Taiwan Food and Drug Administration

Assessment Report

Trade Name：旁必福注射液 /
PARSABIV Solution for Injection

Active Ingredient：Etelcalcetide

License Number：MOHW-PI 027639

Applicant：台灣安進藥品有限公司

Approval Date：2019/04/22

Indication：

PARSABIV 適用於治療罹患慢性腎臟病 (CKD) 且接受血液透析之成人病人的次發性副甲狀腺機能亢進 (secondary HPT)。

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

1. Background Information

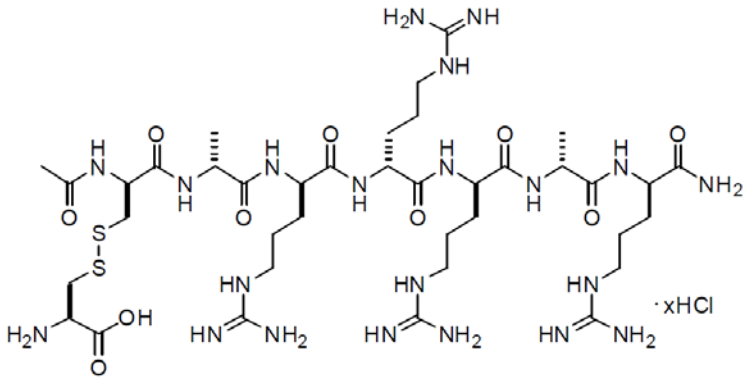
Trade Name	旁必福注射液 / PARSABIV Solution for Injection
Active Ingredient(s)	Etelcalcetide
Applicant	台灣安進藥品有限公司
Dosage Form & Strengths	Solution for Injection 5mg/mL
Indication	PARSABIV 適用於治療罹患慢性腎臟病 (CKD) 且接受血液透析之成人病人的次發性副甲狀腺機能亢進 (secondary HPT)。 PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.
Posology	起始劑量為每週三次 5 mg 靜脈推注，在血液透析治療結束時給藥。 維持劑量是將副甲狀腺素濃度維持在建議目標範圍，並將校正血鈣值維持在正常範圍。PARSABIV 的最低維持劑量為每週三次 2.5 mg，PARSABIV 的最高維持劑量為每週三次 15 mg。 The recommended starting dose of PARSABIV is 5 mg administered by intravenous (IV) bolus injection three times per week at the end of hemodialysis treatment. The maintenance dose of PARSABIV is individualized and determined by titration based on parathyroid hormone (PTH) and corrected serum calcium response. The lowest maintenance dose of PARSABIV is 2.5 mg three times per week, and the highest maintenance dose of PARSABIV is 15 mg three times per week.
Pharmacological Category **ATC Code**	H05BX04

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, etelcalcetide, is chemically designated as N-acetyl-D-cysteinyl-S-(L-cysteine disulfide)-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-alanyl-D-argininamide, hydrochloride salt and has the following structure:



It is a white to off-white, amorphous solid. The molecular formula is $C_{38}H_{73}N_{21}O_{10}S_2 \cdot xHCl$ ($4 \leq x \leq 5$). It is very hygroscopic. It is free soluble in aqueous media and polar organic solvents.

Adequate information of characterization of the drug substance has been provided. The structure of etelcalcetide is confirmed by amino acid analysis, elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, chiral amino acid analysis and ultraviolet/visible (UV/Vis) spectroscopy. The specification for the drug substance includes tests for appearance, identification, residual solvents, water, chloride content, heavy metals, specific optical rotation, impurities, microbial enumeration tests, bacterial endotoxins and assay.

2.1.2 Drug product

PARSABIV is a sterile, single-use preservative-free solution for intravenous injection available in 3 strengths containing 2.5, 5 or 10 mg of active substance. The liquid solution packaged in a 3-cc Type I glass vial. The excipients used in the drug product formulation comply with the compendial monographs. The established operating parameters and test results are acceptable.

The release specification for the drug product includes appearance, identification, assay, impurities, sub-visible particles, pH, osmolarity, deliverable volume, sterility and endotoxins. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (2-8°C) and accelerated condition (25°C/60% RH) have been carried out. The parameters evaluated during the stability study are appearance, assay, impurities, pH, sub-visible particles, container closure integrity and sterility.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Etelcalcetide is a synthetic peptide that functions as an allosteric activator of the calcium-sensing receptor (CaSR) in parathyroid tissue. *In vitro* studies demonstrated that etelcalcetide is an allosteric agonist of the CaSR, binding directly to the extracellular domain and activating the receptor at a site which is distinct from the calcium activating site. In normal rats and dogs, etelcalcetide suppressed PTH secretion in a dose-dependent manner in an hour, which was reversible. In rat models of uremia and secondary HPT, etelcalcetide was effective in reducing circulating levels of PTH when etelcalcetide was either given during disease progression of secondary HPT or given after establishment of secondary HPT. Etelcalcetide prevented parathyroid hyperplasia and development of vascular calcification. In a rat model of bone disease due to established secondary HPT, etelcalcetide reduced PTH and bone turnover, and preserved cortical bone structure and bone strength. These results indicate that etelcalcetide was effective in controlling elevated PTH, parathyroid hyperplasia, and preventing adverse bone, mineral and vascular consequences associated with secondary HPT in animal models. Safety pharmacology studies demonstrated no significant effects on CNS or respiratory function. A slight increase in QTc interval was observed in the dog, which was associated with maximal reductions in serum calcium. There were no effects on hERG current.

