Taiwan Food and Drug Administration

Assessment Report

Trade Name：克巨染膜衣錠 200 毫克 / Livtencity Film-coated tablet 200 mg

Active Ingredient：Maribavir

License Number：MOHW-PI 028492

Applicant：台灣武田藥品工業股份有限公司

Approval Date：2023.06.13

Indication：

適用於治療造血幹細胞或固體器官 (solid organ)移植後發生巨細胞病毒 (cytomegalovirus，CMV)感染或疾病，且對一種或多種先前療法具抗藥性、難治或耐受度不佳的成人病人。

Indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are resistant, refractory or intolerant to one or more prior therapies in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).

1. Background Information

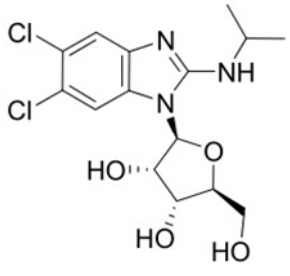
Trade Name	克巨染膜衣錠 200 毫克 / Livtencity Film-coated tablet 200 mg
Active Ingredient(s)	Maribavir
Applicant	台灣武田藥品工業股份有限公司
Dosage Form & Strengths	膜衣錠/ 200 mg
Indication	適用於治療造血幹細胞或固體器官 (solid organ)移植後發生巨細胞病毒(cytomegalovirus，CMV)感染或疾病，且對一種或多種先前療法具抗藥性、難治或耐受度不佳的成人病人。 Indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are resistant, refractory or intolerant to one or more prior therapies in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).
Posology	LIVTENCITY 的建議劑量為 400 mg (兩顆 200 mg 錠劑)，一天兩次，因此每日劑量為 800 mg，為期 8 週。需依據每位病人的臨床特性個別化治療時間長度。
Pharmacological Category ATC Code	J05AX10

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance, maribavir, is chemically designated as 5,6-dichloro-*N*-(1-methylethyl)-1-β-L-ribofuranosyl-1*H*-benzimidazol-2-amine and has the following structure:



It is a white to off-white solid. The molecular formula and the molecular weight are

$C_{15}H_{19}Cl_2N_3O_4$ and 376.24 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of maribavir has been confirmed by elemental analysis, infrared spectrophotometry (IR), nuclear magnetic resonance (NMR), mass spectrometry (MS) and UV spectrophotometry. Stereochemistry is determined by single crystal X-ray diffraction analysis.

Adequate specification has been presented for the drug substance and the test items include appearance, identification, solid form, water content, sulphated ash, residual solvents, residual benzene, related substances, assay, particle size distribution and microbiological examination. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug Product

The drug product is provided as an immediate release tablets for oral administration. Each tablet contains 200 mg maribavir. The specifications for excipients used in the drug product formulation are adequate.

Adequate specification has been presented for the drug product and the test items include appearance, identification, uniformity of dosage units, dissolution, related substances, assay and microbiological examination. Batch analysis data from representative batches of the drug product are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of the drug product under long term conditions (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 36 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of drug product can be granted for 36 months under the storage condition up to 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Maribavir, an oral inhibitor of the UL97 protein kinase, effectively blocks CMV DNA replication and maturation, CMV DNA encapsidation, and CMV DNA nuclear egress. It selectively inhibits HCMV replication in vitro at noncytotoxic submicromolar concentrations with a mean EC_{50} of 0.11 μM. It has high selectivity for HCMV with no significant variance in baseline EC_{50} values across HCMV glycoprotein B genotypes. When combined with other antiviral compounds in vitro, maribavir shows additive interactions with letermovir, foscarnet,

cidofovir, and GW275175X against wild type and mutant HCMV, strong antagonism with ganciclovir, and strong synergy with the mTOR inhibitor rapamycin (sirolimus).

Identified mutations on the UL97 gene including L337M, F342Y, V353A, L397R, T409M, H411L/N/Y, and C480F confer resistance to maribavir, increasing EC_{50} values by 3.5- to >200-fold. UL27 gene variants have been identified in vitro to result in a <5-fold increase in EC_{50}. Cross-resistance between maribavir and ganciclovir/valganciclovir has been observed. Certain pUL97 substitutions reduced susceptibility to maribavir, but pUL54 DNA polymerase substitutions remained susceptible. Two pUL97 substitutions showing maribavir resistance potentially affect ganciclovir resistance, but their clinical impact is unknown. Maribavir-resistant viruses remain susceptible to cidofovir and foscarnet. pUL27 maribavir resistance-associated substitutions aren't expected to show cross-resistance with other drugs.

