Approved on:

Revised on:

Prescribing Information of Tunlametinib Capsules

This product is conditionally approved for marketing. Please read the package insert carefully and use the product as instructed by a physician.

[Drug Name]

Generic Name: 妥拉美替尼胶囊

Trade Name: Keluping®

English Name: Tunlametinib Capsules

Chinese Pinyin: Tuolameitini Jiaonang

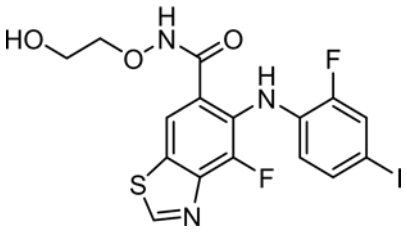
国家药品监督管理局
药品批准证明文件
附件骑缝章

[Ingredients]

The active pharmaceutical ingredient is Tunlametinib.

Chemical Name: 4-fluoro-5-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)-1,3-benzothiazole-6-carboxamide

Chemical Structural Formula:



Molecular Formula: $C_{16}H_{12}F_2IN_3O_3S$

Molecular Weight: 491.25

Excipients: Sugar spheres, hypromellose, talc, and vacant gelatin capsules.

[Description]

Tunlametinib Capsules is a white opaque hard-shell capsule containing white or off-white pellets.

[Indications]

Tunlametinib Capsules is indicated for patients with advanced NRAS-mutant melanoma who have failed anti-PD-1/PD-L1 therapy. Tunlametinib Capsules is conditionally approved for marketing based on surrogate endpoints. The clinical endpoint data are not yet available, and the efficacy and safety need to be further confirmed after marketing.

[Strengths]

(1) 3 mg (2) 6 mg

[Dosage and Administration]

Tunlametinib Capsules must be used under the guidance of a physician experienced in anti-tumor treatment.

NRAS Testing

Patients must have a documentation of NRAS mutations in their tumor sample prior to initiating treatment with Tunlametinib Capsules. The NRAS mutation status should be assessed

using a validated assay. Patients confirmed to have NRAS mutations based on local hospital or laboratory testing are eligible for treatment with Tunlametinib Capsules. An investigational companion diagnostic assay should be performed by an independent third party designated by Shanghai KeChow Pharma Inc. to confirm that the patient carries NRAS mutations before continuing treatment.

Dosage and Administration

The recommended dosage of Tunlametinib is 12 mg orally twice daily (approximately every 12 hours), with or without food. Do not chew, dissolve, or open the capsule.

If a dose is missed, it can be taken at least 8 hours prior to the next scheduled dose; if it is less than 8 hours to the next dose, the missed dose should not be taken.

Dosage Modification for Adverse Reactions

Dose reduction, interruption, or discontinuation may be necessary to manage adverse reactions (see Table 1).

Dose modifications for Tunlametinib Capsules -related adverse reactions are listed in Table 2.

Table 1 Dose Reduction Guidelines

Dose Level	Dosage of Tunlametinib Capsules
Initial dose	12 mg twice daily
First dose reduction	9 mg twice daily
Second dose reduction	6 mg twice daily

Table 2 Recommended Dose Modifications for Tunlametinib Capsules for Tunlametinib related Adverse Reactions

Adverse Reactions	Severity	Dose Modification
Left ventricular ejection fraction (LVEF) decreased (see [Warnings and Precautions])		
	• Asymptomatic, LVEF below the lower limit of normal (LLN) and absolute reduction ≥ 10% from baseline	Withhold Tunlametinib Capsules for ≤ 4 weeks: • Until LVEF is ≥ LLN and the absolute reduction is ≤ 10% from baseline, and then resume at a lower dose level. • If LVEF remains < LLN or the absolute reduction remains > 10% from baseline for more than 4 weeks, permanently discontinue Tunlametinib Capsules
	• Symptomatic congestive cardiac failure, or LVEF below LLN and absolute reduction ≥ 20% from baseline	• Permanently discontinue Tunlametinib Capsules and seek immediate medical advice from the Department of Cardiology.
Ocular toxicity (see [Warnings and Precautions])		
Retinal pigment epithelial detachment (RPED)		Withhold Tunlametinib Capsules for ≤ 4 weeks: • Until symptoms disappear, and resume at same dose or at a lower dose level. • If symptoms persist for more than 4 weeks, lower the dose by one level or permanently

