Taiwan Food and Drug Administration

Assessment Report

Trade Name：益副蓋錠 1 毫克 / ORKEDIA Tablets 1 mg
益副蓋錠 2 毫克 / ORKEDIA Tablets 2 mg

Active Ingredient：Evocalcet

License Number：MOHW-PI 028602
MOHW-PI 028603

Applicant：台灣協和麒麟股份有限公司

Approval Date：2023/12/1

Indication：
治療罹患慢性腎臟病(CKD)且接受透析之成人病人的次發性副甲狀腺機能亢進。

ORKEDIA® is indicated for treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis.

Background Information

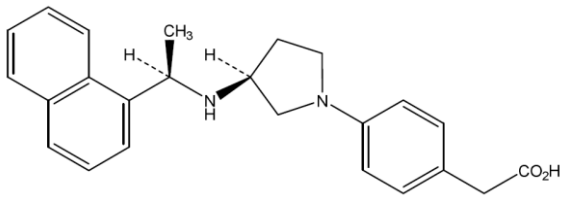
Trade Name	益副蓋錠 1 毫克 / ORKEDIA Tablets 1 mg 益副蓋錠 2 毫克 / ORKEDIA Tablets 2 mg
Active Ingredient(s)	Evocalcet
Applicant	台灣協和麒麟股份有限公司
Dosage Form & Strengths	膜衣錠 1mg、2mg
Indication	治療罹患慢性腎臟病(CKD)且接受透析之成人病人的次發性副甲狀腺機能亢進。
Posology	詳如仿單
Pharmacological Category **ATC Code**	NA

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, evocalcet, is chemically designated as 2-{4-[(3*S*)-3-{[(1*R*)-1-(Naphthalen-1-yl)ethyl]amino}pyrrolidin-1-yl]phenyl} acetic acid and has the following structure:



It is a white to pale yellowish white powder. The molecular formula and the molecular weight are $C_{24}H_{26}N_2O_2$ and 374.48 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of evocalcet has been confirmed.

Adequate specification has been presented for the drug substance and the test items.

2.1.2 Drug product

The drug product is provided as an immediate release film-coated tablet for oral administration formulated with evocalcet as drug substance. The drug products are available in 2 strengths (1 and 2 mg) and are packaged in blisters. The specifications for excipients used in the drug product formulation are adequate.

Adequate specifications have been presented for the drug products and the test items include appearance, identification, assay, related substances, uniformity of dosage units and dissolution.

Batch analysis data from commercial scale 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 accelerated conditions (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 the drug product can be granted for 36 months under the storage condition of 25°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Evocalcet is a small molecule agonist of the Calcium-sensing receptor (CaSR). The mechanism of action of evocalcet is to activate CaSR, inhibit the secretion of parathyroid hormone (PTH), and enhance the Ca^{2+} excretion from kidney. The *in vitro* pharmacology studies used CaSR-expressing HEK293 cells to evaluate the effects of evocalcet. Evocalcet increased intracellular Ca^{2+} concentration dose-dependently with an EC_{50} of approximately 6.70×10^{-8} to 1.59×10^{-7} M. The Ca^{2+} concentration-response curves of evocalcet were shifted to a lower extracellular Ca^{2+} concentration range in the same manner.

The *in vivo* studies showed that repeated oral doses (0.3 to 3 mg/kg) of evocalcet for 2 weeks in mice significantly decreased the serum PTH concentration at a dose level of 0.3 mg/kg and above. Serum Ca^{2+} concentration was also decreased at a dose level of 1 mg/kg and above. In rats, a single oral dose of evocalcet decreased serum PTH concentration at 0.03 mg/kg and above and decreased serum Ca^{2+} concentration at 0.1 mg/kg and above. The effects were also presented in 5/6 nephrectomized rats, mimicking renal dysfunction patients. Besides, evocalcet suppressed the cell proliferation and the hypertrophy of the parathyroid gland caused by 5/6 nephrectomy.

The results of safety pharmacology studies indicated that oral administration of 10 mg/kg evocalcet had no significant effects on CNS and respiratory system, but exhibited the potential to affect heart rate and blood pressure in rats and monkeys. Evocalcet increased Ca^{2+} and Cl excretion and diminished P excretion in urine.

2.2.2 Toxicological Studies

In the results of pivotal repeated-dose toxicity studies in rats and monkeys, some changes were due to the pharmaceutical effects of evocalcet, e.g., the mineralization of tissues was due to evocalcet bound to CaSR to inhibit PTH secretion and promote Ca^{2+} excretion from kidney. Inhibition of PTH release also caused atrophy of the parathyroid gland. The calcification failure of enamel was observed in the mid- and high-dose groups in rats; however, a literature mentioned that short-term PTH reduction and hypocalcemia in rats did not affect the enamel.