Maribavir did not inhibit the hERG channel in vitro up to 1,500 μg/mL, offering a safety margin over 4000-fold the clinical C_{max}. In anesthetized dogs, transient increases in heart and respiratory rates were observed at certain doses, but no changes were seen in monkey electrocardiograms. A thorough QT interval study showed no significant repolarization effect of maribavir at single oral doses in healthy humans.

2.2.2 Toxicological Studies

Maribavir's acute toxicity was tested in mice and rats. Mortality occurred in mice at doses ≥500 mg/kg and ≥1,000 mg/kg in rats. Mice showed signs like prostration, convulsions, vocalization, gasping, and ataxia at high doses. Rats exhibited salivation, reduced activity, labored breathing, tremors, prostration, and soft feces. Maribavir's repeated-dose toxicology was assessed in studies up to 13 weeks in mice, 26 weeks in rats, and 52 weeks in monkeys. Mortality was observed in mice at doses ≥300 mg/kg/day and in rats at 400 mg/kg/day. Some monkeys had to be euthanized at high doses in the 52-week study. The major findings were regenerative anemia and gastrointestinal effects, including soft to liquid stool and dehydration, which were reversible or progressed toward recovery after stopping dosing. These toxicities were present across all pivotal rat studies but absent in a 30-day monkey study. These key toxicities are monitorable clinically and were reversible upon treatment discontinuation. Exposures at the NOAEL/LOAEL in these studies were less than human exposures at the recommended dose. In clinical trials, maribavir was associated with mild to moderate dysgeusia, nausea, and diarrhea, reflecting the main toxicities observed in nonclinical species.

Maribavir showed no mutagenesis in vitro or clastogenicity in vivo in rats but indicated weak clastogenic potential in mouse lymphoma assays in vitro without metabolic activation and the results were equivocal in the presence of metabolic activation (not concentration-dependent

and not reproduced in the repeat assay). Despite this, given its negative in vivo and bacterial mutation results, maribavir's genotoxic potential seems unlikely. Two-year carcinogenicity studies in mice and rats showed no carcinogenic effects in rats, and only male mice at high doses exhibited an increased incidence of hemangiosarcoma at exposures less than human ones at the recommended dose. No carcinogenic findings were found in male mice at lower doses or in female mice.

In a combined fertility and embryofetal development study in male and female rats, decreased viable fetuses, increased early resorptions, and post-implantation losses were observed at ≥100 mg/kg/day. Reduced body weight gain was seen in pregnant animals at ≥200 mg/kg/day. Although decreased sperm velocity was noticed, there were no effects on fertility. Maribavir did not affect embryo-fetal growth or development in rats at doses up to 400 mg/kg/day, similar to recommended human dose (RHD) exposures. No drug-related effects were observed on embryo-fetal growth or development in rabbits at exposures less than human ones at RHD. In the PPND study, maribavir was given to pregnant rats from gestation day 7 to postnatal day 21. Developmental delays and decreased fetal survival were noted at doses ≥150 mg/kg/day. Reduced offspring weight gain was observed at 400 mg/kg/day. No effects were seen at 50 mg/kg/day, less than the recommended human exposure. However, no adverse effects were observed in the second-generation offspring at any dose.

Maribavir was evaluated in 4-week juvenile toxicity studies in rats dosed from postnatal day 7 to 34, followed by post-dose recovery periods. These studies had no significant maribavir-related findings, with the highest doses tested showing no observed adverse effects. Exposures in these studies at the NOAEL were similar to or less than those observed in adult humans at the recommended human dose. Maribavir showed no phototoxic response in tests up to 100 μg/mL. Although maribavir caused eye irritation in rabbits, no skin irritation was observed in rats, rabbits, or guinea pigs. Maribavir showed no immunotoxic effects in rats at doses up to 100 mg/kg/day.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Plasma exposure to maribavir increased approximately dose proportionally following a single dose from 50 to 1600 mg or multiple doses from 300 to 2400 mg. Maribavir is rapidly absorbed with peak plasma concentrations observed 1 to 3 hours post dose. The mean apparent steady-state volume of distribution is 27.3 L. The extent of in vitro binding of maribavir to human plasma proteins was 98.0% mean over the concentration range of 0.05-200 μg/mL. A major metabolic pathway for maribavir is through hepatic CYP3A4-mediated oxidative dealkylation with the formation of the primary metabolite, VP