		discontinue Tunlametinib Capsules
Retinal vein occlusion (RVO)		• Permanently discontinue Tunlametinib Capsules
Retinal artery occlusion (RAO)		• Permanently discontinue Tunlametinib Capsules
Interstitial lung disease/pneumonia (see [Warnings and Precautions])		• Permanently discontinue Tunlametinib Capsules.
Skin toxicity (see [Warnings and Precautions])		
Rash	• Intolerable Grade 2	• If the Grade 2 rash does not resolve within 2 weeks after active treatment, withhold Tunlametinib Capsules until recovery to Grade 0-1, and then resume at same dose or at a lower dose level.
	• Grade 3	Withhold Tunlametinib Capsules for ≤ 2 weeks: • Until recovery to Grade 0-1, and then resume at a lower dose level. • If symptoms persist for more than 2 weeks, permanently discontinue Tunlametinib Capsules.
	• Grade 4	• Discontinue Tunlametinib Capsules.
Blood creatine phosphokinase (CPK) increased (see [Warnings and Precautions])		
	• Grade 3	• If no symptoms such as obvious myalgia, asthenia, tight chest, and chest pain appear, lower the dose by one level, or withhold Tunlametinib Capsules (for ≤ 2 weeks) until CPK recovers to Grade 0-1 and then resume at same dose. • If there are symptoms such as obvious myalgia, asthenia, tight chest, and chest pain, withhold Tunlametinib Capsules (for ≤ 2 weeks) until the symptoms disappear and CPK recovers to Grade 0-1, and then resume at a lower dose level. • If symptoms do not improve or CPK does not recover to Grade 0-1 for more than 2 weeks, permanently discontinue Tunlametinib Capsules.
	• Grade 4	• Withhold Tunlametinib Capsules for ≤ 2 weeks: • Until CPK recovers to Grade 0-1 and there is no obvious discomfort, and then resume at a lower dose level. • If CPK is not recovered or the risk is not eliminated for more than 2 weeks, permanently

		discontinue Tunlametinib Capsules.
Other adverse reactions		
	• Intolerable Grade 2 • Grade 3	Withhold Tunlametinib Capsules for ≤ 4 weeks: • Until recovery to Grade 0-1, and then resume at same dose or at a lower dose level based on benefit-risk assessment. • If there is no improvement, permanently discontinue Tunlametinib Capsules.
	• Grade 4	Withhold Tunlametinib Capsules for ≤ 4 weeks: • Until recovery to Grade 0-1, and then resume at a lower dose level. • If there is no improvement, permanently discontinue Tunlametinib Capsules.

Use in Specific Populations

Hepatic Impairment

No formal clinical study has been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of Tunlametinib. Tunlametinib Capsules should be used with caution in patients with hepatic impairment (see [Clinical Pharmacology]).

Renal Impairment

No initial dose modification is required in patients with mild renal impairment (60 mL/min ≤ eGFR ≤ 89 mL/min). There is limited experience with Tunlametinib in patients with moderate/severe renal impairment, and Tunlametinib Capsules should be used with caution in patients with moderate/severe renal impairment (see [Clinical Pharmacology]).

[Adverse Reactions]

Summary of Safety Profile

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates of another drug in different trials and may not reflect the rates observed in practice.

Patients with Advanced NRAS-mutant Melanoma:

A phase II single-arm clinical study (HL-085-101-II) was conducted in patients with advanced NRAS-mutant melanoma (N=100), 100 patients with advanced NRAS-mutant melanoma were treated with Tunlametinib Capsules 12 mg orally twice daily until disease progression, intolerable toxicity, or until the investigator judged that the risks outweighed the benefits.

The median duration of exposure to Tunlametinib Capsules was 106.5 days, and the average actual exposure was 17.91 mg/day. The most common (≥ 20%) adverse drug reactions (ADRs) of any grade were diarrhea, rash, face oedema, oedema peripheral, anemia, asthenia, dermatitis acneiform, and hypoalbuminemia. The most common (≥ 5%) Grade 3 ADRs were anemia, dermatitis acneiform, asthenia, and rash.

There was a 73% incidence of ADRs leading to dose interruption, 37% leading to dose reduction, 50% leading to dose interruption and reduction, and 9% leading to permanent discontinuation of the investigational drug.

Tables 3 and 4 summarize the ADRs and abnormal laboratory values that occurred in ≥ 10% of patients with advanced NRAS-mutant melanoma, respectively.

