokinetics of naldemedine between subjects in all groups were similar. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine was not evaluated.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 0Efficacy Results

The Sponsor provided four Phase III studies (1314V9231, 1315V9232, 1326V9235 and 1331V9236) to support the efficacy of Symproic (naldemedine tosylate) for the claimed indication. The efficacy findings for this study are summarized below.

- ***Studies[1314V9231] and [1315V9232]:***

Studies [1314V9231] and [1315V9232] were identically in design. Both were Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of naldemedine 0.2 mg QD versus placebo in subjects with opioid-induced constipation (OIC) and non-malignant chronic pain receiving opioid therapy.

The primary efficacy endpoint was the proportion of responders, where a responder was defined as having $\geqq$ 9 positive-response weeks out of the 12-week treatment period and 3 positive-response weeks out of the last 4 weeks of the 12-week treatment period.

A positive-response week was defined as $\geqq$ 3 spontaneous bowel movements (SBMs) per week

and an increase from baseline of ≧ 1 SBM per week for that week. Moreover, if a subject had <4 days of eDiary entries related to defecation for a week, that week was considered non-evaluable and was treated as a "non-response" week. The frequency of SBMs per week in a specific week was defined as follows:

Frequency of SBMs per week = (total number of SBMs in the week) X 7 / (number of days of observation related to defecation in the week)

Study 1314V9231 and 1315V9232 enrolled 1959 non-cancer OIC patients (1100 subjects were randomized). The median daily dose of opioid at baseline was 80mg/day and 82.5mg/day in naldemedine and placebo arm.

The difference between the treatment groups in the proportion of SBM responders was statistically significant in both studies: 13.0% (naldemedine 47.6%, placebo 34.6%; P = 0.0020) in Study V9231 and 18.9% (naldemedine 52.5%, placebo 33.6%; P <0.0001) in Study V9232.

Results of all 4 secondary efficacy endpoints were consistent with the outcome of the primary endpoint. A greater change in the frequency of SBMs/week from baseline to the last 2 weeks of the treatment period was observed in the naldemedine group relative to the placebo group and the difference between treatment groups was statistically significant (Study V9231: 3.42 vs. 2.12, respectively, between-group difference of 1.30 SBMs/week [P < 0.0001]; Study V9232: 3.56 vs. 2.16, respectively, between-group difference of 1.40 SBMs/week [P < 0.0001]).

A greater change in the frequency of SBMs/week from baseline to Week 1 of the treatment period was observed in the naldemedine group relative to the placebo group and the difference between treatment groups was statistically significant (Study V9231: 3.48 vs. 1.36, respectively, between-group difference of 2.11 SBMs/week [P < 0.0001]; Study V9232: 3.86 vs. 1.69, respectively, between-group difference of 2.17 SBMs/week [P < 0.0001]).

A significantly greater change in the frequency of complete spontaneous bowel movements (CSBMs)/week from baseline to the last 2 weeks of the treatment period was observed in the naldemedine group relative to the placebo group and the difference between treatment groups was statistically significant (Study V9231: 2.58 vs. 1.57, respectively, between-group difference of 1.01 CSBMs/week [P < 0.0001]; Study V9232: 2.77 vs. 1.62, respectively, between-group difference of 1.15 CSBMs/week [P < 0.0001]).

A significantly greater change in the frequency of SBMs without straining/week from baseline to the last 2 weeks of the treatment period was observed in the naldemedine group relative to the placebo group and the difference between treatment groups was statistically significant (Study V9231: 1.46 vs. 0.73, respectively, between-group difference of 0.73 SBMs without straining/week [P = 0.0003]; Study V9232: 1.85 vs. 1.10; respectively, between-group

difference of 0.75 SBMs without straining/week [P = 0.0011]).

- A Study[*1331V9236*]:

This was a Phase 3, randomized, double-blind, placebo-controlled, 2-week, parallel-group study in which 190 cancer patients with OIC were to be enrolled.

Study 1331V9236 enrolled 193 cancer OIC patients receiving study treatments. The median total daily dose of opioid at baseline was 46.5mg/day and 35mg/day in naldemedine and placebo arm. The primary efficacy endpoint was the proportion of SBM responders during the 2-week treatment period. An SBM responder was defined as a patient having≥ 3 SBMs per week and an increase of ≥ 1 SBM per week from baseline.