The results of *in vitro* and *in vivo* genotoxicity studies were negative. The carcinogenicity studies suggested that evocalcet had no carcinogenic potential. Evocalcet had no direct reproductive toxicity; however, the pharmaceutical effects (e.g., decreased Ca^{2+} concentration) would influence pre- and post-natal development. *In vitro* and *in vivo* studies indicated that evocalcet had no phototoxicity to the skin or eye in pigmented rats treated with a single dose of up to 6 mg/kg.

The relationship between the toxicity of evocalcet and the hypocalcemic effect was investigated in rats under a preventing hypocalcemic condition by continuous IV infusions of calcium gluconate. The results suggested that lens opacity, which appeared after repeated administration of evocalcet, may be attributable to a decrease in blood Ca^{2+} concentration. Besides, since lens opacity occurred in repeated-dose toxicity studies in rats but not in monkeys, the evocalcet concentration in aqueous humor was determined. The uptake of evocalcet into the aqueous humor, as calculated from plasma concentration, was about 2.7% in rats and 1.2 to 1.5% in monkeys. It suggested that the occurrence of lens opacity was limited to rats, but the exposure of evocalcet to the aqueous humor was detected in both rats and monkeys.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

ORKEDIA (evocalcetc) is a calcimimetic agent and act on calcium receptors on the surface of parathyroid cells to inhibit the secretion of intact parathyroid hormone (iPTH). ORKEDIA is indicated for the treatment of secondary hyperparathyroidism (SHPT) in patients undergoing maintenance dialysis.

The absolute bioavailability of evocalcet was 62.7%. In the range of 1-12 mg, the exposure of evocalcet increased dose proportionally. Following a single dose of evocalcet 2 mg Tablet, T_{max} occurred at 1 hour post-dose. When combining with high-fat meal, T_{max} and AUC did not affect by meal, but C_{max} decreased by 19%. Thus, it did not set any conditions on food in Phase 3 clinical trials. Steady state was reached rapidly approximately at Day 2-3, and low accumulation was observed after multiple-dose oral administration of evocalcet. Based on updated population PK analysis, the model predicted Cminss, Cmaxss, and AUCss (Geo-Mean) after receiving the lowest dose of 1 mg once daily (QD) dosing regimen were 18.0 ng/mL, 81.7 ng/mL, and 42.3 ng·h/mL. The model predicted Cminss, Cmaxss, and AUCss after receiving the highest dose of 12 mg QD dosing regimen were 216 ng/mL, 980 ng/mL, and 507 ng·h/mL, respectively.

In plasma, evocalcet is the main compound (79.8%), and M1 and M2 were active and major two metabolites. The estimated percent contributions of KHK7580, M1, and M2 to the overall

pharmacological effects were 80.7%, 15.7% and 3.6%.

The human plasma protein binding ratios is about 98%, regardless of concentration. Evocalcet is widely distributed and could transfer to placenta and secrete to milk. Metabolism was recognized the major elimination pathway of evocalcet, but CYP and UGT did not involve in the formation of M1 and M2. The apparent volume of central compartment (Vc/F), peripheral compartment (Vp/F) and apparent clearance (CL/F) were 2.30 L, 16.6 L and 1.09 L/hr, respectively, based on population PK analysis. The cumulative recovery of total radioactivity in urine, feces and total were 61.2% (no unchanged parent), 32.7% (unchanged parent: 8.6% of dose) and 93.9%, respectively.

2.3.2 Interaction Studies

Evocalcet have no marked effects on the PK of substrate drugs of each P450 isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A).

2.3.3 Special Populations

No formal renal impairment study was conducted. ORKEDIA should be used with cautions in patients with mild and moderate hepatic impairment. The PK of ORKEDIA have not been established in severe hepatic impairment patients. The dose of ORKEDIA is not necessary adjusted according to gender, age (> 60 years), body weight and albumin (≤3.5 g/dL).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Two Phase III, randomized, double-blind, active-controlled clinical studies, 7580-010 and 7580-201, had demonstrated the efficacy of ORKEDIA® (Evocalcet) in adult subjects with chronic kidney disease receiving hemodialysis and secondary hyperparathyroidism. One Phase III, single-arm study 7580-012 supported the efficacy of ORKEDIA® (Evocalcet) in adult subjects with chronic kidney disease receiving peritoneal dialysis and secondary hyperparathyroidism.

Study 7580-010 randomized subjects in a 1:1 ratio to the two treatment groups for treatment duration of 30 weeks which consisted of a dose adjustment period of 28 weeks and an evaluation period of 2 weeks.