Table 3 ADRs Occurring in ≥ 10% of Patients with Advanced NRAS-mutant Melanoma Treated with Tunlametinib

Adverse Reactions (≥ 10%)	Tunlametinib N = 100	
	All Grades (%)	≥ Grade 3 (%)
Skin and subcutaneous tissue disorders		
Rash	53	5
Dermatitis acneiform	24	7
Pruritus	18	0
Palmar-plantar erythrodysesthesia syndrome	17	0
Dry skin	11	1
General disorders and administration site conditions		
Face oedema	64	0
Oedema peripheral	62	4
Asthenia	36	5
Pyrexia	17	0
Gastrointestinal disorders		
Diarrhoea	74	4
Vomiting	19	0
Stomatitis	15	2
Dry mouth	10	0
Metabolism and nutrition disorders		
Hypoalbuminemia	34	0
Hypokalemia	19	4
Hypocalcemia	16	0
Hyperglycemia	14	0
Hyponatremia	11	1
Hyperuricemia	11	0
Eye disorders		
Vision blurred	14	0
Blood and lymphatic system disorders		
Anaemia	39	6
Renal and urinary disorders		
Proteinuria	13	0
Hepatobiliary disorders		
Hepatic function abnormal	10	1
Investigations		
Weight increased	16	1

* ADRs were reported using MedDRA and toxicity evaluation results were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0, NCI Common Toxicity Criteria). The data cutoff date was February 19, 2023.

Table 4 Abnormal Laboratory Values Occurring in ≥ 10% of Patients with Advanced NRAS-mutant Melanoma Treated with Tunlametinib

Laboratory Abnormalities (≥ 10%)	**Tunlametinib N = 100**	
	All Grades (%)	**≥ Grade 3 (%)**

Blood Chemistry		
Blood creatine phosphokinase increased	91	38
Aspartate aminotransferase increased	60	2
Blood lactate dehydrogenase increased	47	0
Alanine aminotransferase increased	40	0
Blood creatine phosphokinase MB increased	31	0
Gamma-glutamyltransferase increased	16	0
Myoglobin blood increased	16	0
Lymphocyte count decreased	14	2
White blood cell count decreased	11	0
Blood creatinine increased	10	1
Blood alkaline phosphatase increased	10	0

* ADRs were reported using MedDRA and toxicity evaluation results were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0, NCI Common Toxicity Criteria). The data cutoff date was February 19, 2023.

Other clinically important adverse reactions observed in ≤10% of patients were: retinal artery occlusion, retinal vein occlusion, retinal pigment epithelial detachment, interstitial lung disease, left ventricular dysfunction, and gastrointestinal bleeding.

Description of Selected Adverse Reactions

Left Ventricular Ejection Fraction (LVEF) Decreased

Of the 100 patients included in Study HL-085-101-II, 8 (8%) patients reported LVEF decreased, with Grade 3 LVEF decreased accounting for 1%. Dose withholding occurred in 2% of patients, and dose reduction in 1%. The outcome of 88% of patients was improved. No patient discontinued the investigational drug permanently due to LVEF decreased. The median time from the first dose to LVEF decreased was 45 days, with 1 patient experiencing Grade 3 LVEF decreased at 42 days. For the clinical management of LVEF decreased, see **[Dosage and Administration]** and **[Warnings and Precautions]**.

Ocular Toxicity

In Study HL-085-101-II, blurred vision was reported in 14 (14%) patients, all of which were Grade 1-2. Dose withholding occurred in 2% of patients. No dose reduction occurred in any patient. The outcome of 86% of patients was improved. Retinal artery occlusion (RAO) and retinal vein occlusion (RVO) each occurred in 1% of patients and the outcome was not improved. For the clinical management of ocular toxicity, see **[Dosage and Administration]** and **[Warnings and Precautions]**.

Skin Toxicity

In Study HL-085-101-II, rash was reported in 53 (53%) patients, mostly Grade 1-2, with Grade 3 rash accounting for 5%. Dose withholding occurred in 7% of patients, and dose reduction in 4%. The outcome of 94% of patients was improved. No patient discontinued the investigational drug permanently due to rash. The median time from the first dose to rash was 9 days, and that for Grade 3 rash was 62 days. The median duration was 10 days. For the clinical management of skin toxicity, see **[Dosage and Administration]** and **[Warnings and Precautions]**.

Blood Creatine Phosphokinase (CPK) Increased

In Study HL-085-101-II, CPK increased was reported in 91 (91%) patients, predominantly Grade 1-2. The median time from the first dose to CPK increased was 20 days, and that for ≥ Grade 3 CPK increased was 30.5 days, with the median duration of 7 days. Serious conditions

such as myocardial infarction and rhabdomyolysis must be ruled out based on symptoms, signs, and laboratory tests (and consultation with cardiology and other departments, if necessary) before dose modifications. In this study, CPK increased leading to dose interruption accounted for 31%, CPK increased leading to dose reduction for 19%, and CPK increased leading to dose interruption and reduction for 22%. The outcome of 98% of patients was improved. No patient discontinued the investigational drug permanently due to CPK increased. For the clinical management of CPK increased, see **[Dosage and Administration]** and **[Warnings and Precautions]**.

