Taiwan Food and Drug Administration

Assessment Report

Trade Name：Kepida tablets

Active Ingredient：Tucidinostat (chidamide)

License Number：MOHW-PM-061429

Applicant：華上生技醫藥股份有限公司

Approval Date：2023/4/11

Indication：併用 exemestane，適用於荷爾蒙受體陽性且第二型人類表皮生長因子接受體(HER2)陰性，且經內分泌治療後復發或惡化之停經後局部晚期或轉移性乳癌婦女。

In combination with exemestane, indicated for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with disease recurrence or progression following endocrine therapy.

Background Information

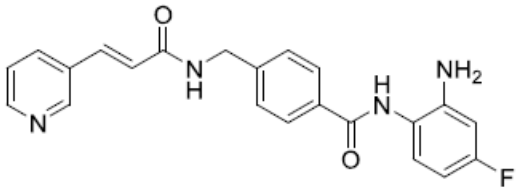
Trade Name	**Kepida tablets**
Active Ingredient(s)	**Tucidinostat (chidamide)**
Applicant	**華上生技醫藥股份有限公司**
Dosage Form & Strengths	**Tablet 5mg**
Indication	**併用 exemestane，適用於荷爾蒙受體陽性且第二型人類表皮生長因子接受體(HER2)陰性，且經內分泌治療後復發或惡化之停經後局部晚期或轉移性乳癌婦女。** **In combination with exemestane, indicated for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with disease recurrence or progression following endocrine therapy.**
Posology	**Please refer to the approved package insert**
Pharmacological Category **ATC Code**	**Antineoplastic agents** **WHO 尚無相關編碼**

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The chemical name of tucidinostat is (E)-N-(2-amino-4-fluorophenyl)-4-((3-(pyridin- 3-yl)acrylamido)methyl)benzamide. Tucidinostat is a white to off-white powder. The molecular formula and the molecular weight for tucidinostat are $C_{22}H_{19}FN_4O_2$ and 390.41 g/mol, respectively. It has the following structure:



Adequate information of characterization of the drug substance has been provided. The chemical structure of tucidinostat is elucidated by elemental analysis, mass spectroscopy,

ultraviolet spectrum, infrared spectrum, ^{1}H-NMR and ^{13}C-NMR.

Adequate specification has been presented for the drug substance and the test items include appearance, solubility, identification, pH, chloride, loss on drying, water content, residue on ignition, heavy metals, assay, related substances, residual solvents and microbial limit test. 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 a tablet for oral administration containing 5 mg of tucidinostat. The specifications for the excipients are adequate.

Adequate specification has been presented for the drug product and the test items include description, identification, assay, uniformity of dosage units, dissolution, impurities, residual solvent and microbial limits. Analytical methods are described and well validated. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications.

Stability studies of drug product under long term condition (25°C/60% RH), intermediate condition (30°C/65% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 24 months of long-term, 24 months of intermediate and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf-life of the drug product can be granted for 24 months under the storage condition of 25°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Tucidinostat is a histone deacetylase inhibitor (HDI) that inhibits Class I HDAC1, HDAC2, HDAC3, as well as Class IIb HDAC10. In the pharmacology studies, entinostat was used to be a positive control article. The *in vitro* studies indicated that tucidinostat inhibited the activity of HDAC, increased acetylated histone, inhibited the proliferation of cancer cell lines, and blocked the cells from entering the DNA synthesis phase. Tucidinostat exhibited a lower anti-proliferation effect than other chemotherapy drugs in non-cancer cell lines.

In vivo studies indicated that tucidinostat inhibited tumor growth in the allograft or xenograft models in mice. The combination of tucidinostat and etoposide exhibited a synergistic effect in the *in vitro* study but an additive effect in the *in vivo* study. The secondary pharmacology was not conducted and was acceptable due to the existence of tucidinostat's clinical data. The NOEL values of the safety pharmacology studies were

higher than the NOAEL values of the repeated-dose toxicity studies and clinical doses (based on body surface conversion).

