Taiwan Food and Drug Administration

Assessment Report

Trade Name：達衛眠錠 5 毫克 / Dayvigo Tablets 5 mg

達衛眠錠 10 毫克 / Dayvigo Tablets 10 mg

Active Ingredient：Lemborexant

License Number：MOHW-PI 028145

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Applicant：衛采製藥股份有限公司

Approval Date：2021/08/10

Indication：失眠症

Indicated for the treatment of insomnia

1. Background Information

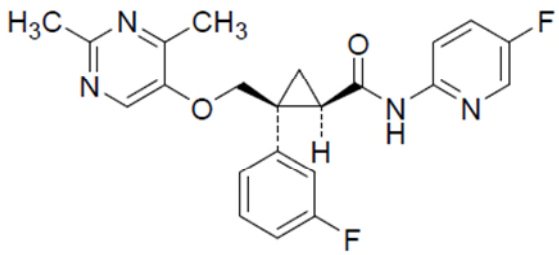
Trade Name	達衛眠錠 5 毫克 / Dayvigo Tablets 5 mg 達衛眠錠 10 毫克 / Dayvigo Tablets 10 mg
Active Ingredient(s)	Lemborexant
Applicant	衛采製藥股份有限公司
Dosage Form & Strengths	膜衣錠 5 mg, 10 mg
Indication	失眠症 Indicated for the treatment of insomnia.
Posology	詳見仿單
Pharmacological Category **ATC Code**	N05CM21

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, lemborexant, is chemically designated as (1*R*,2*S*)-2-{[(2,4-Dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-*N*-(5-fluoropyridin-2-yl) cyclopropanecarboxamide and has the following structure:



It is a white to off-white powder. The molecular formula and the molecular weight are $C_{22}H_{20}F_2N_4O_2$ and 410.42 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The structure of lemborexant is confirmed by UV spectrum, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, single-crystal X-ray diffraction, mass spectrometry and elemental analysis. The specification for the drug substance includes tests for appearance, identification, residual solvents, related substances, residue on ignition, water content, assay and microbial limits.

2.1.2 Drug product

The drug product is supplied for oral use as film-coated tablets containing 5 mg and 10 mg of lemborexant. The excipients used in the drug product comply with compendial monographs or in-house.

The specification for the drug product includes appearance, identification, assay, related substances, dissolution, uniformity of dosage units and microbial limits. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (30°C/65% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Lemborexant is a drug for treating insomnia. Lemborexant is a competitive dual antagonist of OX1R and OX2R with a higher affinity for the OX2R. Blocking the binding of wake-promoting neuropeptides orexin to orexin receptors is thought to balance sleep-wake circuitry by suppressing excessive wake drive. The nonclinical pharmacology studies indicated that lemborexant increased non-REM sleep time and total sleep time but not affected REM sleep time and REM sleep ratio. The effect of lemborexant did not rebound, and there were no withdrawal signs after cessation of treatment. In the secondary pharmacodynamics, lemborexant exhibited antagonist activity on human MT1 receptor, promoted emotion-induced cataplexy, had no effects on motor coordination and balance, and did not affect ethanol-induced anesthesia. Although lemborexant and its metabolites exhibited the potential to inhibit the hERG channel and induced QTc prolongation in monkeys, the plasma concentration of inducing QTc prolongation in monkeys was approximately 20-fold higher than the C_{max} of the clinical therapy dose in humans.

2.2.2 Toxicological Studies

The results of pivotal toxicity studies indicated that the target organs of lemborexant included bone (decrease of trabecular bone and mature lamellar bone), teeth (discoloration), and liver (hepatocellular hypertrophy). Lemborexant exhibited no genotoxicity and carcinogenicity. In the reproductive and developmental toxicity, lemborexant might cause irregular estrous cycles by affecting the endocrine system. Lemborexant presented a teratogenic effect in rats at maternally toxic doses but was not teratogenic in rabbits. The *in vitro* study indicated that lemborexant had no phototoxicity.

2.3 Clinical Pharmacology Evaluation

Lemborexant is a dual orexin receptor antagonist (DORA) that competitively antagonizes orexin’s binding to 2 subtypes of orexin receptors (OX1R and OX2R), with a higher affinity for OX2R. The indication of lemborexant is for the treatment of adult patients with insomnia. The recommended dose is 5 mg taken no more than once per night. The maximum recommended dose of lemborexant is 10 mg once daily.

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following single doses of lemborexant 2.5 to 75 mg, geometric mean C_{max} and AUC_{0-24h} increased slightly less than in proportion to dose. The extent of accumulation of lemborexant at steady-state is 1.5- to 3-fold across this dose range. The t_{max} of lemborexant is approximately 1 to 3 hours. Lemborexant C_{max} decreased by 23%, AUC_{0-inf} increased by 18%, and t_{max} was delayed by 2 hours following administration of a high-fat and high-calorie meal.

The volume of distribution of lemborexant is 1970 L. Protein binding of lemborexant is approximately 88% *in vitro*. The blood to plasma concentration ratio of lemborexant is 0.65.