Hepatotoxicity

In Study HL-085-101-II, AST increased and ALT increased were reported in 60 (60%) and 40 (40%) patients, respectively. The median time from the first dose to AST increased was 23 days, and that for ALT increased was 27 days. Both AST increased and ALT increased were predominantly Grade 1-2, with Grade 3 AST increased occurring in 2% of patients. There were no reports of Grade 4 AST increased or ≥ Grade 3 ALT increased. 3% and 2% of patients withheld the dose due to AST increased and ALT increased, respectively; 1% of patients reduced the dose due to AST increased; no patients reduced the dose due to ALT increased, and no patients discontinued the investigational drug permanently due to AST or ALT increased. The outcome of 95% of patients with AST increased and 95% of patients with ALT increased were improved. Blood bilirubin increased was reported in 5% of patients, all Grade 1, and no dose modification was required. For the clinical management of hepatotoxicity, see other adverse reactions in **[Dosage and Administration]**.

Haemorrhage

In Study HL-085-101-II, bleeding was reported in 12 (12%) patients, predominantly Grade 1-2, with Grade 3 bleeding accounting for 1%. No fatal bleeding events were reported. The outcome of 83% of patients was improved. Of the patients with bleeding, 3% of them had gastrointestinal bleeding (including 1 case of hematochezia, 1 case of gastrointestinal bleeding, and 1 case of lower gastrointestinal bleeding), all of which were Grade 1-2. Patients should be closely monitored for bleeding in the gastrointestinal tract and other sites during medication. For the clinical management of bleeding, see other adverse reactions in **[Dosage and Administration]**.

Interstitial Lung Disease (ILD)

In Study HL-085-101-II, ILD was reported in 3 (3%) patients, of which 2% were Grade 1 and 1% were Grade 2. The outcome of 1 patient was improved. Patients should receive periodic imaging examinations during the treatment and permanently discontinue Tunlametinib Capsules if ILD is diagnosed (see **[Dosage and Administration]**).

Gastrointestinal Reactions

In Study HL-085-101-II, diarrhea was reported in 74 (74%) patients, mostly Grade 1-2, with Grade 3 accounting for 4%. No Grade 4 diarrhea was reported. The outcome of 97% of patients was improved. The median time from the first dose to diarrhea was 4 days, and that for Grade 3 diarrhea was 59.5 days. The median duration was 7 days. Vomiting was reported in 19 (19%) patients, all Grade 1-2. Patients should be monitored for gastrointestinal symptoms during the treatment with Tunlametinib Capsules. If diarrhea occurs, symptomatic treatment such as anti-diarrheal measures and electrolyte supplementation should be given as soon as possible, and other possible causes should be ruled out. Patients with Grade 3 diarrhea should suspend the use of Tunlametinib Capsules, and patients with Grade 4 diarrhea should withhold the use of Tunlametinib Capsules permanently.

Pyrexia

In Study HL-085-101-II, fever was reported in 17 (17%) patients, all Grade 1-2. The

median time from the first dose to fever was 33 days. Drug withholding occurred in 7% of patients, and dose reduction in 4%. The outcome of all patients was improved. No patient discontinued the investigational drug permanently due to fever.

[Contraindications]

Patients allergic to the active ingredient or any of the excipients of Tunlametinib Capsules.

[Warnings and Precautions]

Left Ventricular Ejection Fraction (LVEF) Decreased

In Study HL-085-101-II, the incidence of LVEF decreased related to the investigational drug was 8% (of which 1% were ≥ Grade 3). Patients should receive echocardiography before starting treatment to fully assess and determine the baseline LVEF, which should be above the lower limit of normal established by the testing organization. Regular echocardiography is also recommended during the treatment (at 1 month after the first dose, and every 2 months thereafter). Patients experiencing cardiovascular symptoms and signs during the treatment with Tunlametinib Capsules should receive temporary cardiac function monitoring, including echocardiography, and consult the Department of Cardiology if necessary. If LVEF decreases, dose modifications such as withholding, reduction, or permanent discontinuation should be considered (see **[Dosage and Administration]**).