2.2.2 Toxicological Studies

The major toxic effects of tucidinostat in rats and dogs included inhibition of hematopoiesis, inflammation in the GI tract, and cardiomyocyte degeneration in the heart. Most findings recovered after drug withdrawal. The toxicity studies were not GLP-compliant because these studies were conducted more than 10 years ago. The toxicokinetics was not evaluated in these studies; therefore, determining the exact safety margin of tucidinostat is challenging and can only be achieved through the body surface area conversion. As a result, the NOAELs are approximately equal to or higher than the clinical dose. The genotoxicity studies presented negative results. Tucidinostat might affect reproductive function since decreased sperm density and uterus weight were observed. Tucidinostat also exhibited teratogenic effects.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The absolute bioavailability of tucidinostat is unknown. The single and repeated dose PK of tucidinostat were evaluated in patients with breast cancer (BC) received 30 mg tucidinostat orally twice per week after breakfast. After single dose administration, tucidinostat C_{max} was reached ~2 hours, and declined with a mean half-life of 18 hr. Compared to 1st dose, tucidinostat trough concentration increased by approximately 1.8-fold following 8th dose administration. The inter-subject variability for tucidinostat PK parameters was high. The apparent Vd/F ranged 359-551 L in patients. The protein binding rate in human plasma was 89.1~99.3% at concentration range of 2~150 ng/mL. Tucidinostat was metabolized primarily by CYP3A4 *in vitro*. Following a single dose of 30 mg radio (^{19}F)-labelled tucidinostat by oral administration, 67.6% and 12.6% of the dose was excreted in urine and feces, respectively. Unchanged tucidinostat was the predominant drug-related entity in urine and feces.

The dose proportionality and food effect were evaluated in one Phase I and one Phase II study, respectively, conducted in patients with solid tumors and T cell lymphoma. Calculations of tucidinostat PK parameters in above two studies are based upon measurements using non-validated bioanalytical methods. This has to be taken into consideration when interpreting PK parameters. Compared to fasted condition, tucidinostat $AUC_{0\text{-last}}$ increased by ~140% under fed condition (~600 kcal meal). The dose proportionality across the dose range of 25 mg, 32.5 mg and 50 mg (1: 1.3: 2) was not apparent with tucidinostat $AUC_{0\text{-last}}$ increased less than linearity (1: 1.0 :1.4), suggesting the absorption of tucidinostat might be saturated.

2.3.2 Interaction Studies

No specific *in vivo* drug-drug interactions were investigated for tucidinostat. From literature study, co-administration with itraconazole increased tucidinostat exposures with C_{max} by ~41% and $AUC_{0\text{-}inf}$ by ~46%. Based on PK results in Study CDM-301, no clinically relevant drug interactions is observed between tucidinostat and exemestane.

2.3.3 Special Populations

A population PK approach was used to investigate the influence of covariates. Effects of gender, age and body weight were not found to influence tucidinostat PK with clinical relevance.

No specific PK studies have been conducted in renal or hepatic impairment patients. From Pop PK analysis, tucidinostat C_{avg} in patients with mild renal impairment (CrCL: 90 mL/min> CrCL≧60 mL/min) were increased by 21.6% compared to patients with normal renal function. The number of BC patients with moderate renal impairment was limited (N=2). There is no PK data available in patients with severe renal impairment so far. In BC patients with mild hepatic impairment (BIL≤ 20.5 μmol/L and AST>40 U/L or BIL<1.5 x 20.5 μmol/L), the C_{avg} was 73% higher compared to patients with normal hepatic function. There is no PK data available in patients with moderate and severe hepatic impairment so far.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study CDM301 was reviewed to evaluate the efficacy of tucidinostat in combination with exemestane for the claimed indication. Part 2 of Study CDM301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III trial conducted in Taiwan and China.

For overall population (Taiwan + China; 420 subjects), 292 subjects had PFS events (187 (66.5%) subjects in the tucidinostat group and 105 (75.5%) subjects in the placebo group). A statistically significant improvement in PFS was observed for tucidinostat plus exemestane over placebo plus exemestane, with the median PFS based on investigator assessment of 7.4 months in the tucidinostat group and 3.7 months in the placebo group (stratified HR: 0.716; 95% CI: 0.562, 0.911; p=0.0066).