44469. CYP1A2 may also be involved in VP 44469 formation. Maribavir is a substrate of P-gp, OCT1, BCRP, UGT1A1, UGT1A3, UGT2B7, and possibly UGT1A9. The $t_{1/2}$ was estimated 4.32 hours in transplant patients with CMV infections. In the popPK analysis, the geometric mean CL/F was 3.77 L/h in healthy subjects and 2.85 L/h in transplant patients with CMV infections.

Maribavir can be taken with or without food, as the slight to moderate decrease in C_{max} with food is not considered clinically significant. Bioavailability of maribavir is unaffected by crushing the tablet, and crushed tablets can be administered via nasogastric or orogastric tubes with negligible drug loss.

2.3.2 Interaction Studies

Maribavir is primarily eliminated by hepatic metabolism via CYP3A4, with secondary contribution from CYP1A2. Strong or moderate CYP3A inducers may significantly decrease the plasma exposure to maribavir. Therefore, it is not recommended due to the potential for a decrease in efficacy of maribavir based on the magnitude of the reduction in maribavir C_{trough}. When maribavir is co-administered with strong or moderate CYP3A inducers, a dose increase is recommended based on PBPK modeling. In addition, strong CYP3A4 inhibitors may increase the plasma exposure to maribavir. Based on the less than 3-fold increase in maribavir exposure expected, lack of dose-limiting toxicity and a wide therapeutic window, maribavir can be co-administered with a strong CYP3A4 inhibitor without dose adjustment.

Maribavir can be given together with most HIV drugs without dose adjustment. However, co-administration with HIV drugs that are strong and moderate CYP3A inducers, such as efavirenz and etravirine, may significantly decrease the plasma exposure to maribavir; a dose increase is recommended based on PBPK modeling. When immunosuppressants tacrolimus, cyclosporine, everolimus or sirolimus are co-administered with maribavir, their whole blood concentrations should be frequently monitored.

2.3.3 Special Populations

No clinically relevant impact on maribavir PK related to age (18-79 years), gender, race (Caucasian, Black, Asian or others), ethnicity (Hispanic/Latino, or non-Hispanic/Latino) or weight (36 to 141 kg) was identified based on population PK analysis.

No clinically significant effect of mild, moderate or severe renal impairment was observed on maribavir PK. Compared to healthy control subjects, the difference in maribavir exposure in subjects with mild, moderate or severe renal impairment was no greater than 8.4%. In addition, the modest increase in maribavir exposure (26% for AUC and 35% for C_{max}) and VP 44469 exposure (31% for AUC and 19% for C_{max}) in subjects with moderate hepatic

impairment is not considered clinically significant. Therefore, no dose adjustment is required for patients with hepatic impairment (mild or moderate) or renal impairment (mild, moderate, or severe). The PK of maribavir in patients with severe hepatic impairment or with end-stage renal disease, including patients on dialysis, is unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The pivotal Phase 3 Study SHP620-303 was reviewed to evaluate the efficacy of maribavir (400 mg twice daily) for the treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease who are resistant and/or refractory to one or more prior therapies. Patients were randomized and treated with maribavir (N=235) or investigator-assigned anti-CMV treatment (IAT, N=117) for 8 weeks, with a 12-week follow-up. The primary endpoint was confirmed CMV viremia clearance (ie, plasma CMV DNA concentration <LLOQ; ie, <137 IU/mL in 2 consecutive samples tested ≥5 days apart) at the end of Week 8. The key secondary endpoint was achievement of CMV viremia clearance and symptom control at Week 8, with maintenance through Week 16. Hypothesis testing of primary and key secondary endpoints was adjusted for multiple comparisons using a fixed-sequence testing procedure to control the family- wise type 1 error rate at a 2-sided 5% level.