Skin Toxicity

In Study HL-085-101-II, the incidence of rash related to the investigational drug was 53% (of which 5% were ≥ Grade 3, and no patient discontinued the investigational drug permanently due to rash). If any skin reaction occurs during the treatment with Tunlametinib Capsules, symptomatic treatment should be initiated at the onset of symptoms to relieve them. If intolerable Grade 2 skin toxicity occurs (Grade 2 rash does not resolve within 2 weeks after active treatment), appropriate dose modifications should be made. For the principles for managing skin toxicity, see **[Dosage and Administration]**.

Ocular Toxicity

In study HL-085-101-II, the incidences of RPEDs, RVOs and RAOs related to the investigational drug were all 1%. Regular clinical ophthalmological evaluation is recommended during the administration of this product, and the evaluation should be performed in a timely manner when patients report visual impairment. Dose withholding is recommended upon diagnosis of RPED. If repeated ophthalmic evaluation results indicate that symptoms of RPED have recovered within 4 weeks, treatment with this product should be resumed at the same dose or a reduced dose; if symptoms do not recover after more than 4 weeks, treatment with this product should be resumed at a reduced dose or permanently discontinued.

RAO may lead to sudden loss of vision or even visual loss. Ophthalmological evaluation should be performed as soon as possible for patients with significant visual acuity loss or other visual impairments in the short term. Permanent discontinuation of this product is required for patients who experience RVO/RAO. Dose adjustment for ocular toxicity (see **[Dosage and Administration]**).

Interstitial Lung Disease (ILD)

In study HL-085-101-II, the incidence of ILDs related to the investigational drug was 3%, all of which were Grade 1–2. Patients who experience acute onset and/or unexplained new or exacerbated pulmonary symptoms (e.g., dyspnea, cough, pyrexia) or imaging abnormalities (e.g., ground-glass changes) during medication should suspend the administration of this product immediately and be evaluated for ILD. If ILD is diagnosed, this product should be permanently discontinued, and symptomatic treatment (including anti-infection) and management of adverse reactions should be provided (see **[Dosage and Administration]**).

Gastrointestinal Reactions

In study HL-085-101-II, the incidence of diarrhoea related to the investigational drug was 74%, most of which were Grade 1–2, Grade 3 accounted for 4%, and no Grade 4 diarrhea occurred. Patients should be monitored for gastrointestinal symptoms during the treatment with Tunlametinib Capsules. If diarrhea occurs, symptomatic treatment such as anti-diarrheal measures and electrolyte supplementation should be given as soon as possible, and other possible causes should be ruled out. Patients with Grade 3 diarrhea should withhold the use of Tunlametinib Capsules, and patients with Grade 4 diarrhea should discontinue the use of Tunlametinib Capsules permanently. Other adverse reactions in the Management of Adverse Reactions (see **[Dosage and Administration]**).

Blood Creatine Phosphokinase (CPK) Increased

In study HL-085-101-II, the incidence of CPK increased related to the investigational drug was 91%. Most of them were Grade 1–2. Patients with Grade 3 CPK increased should be advised to immediately report the presence of unexplained chest tightness or asthenia and other symptoms, and the dose should be adjusted accordingly based on the patient's condition. It is also necessary to rule out the presence of myocardial infarction, rhabdomyolysis, etc. Patients' ECG, CPK, myoglobin, troponin and renal function (such as serum creatinine, blood urea nitrogen and urine protein) should be closely monitored, and examined once a week by recommendation. Dose adjustment for CPK increased (see **[Dosage and Administration]**).

[Pregnancy and Lactation]

Pregnancy

There are currently no available data on the use of Tunlametinib in pregnant women to assess drug-related risks. This product should not be used in pregnant women.

Breastfeeding

No data are available on the presence of Tunlametinib in human milk and the effect of Tunlametinib on breastfed infants or lactation. Because of the potential for serious adverse reactions from tunlametinib in breastfed infants, advise women not to breastfeed during treatment with tunlametinib and for 30 days after the final dose.

Contraception

Females: Women of childbearing potential are advised to use effective contraception while taking this product until 30 days after the last dose. If this product is used during pregnancy or a patient becomes pregnant while taking it, the patient should be apprised of the potential hazard to the fetus from Tunlametinib.

Males: Men are advised to take highly effective contraceptive measures while taking this product until 30 days after the last dose.

Fertility

The effects of this product on male and female fertility are unknown.

[Pediatric Use]

The safety and efficacy of this product in children and adolescents (under 18 years of age) have not been established, thus the use of this product is not recommended.