Lemborexant is primarily metabolized by CYP3A4, and to a lesser extent by CYP3A5. The major circulating metabolite is M10.

Following administration of an oral dose, 57.4% of the dose was recovered in the feces and 29.1% in the urine (<1% as unchanged). The effective half-life for lemborexant 5 mg and 10 mg is 17 and 19 hours, respectively.

2.3.2 Interaction Studies

In vitro metabolism studies demonstrated that lemborexant and M10 had the potential to induce CYP3A and the weak potential to inhibit CYP3A and induce CYP2B6. Lemborexant and M10 do not inhibit other CYP isoforms or transporters. Lemborexant is a potential poor substrate of P-gp, but M10 is a substrate of P-gp. Lemborexant and M10 are not substrates of BCRP, OATP1B1, or OATP1B3.

Co-administration of an oral contraceptive containing norethindrone (NE) and ethinyl estradiol (EE) with lemborexant (10 mg) did not affect the C_{max} and AUC of NE or the C_{max} of EE, and increased AUC of EE by 13%. This latter small change is not considered clinically relevant. Clinical studies with substrates of CYP3A or CYP2B6 showed that lemborexant did not induce or inhibit CYP3A. Lemborexant weakly induces CYP2B6.

Using a physiologically based pharmacokinetic (PBPK) model, a weak effect is predicted when weak CYP3A inhibitors (e.g., fluoxetine) are co-administered with lemborexant. Co-administration of moderate (e.g., fluconazole) or strong (e.g., itraconazole) CYP3A inhibitors significantly increased lemborexant exposure. CYP3A inducers (e.g., rifampin) significantly decreased lemborexant exposure.

Lemborexant C_{max} and AUC increased by 35% and 70%, respectively, when co-administered with alcohol. Alcohol should not be consumed with lemborexant. Co-administration of an H_2 blocker (famotidine) with lemborexant decreased C_{max} by 27% and delayed t_{max} by 0.5 hours,

but had no statistically significant effect on overall lemborexant exposure (AUC).

Co-administration of an oral contraceptive containing norethindrone (NE) and ethinyl estradiol (EE) with lemborexant had no statistically significant effect on lemborexant pharmacokinetics.

2.3.3 Special Populations

No clinically significant differences in the pharmacokinetics of lemborexant were observed based on age, sex, race/ethnicity, or body mass index. No studies have been conducted to investigate the pharmacokinetics of lemborexant in pediatric patients.

Severe renal impairment (urinary creatinine clearance ≤30 mL/min/1.73m^2) increased lemborexant exposure (AUC) 1.5-fold but had no effect on C_{max}. No dose adjustment is required in patients with renal impairment.

Lemborexant has not been studied in patients with severe hepatic impairment. Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic insufficiency increased lemborexant AUC and C_{max} by 1.5-fold. Terminal half-life was only increased in patients with moderate hepatic impairment (Child-Pugh class B).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Results of phase II study 201 showed effective dose range of lemborexant from 2.5 mg to 25 mg for the endpoint LPS (latency to persistent sleep).

Results of Study 303 showed the statistically significant improvements in sleep parameters in terms of sSOL (subjective sleep onset latency), sSE (subjective sleep efficiency), and sWASO (subjective wake after sleep onset), which were subjective assessments. Results of Study 304 demonstrated that lemborexant increased the statistically significant improvements in LPS, SE, WASO2H (WASO in the second half of the night), and WASO, which were objective assessments.

In summary, the phase II study and both two Phase III (Studies 303 and 304) studies provided consistent efficacy results with several sensitivity analyses. Therefore, the clinical studies showed enough evidence to support the efficacy of lemborexant as a treatment of insomnia.

2.4.2 Safety Results

Important TEAEs are somnolence, nightmare, next morning cognitive dysfunction and postural instability at middle-of-the-night. In subjects with a history of drug abuse, abuse

liability of lemborexant was observed compared to placebo.

No risk of increased AHI (apnea-hyponea index) was found in mild OSA (obstructive sleep apnea) subjects. However, the risks for moderate and severe OSA are not studied.

No evidence of rebound insomnia was observed.

2.5 Bridging Study Evaluation

Lemborexant exposure (C_{max} and AUC) was comparable between healthy Japanese and White subjects following single and multiple-dose administration. Population PK analysis also suggested that race (Japanese versus Non- Japanese) was not found to be a significant covariate on lemborexant PK. Overall, there was no significant race/ethnicity different in lemborexant PK.

There were 55 East Asian subjects (17.3% out of 318 overall population) in Study 303; the efficacy and safety results of East Asian subgroup was consistent with those of overall population.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. Efficacy of lemborexant 5 mg and 10 mg HS was demonstrated in one phase II and two phase III studies. The safety profile is acceptable, although some residual sedation was observed. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required to ensure that the benefits of the drug outweigh the risks.

Regular approval of Dayvigo for the indication of “insomnia” is recommended.

3. Post-Marketing Requirements

(1) Routine pharmacovigilance