2.2.2 Toxicological Studies

The Repeat-dose toxicology studies were conducted in rat and dog. The toxicity effects were related, either directly or indirectly, to the pharmacologic activity of etelcalcetide and associated with hypocalcemia that ensues from suppression of PTH secretion. These toxicity effects were seen only at the highest dose levels tested, and showed evidence of ongoing reversibility. Etelcalcetide was mutagenic in some strains in the Ames assay. Mechanistic studies indicate that a thiol or thiolate anion in etelcalcetide is important for mutagenic activity in bacteria. Etelcalcetide was nongenotoxic in mammalian cells in the *in vitro* and *in vivo* genotoxicity studies, including a 28-day repeat-dose mutation assay in the Muta™ mouse. Importantly, etelcalcetide was not carcinogenic in the mouse or rat at maximum tolerated dose levels. There were no significant effects on reproductive organ weights, sperm parameters or mating and fertility parameters. There were no etelcalcetide-related effects observed in the absence of maternal toxicity. There were no etelcalcetide-related effects on embryo-fetal survival, fetal body weights, and fetal external, visceral, or skeletal malformations or variations. At maternal toxicity dose, lower mean fetal body weight, small delays in time to parturition, increased pup mortality, and transient decreases in pup growth rates were observed associated with maternal toxicities of hypocalcemia, tremor, and reductions in body weight and food consumption.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The pharmacokinetics of etelcalcetide is linear following single (5 to 60 mg) and multiple intravenous doses (2.5 to 20 mg) in chronic kidney disease patients with secondary hyperparathyroidism requiring hemodialysis. Multiple dosing for four weeks in CKD patients on dialysis is associated with etelcalcetide accumulation of approximately 3 folds. The plasma etelcalcetide pre-dialysis concentrations reached near steady state at week 4 after multiple dose administration. Etelcalcetide is primarily bound to plasma albumin by reversible covalent binding. Etelcalcetide was biotransformed by disulfide exchange in human whole blood. Etelcalcetide is not a substrate for cytochrome P450 enzymes. The predominant biotransformation product, SAPC, is formed by reversible covalent binding of the etelcalcetide to albumin. Based on the population pharmacokinetic analysis, the volume of distribution at steady state (V_{ss}) in CKD patients receiving hemodialysis is approximately 796 L and the CL was estimated to be 7.66 L/hr. The effective half-life is around 5 to 7 days in CKD patients with hemodialysis. Hemodialysis was the primary route of elimination for etelcalcetide and approximately 59.6% of the administered dose was eliminated in dialysate. Minor amounts of the dose were excreted in urine (3.2% of the administered dose) and in feces (4.5% of the administered dose).

2.3.2 Interaction Studies

In vitro studies indicated etelcalcetide is not shown to inhibit or induce cytochrome P450 enzymes. In addition, etelcalcetide is neither a substrate nor an inhibitor of common human efflux and uptake drug transporters. No clinical drug-drug interaction study was conducted for etelcalcetide.

2.3.3 Special Populations

Based on the population pharmacokinetic analysis, body weight, sex, race and age do not influence the pharmacokinetics of etelcalcetide. Hepatic impairment PK study was not conducted. The presence of binding anti-etelcalcetide antibodies had no apparent impact on plasma etelcalcetide concentrations. No dose adjustment is recommended for special populations.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A total of three randomized, controlled, Phase 3 studies (20120229, 20120230 and 20120360) were reviewed to evaluate the efficacy of PARSABIV (etelcalcetide) for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

The first two studies (20120229 and study 20120230) were randomized, multicenter,

double-blind, placebo-controlled trials to assess the efficacy and safety of etelcalcetide in the treatment of secondary HPT in subjects with CKD receiving hemodialysis. Study 20120360 was a multicenter, randomized, active-controlled, double-blind, double-dummy, dose-titration trial to compare etelcalcetide and cinacalcet in subjects with CKD and secondary HPT receiving hemodialysis.

The primary endpoint for all three studies was the proportion of subjects with > 30% reduction from baseline in predialysis PTH during the efficacy assessment phase (EAP). In both placebo-controlled studies, subjects who did not have any scheduled assessments during the EAP were considered as non-responders for the primary analysis. In Study 20120360, a multiple imputation method was applied to subjects who did not have data during the EAP. The primary analysis of the primary endpoint in all three studies was based on Full Analysis Set (FAS).