[Geriatric Use]

No initial dose adjustment is required for subjects aged ≥ 65 years (see [Clinical Pharmacology]).

[Drug Interactions]

Tunlametinib is mainly metabolized by CYP2C9, and a small amount is metabolized by CYP2C8 and CYP3A4. Tunlametinib basically had no inhibitory effect on CYP3A4, CYP1A2, CYP2D6, CYP2C8 and CYP2B6, but had some inhibitory effect on CYP2C9 and CYP2C19, which was not clinically significant.

Tunlametinib is not a substrate of the transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Tunlametinib did not significantly inhibit the transport activities of OCT2 and MATE2-K, but inhibited the transport activities of OATP1B1, OATP1B3, OAT1, OAT3 and MATE1. However, its inhibitory effect was not clinically significant.

Tunlametinib is not a substrate of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), and its inhibitory effect on P-gp and BCRP is not clinically significant.

No formal clinical drug-drug interaction studies have been formally conducted with this product. Co-administration with inhibitors and inducers of CYP2C9 should be avoided.

[Overdosage]

There is no specific treatment for overdose with this product. In the event of an overdose, the patient should be closely monitored for signs and symptoms as needed and given supportive treatment if necessary. Since Tunlametinib is highly bound to plasma proteins, hemodialysis is not expected to be effective against drug overdose.

[Clinical Pharmacology]

Mechanism of Action

This product is a selective mitogen-activated protein kinase 1 and 2 (MEK1/2) inhibitor (see [Pharmacology and Toxicology]).

Pharmacodynamics

The relationship between Tunlametinib exposure and pharmacodynamic (PD) levels has not been established.

Pharmacokinetics

Absorption

Tunlametinib Capsules are rapidly absorbed after oral administration, and the median time to peak plasma concentration at steady state is 1 hour after administration. After oral administration of Tunlametinib (12 mg) twice daily, the mean peak concentration (C_{max}), trough concentration (C_{min}) and area under the concentration-time curve over the dosing interval ($AUC_{0\text{-}tau}$) at steady state were 122 ± 69.3 ng/mL (arithmetic mean ± standard deviation, same below), 8.87 ± 4.60 ng/mL and 360 ± 102 h*ng/mL, respectively.

After oral administration of Tunlametinib Capsules (12 mg) twice daily for 8 days, the plasma concentration approached steady state, with an accumulation ratio of 1.66 measured by the area under the concentration-time curve (AUC). In the dose range of 0.5 ~ 15 mg, the AUC of Tunlametinib increased with dose, and the PK profile was approximately dose-proportional.

Food Effect

Tunlametinib can be taken on an empty stomach or with a meal. High-fat meals do not affect the extent of Tunlametinib absorption. Compared with administration under fasting conditions, the median time to peak concentration (T_{max}) was prolonged by about 1.5 hours and the mean peak concentration (C_{max}) was reduced by about 63% under fed conditions.

Distribution

The mean apparent volume of distribution was approximately 1940 L following oral

administration of Tunlametinib Capsules (12 mg). Tunlametinib is highly bound to human plasma proteins (mean plasma protein binding 99.7%).

Metabolism and Elimination

Non-clinical studies have shown that Tunlametinib is mainly metabolized by CYP2C9. The results from a single oral dose study of radio-labeled Tunlametinib showed that feces was the main route of excretion, with approximately 59.6% of Tunlametinib-related substances excreted in feces, about 28.3% in urine and about 2.8% in exhaled air. After oral administration of Tunlametinib Capsules (12 mg), the mean apparent clearance of Tunlametinib in humans was approximately 51.9 L/h and the mean terminal elimination half-life ($T_{1/2}$) was approximately 26.2 hours.

Specific Populations

Hepatic Impairment

Tunlametinib is mainly metabolized through the liver. There was only one patient with mild hepatic impairment in study HL-085-101, so there is limited experience with the use of Tunlametinib in patients with hepatic impairment.

Renal Impairment

The kidney is not a major route of elimination for Tunlametinib. The results from study HL-085-101 showed that steady-state $AUC_{0\text{-}tau}$ at the same dose level was comparable in patients with mild renal impairment (N = 9) and those with normal renal function (N = 24).

Geriatric

The results from study HL-085-101 showed that the steady-state $AUC_{0\text{-}tau}$ at the same dose level was comparable between patients aged over 65 years (N = 3) and younger population (N = 30).

Pharmacogenetics

No relevant studies have been conducted and no reliable references are available.