The proportions of SBM responders during the treatment period were 71.1% for the naldemedine group and 34.4% for the placebo group. The difference between the groups was 36.76% (95% CI: 23.66%, 49.86%) and was statistically significant (P < 0.0001).

- Study[1326V9235]:

This is a Phase 3, multi-center, randomized double-blind, placebo-controlled, parallel-group study designed to evaluate the long -term safety of naldemedine and placebo for the treatment of OIC in subjects with non-malignant chronic pain receiving opioid therapy. The treatment duration was 52 weeks.

The differences between groups in the frequency of BMs per week from baseline to each assessed time point were statistically significant (nominal p≤0.0002 at Visits 6, 8 and 10; nominal p=0.0214 at Visit 13).

The differences between groups in the mean change in the overall score for patient-assessment of constipation symptoms (PAC-SYM) from baseline were statistically significant at all assessed time points (nominal p≤0.0005).

2.4.2 Safety Results

Across the naldemedine Phase 2 and Phase 3 clinical development program, 1644 subjects with OIC were exposed to daily doses of naldemedine ≥ 0.2 mg, 1364 subjects with chronic non-cancer pain and OIC and 280 with cancer and OIC.

The most common AEs among cancer OIC patients were decreased appetite, diarrhea, nausea, vomiting, and protein urine. For non-cancer OIC patients, most AEs belonged to the SOC of GI disorders. The incidence of AEs leading to discontinuation was low among cancer or non-cancer OIC patients. The majority of AEs leading to discontinuation were mild to moderate in severity, and most events resolved after treatment discontinuation. The incidence

of SAEs were also low across studies. During the naldemedine clinical program, there were 39 subjects who died. None were considered by the investigators to be related to study treatment.

There was no case of GI perforation. The incidence of MACE was very low and was comparable between treatment groups. In non-cancer OIC studies, slightly higher proportion of subjects with opioid withdrawal (0.9% vs. 0.5%) or possible opioid withdraw (1.2% vs. 0.3%) were noted for naldemedine-treated patients. Most opioid withdraw events occurred in the first 12 weeks of treatment. In cancer OIC studies, the sample size and treatment duration were too limited to observe opioid withdraw events. For laboratory evaluations, there were no specific findings in hematology, clinical chemistry or urinalysis.

2.5 Bridging Study Evaluation

A comparison of naldemedine phannacokinetics at doses ranging from 0.1 to 2 mg in the fasted state was conducted between Japanese healthy subjects and US healthy subjects. The geometric mean Cmax and AUC values for healthy Japanese and US subjects were consistent at approximately 3 ng/mL and 20 ng hr/mL, respectively, indicating a similar pharmacokinetic profile regardless of the study or ethnic background of the study population when adjusted to 0.2 mg dose. Population pharmacokinetic analysis of naldemedine also showed that there were not statistically significant pharmacokinetic differences between Japanese and non-Japanese.
Overall, there were no clinically meaningful differences in naldemedine pharmacokinetics observed between Japanese and White subjects.

There were two studies conducted in Asian, study V9222 and V9236. Both studies were conducted in patients with cancer OIC from Japan and Korea. There were 227 subjects received randomization in Study V9222, and 193 subjects received randomization in study V9236. The primary endpoint in study V9236 and the key secondary endpoint in study V9222 were SBM responder rate, which was defined as ≥3 SBMs per week and increase in the frequency of SBMs from baseline of ≥1/week.

In study V9222, the SBM responder rate was higher in the 0.2 mg group than the placebo group (77.6% vs. 37.5%, $p < 0.0001$). In study V9236, the SBM responder rate was higher in the 0.2 mg group than the placebo group (71.1% vs. 34.4%, $p < 0.0001$).

In these two Asian studies, the most frequently reported TEAEs occurred more frequently with naldemedine 0.2 mg compared with placebo were diarrhea and decreased appetite. There were very few cases with SAEs and all death was not related to naldemedine treatment.

Generally, the efficacy and safety of naldemedine for Asian patients with cancer OIC was acceptable. Further bridging study could be waived.

2.6 Conclusion

CDE suggests to approve Symproic tablets (naldemedine) for the treatment of opioid-induced constipation (OIC) in adult patients.

3. Post-Marketing Requirements

The sponsor should provide post-authorization safety cohort study after its completion to assess the incidence risk of MACE and GI perforation.