For subjects enrolled in Taiwan (55 subjects), the median PFS improved from 3.7 months in the placebo group to 8.6 months in the tucidinostat group (stratified HR: 0.516; 95% CI: 0.268, 0.993; p=0.0477).

For subjects enrolled in China (365 subjects), the median PFS improved from 3.8 months in the placebo group to 7.4 months in the tucidinostat group (stratified HR: 0.755; 95% CI: 0.582, 0.978; p=0.0336).

In addition, the sample size of China was increased from 328 subjects (subject number for endpoint analysis: 230 PFS events) to 365 subjects (252 PFS events). Based on the first 321 subjects enrolled in China (230 PFS events), the stratified HR was 0.764 (95% CI: 0.582, 1.003; p=0.0525). For the first 328 subjects enrolled in China (233 PFS events), the stratified HR was 0.747 (95% CI: 0.571, 0.979; p=0.0343).

2.4.2 Safety Results

In the overall population of Study CDM301, there were 275 (97. 9 %) subjects in the tucidinostat group and 117 (84.2 %) in the placebo group who experienced at least one TEAE. The SAEs were reported from 56 (19.9%) subjects in the tucidinostat group, and 4 of the events led to death. The incidence of cytopenia (eg, neutropenia, anemia, thrombocytopenia), electrolyte abnormalities (eg, hypokalemia, hypocalcemia), Cardiac disorders (sinus tachycardia, palpitations, cardiac failure, ventricular extrasystoles, atrial fibrillation, and pericardial effusion), electrocardiogram QT prolonged, infections, thrombosis and gastrointestinal side effects (nausea and diarrhea) were more common with the combination of tucidinostat and exemestane than with placebo plus exemestane.

2.5 Bridging Study Evaluation

From PK's perspective, because the PK studies and clinical studies for tucidinostat were conducted in East Asia countries, including China and Taiwan, all the *in vivo* PK data of tucidinostat were from representative East Asian. Single and repeated dose PK of tucidinostat has been fully characterized in Chinese patients. No tucidinostat PK difference is expected between Chinese patients and Taiwanese patients.

Furthermore, the ethnic differences of tucidinostat in breast cancer patients were evaluated by comparing the efficacy and safety results of subjects in Study CDM301 from the Taiwan sites to those from the China sites.

For efficacy evaluation, the median PFS for subjects enrolled in China (365 subjects) was 7.4 months in the tucidinostat group and 3.8 months in the placebo group (stratified HR: 0.755; 95% CI: 0.582, 0.978; p=0.0336). The median PFS for subjects enrolled in Taiwan (55 subjects) was 8.6 months in the tucidinostat group and 3.7 months in the placebo group to (stratified HR: 0.516; 95% CI: 0.268, 0.993; p=0.0477).

Other efficacy results including ORR and OS of these two groups of people also showed consistent trends.

For safety evaluation, 97.3 % of Taiwan subjects in the tucidinostat group reported at least on AE, while 98.0% of China subjects in the tucidinostat group reported at least on AE. The incidences and the preferred terms of the most common hematologic TEAEs and non-hematologic TEAEs were highly consistent between the subjects enrolled in Taiwan and those in China. The incidences of subjects with any SAEs, and TEAE leading to treatment discontinuation were generally compatible. One Taiwan subject in the tucidinostat group reported fatal AE due to dyspnea and 3 China subjects in the tucidinostat group reported fatal AE due to unknown cause, interstitial lung disease and dyspnea. There is no obvious discrepancy in safety results between the Taiwan subjects and China subjects who received tucidinostat treatment.

2.6 Conclusion

After thorough discussion in the Advisory Committee, Tucidinostat is conditionally approved for the indication as below:
In combination with exemestane, indicated for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with disease recurrence or progression following endocrine therapy.

3. Post-Marketing Requirements

Additional efficacy evidence is required after marketing.