[Clinical Trials]

A multicenter, single-arm phase II study (HL-085-101-II) to evaluate the efficacy and safety of Tunlametinib in patients with advanced NRAS-mutant melanoma. Patients with active central nervous system injury, abnormal blood creatine phosphokinase, pre-existing retinopathy, interstitial lung disease, previous treatment with MEK inhibitors, and ECOG performance status score ≥ 2 were excluded.

Patients received 12 mg orally twice daily until intolerable toxicity, disease progression (assessed by the investigator according to RECIST 1.1), withdrawal of consent, death, or when the risk outweighs the benefit as judged by the investigator.

In this study, 64 patients had previously received anti-PD1/PD-L1 therapy. The median age of the 64 patients was 57 years (range: 29–75 years), and 23.4% of them aged ≥ 65 years; men accounted for 46.9%; patients with ECOG score of 0 and 1 accounted for 43.8% and 56.3% respectively; Stage III and IV accounted for 7.8% and 92.2% respectively; 57.8% were acral, 17.2% were mucosal, and 14.1% were cutaneous; of the NRAS mutation sites, 42.2% had Q61R mutations, 25% had Q61K mutations, and 10.9% had G12D mutations; 6.3% of the patients had not received any systemic antitumor therapy before enrollment, 59.4% had received 1st line antitumor therapy, and 34.4% had received ≥ 2nd line antitumor therapy.

The primary efficacy endpoint was objective response rate (ORR) assessed by an Independent Radiological Review Committee (IRRC) according to RECIST 1.1 criteria, and the secondary efficacy endpoints were disease control rate (DCR), duration of response (DOR),

progression-free survival (PFS), 1-year survival, and overall survival (OS). The data cut-off date of this study was February 19, 2023. Sixty-four (64) patients in the FAS had previously received anti-PD1/PD-L1 therapy. The median duration of drug exposure for patients treated with this product was 112.5 days, the mean actual drug exposure was 17.94 mg/day, and the median follow-up time was 16.5 months. Key efficacy results and efficacy subgroup analysis are shown in Table 5 and Table 6, respectively.

Table 5. Efficacy Analysis of Subjects Previously Treated with Anti-PD1/PD-L1 Therapy in FAS (N = 64)

Efficacy Parameters	**FAS , N=64**
ORR* , % (95%CI)	40.6% (28.5%, 53.6%)
DCR* , % (95%CI)	70.3% (57.6%, 81.1%)
mDOR*, months (95% CI)	6.3 (2.9, 8.9)
mPFS*, months (95% CI)	4.1 (3.4, 6.1)
mOS, months (95% CI)	12.3 (8.9, 18.1)

*: Assessed by the Independent Radiological Review Committee (IRRC) according to RECIST 1.1 criteria. CI: confidence interval.

Table 6. Efficacy Subgroup Analysis by NRAS Mutation Status for Subjects Previously Treated with Anti-PD1/PD-L1 in FAS (N = 64)

Mutation Site	**Number of cases**	**ORR* n (%) (95% CI)**	**mDoR* Months (95% CI)**
Q61R	27	12 (44.4%) (25.5%, 64.7%)	8.9 (2.1, NE)
Q61K	16	10 (62.5%) (35.4%, 84.8%)	5.4 (2.5, 8.3)
G12D	7	2 (28.6%) (3.7%, 71.0%)	8.7 (6.3, NE)

*: Assessed by the Independent Radiological Review Committee (IRRC) according to RECIST 1.1 criteria. CI: confidence interval.

Tunlametinib Capsules is conditionally approved for marketing based on surrogate endpoints. The clinical endpoint data are not yet available, and the efficacy and safety need to be further confirmed post-marketing.

[Pharmacology and Toxicology]

Pharmacological Actions

Tunlametinib is a selective mitogen-activated protein kinase 1 and kinase 2 (MEK1/2) inhibitor, which can inhibit the phosphorylation of ERK protein in tumor cells, block cell cycle at G0/G1 phase and induce apoptosis by inhibiting the activity of MEK1/2 kinase and blocking downstream ERK signaling pathway, thus exerting anti-tumor effects. Tunlametinib inhibited the proliferation of various tumor cell lines *in vitro*, and the data are shown in the table below.

Cell Line	Cell Background	IC50 (nM)
A375	Raf mutation	0.86±0.07
COLO-205	Raf mutation	0.94±0.26
LOX	Raf mutation	1067.99±324.79
COLO-829	Raf mutation	3.46±0.27
HT-29	Raf mutation	2.35±0.03
Calu-6	Ras mutation	10.07±1.18
A549	Ras mutation	59.89±11.06
PANC-1	Ras mutation	>1000
HL-60	Ras mutation	0.67±0.28
H1975	Raf/Ras wild-type	>1000
BxPC-3	Raf/Ras wild-type	252.04±81.39

MRC-5	Normal cell line	>1000

Toxicology Study

Genotoxicity

The results of Ames test, Chinese hamster lung (CHL) fibroblast *in vitro* chromosome aberration test and rat *in vivo* micronucleus test of Tunlametinib were all negative.