For the primary endpoint, maribavir was statistically superior to IAT in achievement of confirmed CMV viremia clearance at Week 8 (55.7% [131/235] vs 23.9% [28/117]; adjusted difference [95% CI]: 32.8% [22.80%, 42.74%]; p<0.001). For the key secondary endpoint, maribavir achieved superiority to IAT for virologic response and symptom control at the end of Week 8 and maintained the treatment effect through Week 16 (18.7% vs 10.3%; adjusted difference [95% CI]: 9.5% [2.02%, 16.88%]; p = 0.013).

Overall, Study SHP620-303 met its primary and key secondary objectives.

2.4.2 Safety Results

The safety results of Study 303 were summarized. Similar proportions of subjects in the maribavir and IAT groups had treatment-emergent AEs, severe AEs and SAEs during the on-treatment period. Discontinuation of treatment due to TEAEs occurred more frequently in the IAT group (31.9%) than in the maribavir group (13.2%). A similar pattern was observed for treatment-emergent SAEs leading to discontinuation (IAT: 14.7%; maribavir: 8.5%).

Dysgeusia, the most frequently reported TEAE overall, occurred predominantly in maribavir-treated subjects. Dysgeusia, which included the preferred terms of ageusia, dysgeusia, hypogeusia, and taste disorder, was much more prevalent in the maribavir group (46.2%) compared with IAT (4.3%).

The incidence of TEAEs For the SOC of blood and lymphatic system disorders was lower for the maribavir group (28.2%) than for GCV/valGCV-treated subjects (42.9%). Neutropenia, the most frequently reported TEAE in the IAT group (22.4%) during the on-treatment period, occurred at a lower incidence for maribavir-treated patients(9.4%). The incidence of anemia was comparable between the two groups.

The unadjusted incidence of TEAEs and SAEs in the system organ class (SOC) of infections and infestations during the on-treatment observation period was higher in the maribavir group than the IAT group.

Maribavir-treated subjects had a lower incidence of TEAEs than foscarnet-treated subjects for the TEAEs known related to foscarnet, such as nephrotoxicity and electrolyte disturbance.

The TEAE of immunosuppressant drug level increased was reported in a higher proportion of subjects in the maribavir group (9.0%) compared to the IAT group (0.9%).

2.5 Bridging Study Evaluation

The Phase 1 ethnic sensitivity study (Study TAK-620-1020) provide PK data for cross-race comparison. The PK of maribavir in the subjects of Japanese descent was similar to those in the non-Hispanic, Caucasian healthy subjects. Systemic maribavir exposure following administration of a single oral dose at 400 mg was approximately 10% to 25% higher in the subjects of Japanese descent than in the non-Hispanic, Caucasian subjects and this is likely partially due to the difference in body weight between the subjects of Japanese descent and the non-Hispanic, Caucasian subjects (mean body weight 67.82 kg and 75.32 kg, respectively). Such observed difference in exposure is considered to be not clinically relevant.

Moreover, the population PK analysis suggested that race (Caucasian, Black, Asian, or others) did not have any significant impact on the PK of maribavir. In Asian subjects with CMV, the AUC and Cmax were 96% and 104%, respectively, of values in Caucasian subjects. Overall, the PK properties of maribavir in Asian transplant subjects with CMV are expected to be similar to those in other races. In conclusion, race is not considered a sensitive factor on maribavir PK.

Asian participants in the clinical trials were very limited and their ethnicities were not sure. Both Phase 2 studies demonstrated similar response on CMV viremia clearance across different doses ≥ 400 mg BID of maribavir. Antiviral resistance may be different from area to area. Maribavir directly inhibits UL97 kinase, making it less susceptible to mutations of the

viral DNA polymerase UL54. Moreover, CMV with known characteristic mutations resulting in maribavir resistance has been listed in the label. The difference on extrinsic factors may have minimal impact.

2.6 Conclusion

This multidisciplinary review recommends approval for LIVTENCITY (Maribavir) indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are resistant, refractory or intolerant to one or more prior therapies in adult patients who have undergone a hematopoietic stem cell transplant or solid organ transplant.

3. Post-Marketing Requirements

Provide drug consumption data and estimate drug demand in Taiwan during the 5 years after approval to fulfill the requirement of Rare Disease Designation.