- ORKEDIA® (Evocalcet): starting oral dose 1 mg or 2 mg once daily for subjects with an intact parathyroid hormone (PTH) level of <500 pg/mL or ≥500 pg/mL, then increased/decreased at an increment of 1 mg to maximum of 8 mg, so that intact PTH level ≥60 pg/mL and ≤ 240 pg/mL
- Cinacalcet: starting oral dose 25 mg, then increased/decreased at an increment of 25 mg/12.5 mg to maximum of 100 mg, so that intact PTH level ≥60 pg/mL and ≤240

pg/mL

Non-inferiority (margin -15%) of ORKEDIA® (Evocalcet) to cinacalcet was demonstrated in the primary efficacy endpoint, the number and percentage of subjects (95% CI) who achieved a mean intact PTH level between ≥ 60 pg/mL and ≤ 240 pg/mL during the evaluation period (72.7% (184/253) vs. 76.7% (204/266); difference (95% CI): -4.0% (-11.4, 3.5); PPS).

Study 7580-201 randomized subjects in a 1:1 ratio to the two treatment groups for treatment duration of 52 weeks which consisted of a dose adjustment period of 50 weeks and an evaluation period of 2 weeks.

- ORKEDIA® (Evocalcet): starting oral dose 1 mg or 2 mg once daily for subjects with an intact PTH level of <500 pg/mL or ≥500 pg/mL, then increased/decreased at an increment of 1 mg to maximum of 12 mg, so that intact PTH level ≥150 pg/mL and ≤300 pg/mL
- Cinacalcet :starting oral dose 25 mg, then increased at an increment of 25 mg to maximum of 100 mg, so that intact PTH level ≥150 pg/mL and ≤300 pg/mL

Non-inferiority (margin 15%) of ORKEDIA® (Evocalcet) to cinacalcet was demonstrated in the primary efficacy endpoint, mean percent change in intact PTH level from baseline in the evaluation period (mean (95% CI): -34.7% (-40.8, -28.5) (N=199) vs. -30.2% (-36.3, -24.2) (N=196); difference (95% CI): -4.4% (-13.1, 4.3); FAS).

Study 7580-012 enrolled 39 subjects for treatment duration of 52 weeks which consisted of a dose adjustment period of 30 weeks, an evaluation period of 2 weeks, and an extension period of 20 weeks.

- ORKEDIA® (Evocalcet): starting oral dose 1 mg or 2 mg once daily for subjects with an intact parathyroid hormone (PTH) level of <500 pg/mL or ≥500 pg/mL, then increased/decreased at an increment of 1 mg to maximum of 8 mg (12 mg in the extension period), so that intact PTH level ≥60 pg/mL and ≤ 240 pg/mL

In the evaluation period, 28 (71.8%) subjects achieved the target intact PTH range.

2.4.2 Safety Results

Three Japanese Phase III trials (N = 493) and one Asian multi-regional clinical trial (MRCT) (N = 203) demonstrated the safety of evocalcet in adult subjects with chronic kidney disease requiring dialysis and secondary hyperparathyroidism.

The overall treatment-emergent adverse events (TEAEs) patterns were generally similar between evocalcet and cinacalcet in the two randomized, controlled studies 7580-010 and 7580-201. There were 5 evocalcet-treated subjects with TEAEs leading to death (pancreatitis

acute, cardio-respiratory arrest, septic shock, lower limb fracture, and altered state of consciousness). Two events were considered related to evocalcet (pancreatitis acute and cardio-respiratory arrest).

Adverse events of special interest included hypocalcemia-related events, Torsade de points/QT prolongation, adverse events suggestive of proarrhythmic effect, lens disorders, upper gastrointestinal disorder-related events, and metabolic bone disease. The incidences of these adverse events of special interest were generally comparable between the evocalcet group and the cinacalcet group, except upper gastrointestinal disorder-related events. The incidence of upper gastrointestinal disorder-related events was lower in the evocalcet group comparing to the cinacalcet group.

No new safety signal was identified in the latest Japan Periodic Safety Report.

2.5 Bridging Study Evaluation

Considering (1) most of PK/PD data was from Japanese subjects, (2) both Taiwanese and Japanese belong to East Asian population, (3) evocalcet had ittle metabolism in vivo and did not involve genetic polymorphism enzyme, and (4) the subgroup analysis for country factor presented that the predicted exposure of Taiwanese were similar to that of Japanese. Overall, ethnic difference was negligible and bridging study can be waived form PK perspective

The clinical studies supporting this application were all conducted in East Asian region, including China, Japan, Korea, and Taiwan. The bridging study was therefore considered to be waived.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team leader recommends approval of evocalcet.

1. Recommended Indication: ORKEDIA® is indicated for treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis.
2. Recommended dose: The starting oral dose is 1 mg of evocalcet once daily. The dose may be started with an oral dose of 2 mg of evocalcet once daily, depending on the patient's condition. Therefore, the dose should be adjusted within the range of 1 to 8 mg once daily, with careful monitoring of the patient's parathyroid hormone and serum calcium levels. If the patient dose not respond sufficiently to the treatment, the dose could be adjusted and may be increased up to 12 mg once daily.

3. Post-Marketing Requirements

NA