Reproductive Toxicity

Following oral dose of Tunlametinib to SD rats once a day at 0.25, 0.5 and 1.0 mg/kg, no significant toxic reactions were observed in fertility and early embryonic development of rats at each dose (based on body surface area, the dose of 1.0 mg/kg for rats is about 0.4 times the daily equivalent dose of 12 mg BID recommended human dose). In the repeated-dose toxicity study in SD rats, after oral administration of Tunlametinib once a day for 13 consecutive weeks, decreased ovarian and oviduct weights and reduced follicular/luteal cysts and corpus luteum were observed in female rats at ≥ 0.25 mg/kg dose (calculated by AUC_{0-t}, the dose for female rats was about 5.68 times the daily exposure at the recommended human dose of 12 mg BID). In the repeated-dose toxicity study in Beagle dogs, after oral administration of Tunlametinib once a day for 17 weeks, testicular tubular degeneration/necrosis, epididymal epithelial cell degeneration/necrosis, and vascular/perivascular tissue inflammation in the ovary and uterus were observed in the 0.2 mg/kg dose group (calculated by AUC_{0-t}, about 0.39 times the daily exposure at the recommended human dose of 12 mg BID).

After oral administration of 0.25, 0.5 and 1.0 mg/kg Tunlametinib once daily on gestation days (GD) 6~17 in pregnant SD rats, the incidence rate of incomplete ossification of supraoccipital in fetuses was increased in the ≥ 0.5 mg/kg dose group (calculated by AUC_{0-t}, about 6 times the daily exposure at the recommended human dose of 12 mg BID); in the 1.0 mg/kg dose group (calculated by AUC_{0-t}, about 9.7 times the daily exposure at the recommended human dose of 12 mg BID), the number/incidence of resorptions/dead fetuses, the number/incidence of early resorptions, total number/incidence of resorptions, the number/incidence of post-implantation losses, and the incidence rate of incomplete ossification of 4^{th} sternebra in fetuses were increased, and the number of ossification points of the proximal phalanx toe was decreased.

Carcinogenicity

Carcinogenicity studies have not been conducted with Tunlametinib.

Others

After oral administration of Tunlametinib at 0.5, 1, and 2 mg/kg once a day for 4 consecutive weeks in juvenile SD rats (aged 21–22 days), the main toxicity target organs included mineralization of multiple organs (kidneys, gastric mucosa, cornea ocularis and heart vessels), lymphohematopoietic system (thymus, mesenteric lymph node lymphopenia/necrosis), femur (hematopoietic cell decrease and hemorrhage, growth thickening/structural disturbance in the metaphysis), lung (alveolar macrophage accumulation), ovary (decreased corpus luteum and degeneration/necrosis and increased interstitial cells), spleen (extramedullary hematopoiesis, decreased white pulp lymphocytes), skin (erosion/ulcer), femur (decreased trabecular bone/cortical bone). In the 2 mg/kg dose group (calculated by AUC_{0-t}, about 20.3 times the daily exposure at the recommended human dose of 12 mg BID), a significant decrease in growth hormone was observed in male animals, while no significant abnormality in growth hormone was observed in female animals; the total distance travelled was significantly decreased in the spontaneous locomotor activity test, and shortened margin time was observed in females; sperm density was significantly decreased; decreased BMC was observed, and decreased AREA, BMD, bone length and bone thickness (distal vertical) were also observed in male animals, suggesting that Tunlametinib could affect growth

hormone, spontaneous activity, sperm, bone development, etc.

[Storage]

Sealed and stored below 30℃, protected from light.

[Packaging]

3 mg Strength: HDPE bottles enclosed with HDPE desiccant moisture proof cap; Each bottle contains 56 capsules, Each box contains one bottle..

6 mg Strength: HDPE bottles enclosed with a child resistant PP safety cap; Each bottle contains 30 capsules, Each box contains one bottle.

[Shelf Life]

36 months

[Executive Standard]

YBH03172024

[License No.]

3 mg GYZZ H20240008;

6 mg GYZZ H20240009

Conditional approval for marketing

[Marketing Authorization Holder]

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[Manufacturer]

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