In Study 20120229, the primary analysis based on the non-responder imputation method demonstrated a statistically significant difference between etelcalcetide (74.0%) and placebo (8.3%) in the proportion of subjects with > 30% decrease from baseline in mean PTH during the EAP ($p < 0.001$; odds ratio 32.46, 95% CI=[18.71, 56.31]). The sensitivity analysis based on the multiple imputation method also showed a statistically significant difference between etelcalcetide and placebo (77.2% vs. 11.0%; $p<0.001$).

In Study 20120230, the primary analysis based on the non-responder imputation method demonstrated a statistically significant difference between etelcalcetide (75.3%) and placebo (9.6%) in the proportion of subjects with > 30% decrease from baseline in mean PTH during the EAP ($p < 0.001$; odds ratio 30.80, 95% CI=[18.18, 52.17]). The sensitivity analysis based on the multiple imputation method also showed a statistically significant difference between etelcalcetide and placebo (78.8% vs. 11.2%; $p<0.001$).

In Study 20120360, a higher proportion of subjects in the etelcalcetide group (77.9%) had a >30% decrease from baseline in serum PTH during the EAP compared with the cinacalcet group (63.9%). The estimated treatment difference (cinacalcet - etelcalcetide) was -10.48% (95% CI=[-17.45%, -3.51%]). The upper bound of the 95% CI is less than the pre-specified margin of 12%. Similar results were seen in the Per Protocol Analysis Set (difference= -12.41%, 95% CI= [-19.68%, -5.15%]). Hence, the non-inferiority of etelcalcetide to cinacalcet was demonstrated.

2.4.2 Safety Results

In the two placebo-controlled studies, 503 subjects received at least 1 dose of PARSABIV. The mean duration of exposure was 23.6 weeks. The most common adverse events in clinical studies were blood calcium decreased (64% in PARSABIV group; 10% in placebo), muscle spasms (12%in PARSABIV group; 7% in placebo), diarrhea (11%in PARSABIV group; 9% in placebo), nausea (11%in PARSABIV group; 6% in placebo), vomiting (9% in PARSABIV

group; 5% in placebo), headache (8% in PARSABIV group; 6% in placebo), hypocalcemia (7% in PARSABIV group; 0.2% in placebo), and paresthesia (6% in PARSABIV group; 1% in placebo).

The events of blood calcium decreased (asymptomatic laboratory finding of decreased calcium) and hypocalcemia (symptomatic events) occurred more frequently in PARSABIV group than placebo group. Most events in the hypocalcemia were mild or moderate in severity. In the placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group had hypocalcemia that led to treatment discontinuation. Besides, more patients receiving PARSABIV had a maximum increase from baseline of > 60 msec in QTcF interval (1.2% versus 0%). The incidence of adverse events in of ventricular tachyarrhythmia and Torsade de pointes was low and similar between treatment groups.

In addition, higher proportion of subjects in the PARSABIV group had events of hypophosphatemia in the placebo–controlled studies (1.4% in PARSABIV; 0.4% in placebo). None of the events in the PARSABIV group were severe in severity, nor reported as serious or resulting in discontinuation of the investigational product.
In summary, the safety profile of PARSABIV is acceptable for treating secondary hyperparathyroidism in adult patients with chronic kidney disease (CKD) on hemodialysis.

2.5 Bridging Study Evaluation

The ethnic impact on etelcalcetide PK between Asian and non-Asian populations was assessed from the phase I PK studies. The results showed $AUC_{0\text{-}65hr}$ and half-life for etelcalcetide after single dose administration were comparable between Japanese (N=12) and Western (N=24) healthy subjects. In the target patients, the C_{trough} value at pre-dialysis following 5 mg TIW dose is also similar between Japanese (N=12) and Western (N=11) patients. Overall, there was no essentially difference in PK exposures of etelcalcetide between races. The proposed regimen of PARSABIV solution was therefore considered none to minimal ethnically sensitive in PK perspective.

The bridging data of PARSABIV in efficacy and safety came from a multicenter, randomized, double blind, parallel-group Japanese study, ONO-5163-03. The study enrolled 155 secondary hyperparathyroidism subjects with chronic kidney disease on hemodialysis. Subjects were randomized in 1:1 ratio to receive PARSABIV or placebo for 12 weeks. The starting dose of PARSABIV in study ONO-5163-03 was 5mg administered three times per week, and the minimum and maximum maintenance PARSABIV doses were 2.5 and 15 mg three times per week. The efficacy result showed 76.9% of subjects who had received PARSABIV in study ONO-5163-03 achieve the primary endpoint (>30% reduction in PTH). It was statistic significantly better than the placebo group (Odds ratio 65.1, $p<0.0001$). The safety profile in study ONO-5163-03 was similar to those in the global placebo-controlled trials (study 20120229 and 2012030).

In summary, the bridging data of PARSABIV was provided, and there were no significant identified ethnic factors. To waive the bridging study was suggested.

2.6 Conclusion

The approval of PARSABIV for treatment secondary hyperparathyroidism in adult patients with chronic kidney disease on hemodialysis is suggested.

3. Post-Marketing Requirements

No post-marketing requirements.