1. NAME OF THE MEDICINAL PRODUCT

Parsabiv
5 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Parsabiv
Each mL contains 5 mg etelcalcetide.

Vial of 0.5 mL of solution contains 2.5 mg of etelcalcetide (as hydrochloride).
Vial of 1 mL of solution contains 5 mg of etelcalcetide (as hydrochloride).
Vial of 2 mL of solution contains 10 mg of etelcalcetide (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colorless liquid, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended initial dose of etelcalcetide is 5 mg administered by bolus injection 3 times per week. Corrected serum calcium should be at or above the lower limit of the normal range prior to administration of first dose of Parsabiv, a dose increase, or reinitiation after a dose stop (see also dose adjustments based on serum calcium levels). Parsabiv should not be administered more frequently than 3 times per week.

Dose titration

Parsabiv should be titrated so that doses are individualized between 2.5 mg and 15 mg. The dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve the desired parathyroid hormone (PTH) target.

Dose adjustments based on PTH levels

PTH should be measured after 4 weeks from initiation or dose adjustment of Parsabiv, and approximately every 1-3 months during maintenance. Dose adjustment may be necessary at any time during treatment including the maintenance phase.

If PTH is below 100 pg/mL (10.6 pmol/L), the dose should be reduced or temporarily stopped. If PTH does not return to > 100 pg/mL following dose reduction, the dose should be stopped. For patients in

whom the dose is stopped, Parsabiv should be reinitiated at a lower dose once PTH returns to > 150 pg/mL (15.9 pmol/L) and pre-dialysis serum corrected calcium (cCa) ≥ 8.3 mg/dL (2.08 mmol/L). If the patient's last administered dose was 2.5 mg, Parsabiv may be reinitiated at the 2.5 mg dose level if PTH is > 300 pg/mL (31.8 pmol/L), and the most recent pre-dialysis serum cCa ≥ 8.3 mg/dL (2.08 mmol/L).

Additional recommendations related to the management of low calcium are provided in the table below.

Parsabiv may be used as part of a therapeutic regimen including phosphate binders and/or vitamin D sterols, as appropriate (see section 5.1).

Dose adjustments based on serum calcium levels

Serum calcium should be measured within 1-week of initiation or dose adjustment of Parsabiv. Once the maintenance phase has been established for a patient, corrected serum calcium should be measured approximately every 4 weeks. In the studies total serum calcium was measured using Roche modular analyzers. The lower limit of the normal range for corrected serum calcium was 8.3 mg/dL (2.08 mmol/L). Other laboratory assays may have different cut-offs for the lower limit of the normal range.

In the event that clinically meaningful decreases in corrected serum calcium levels below the lower limit of the normal range occur and/or symptoms of hypocalcemia occur, the following management is recommended:

Corrected serum calcium value or clinical symptoms of hypocalcemia*:	**Recommendations**
< 8.3 mg/dL (2.08 mmol/L) and ≥ 7.5 mg/dL (1.88 mmol/L)	• If clinically indicated: - start or increase calcium supplements, calcium-containing phosphate binders, and/or vitamin D sterols. - increase dialysate calcium concentration. - consider reducing Parsabiv dose.
< 7.5 mg/dL (1.88 mmol/L) or symptoms of hypocalcemia	• Stop Parsabiv until corrected serum calcium levels are ≥ 8.3 mg/dL (2.08 mmol/L) and symptoms of hypocalcemia (if present) have resolved. • If clinically indicated: - start or increase calcium supplements, calcium-containing phosphate binders, and/or vitamin D sterols. - increase dialysate calcium concentration. • Reinitiate Parsabiv at a dose 5 mg lower than the last administered dose. If patient's last administered dose was 2.5 mg or 5 mg, reinitiate at 2.5 mg once corrected serum calcium levels are ≥ 8.3 mg/dL (2.08 mmol/L) and symptoms of hypocalcemia (if present) have resolved.

* Total calcium was measured using Roche modular analyzer. For albumin levels < 4 g/dL cCa (mg/dL) = Total Ca (mg/dL) + (4 - albumin[g/dL])*0.8.

Switch from cinacalcet to etelcalcetide

Etelcalcetide should not be initiated in patients until 7 days after the last dose of cinacalcet and the corrected serum calcium is at or above the lower limit of the normal range (see section 5.1).

Missed doses

If a regularly scheduled haemodialysis treatment is missed, do not administer any missed doses. Parsabiv should be administered at the next haemodialysis treatment at the same dose. If doses are missed for more than 2 weeks, then Parsabiv should be administered at 5 mg, (or 2.5 mg if that was the patients last administered dose), and titrated to achieve the desired PTH.

Special population

Elderly

Dosing recommendations for elderly patients are the same as for adult patients.

Paediatric population

The safety and efficacy of etelcalcetide in children and adolescents less than 18 years have not yet been established. No data are available.

Method of administration

Parsabiv is administered into the venous line of the dialysis circuit at the end of the hemodialysis treatment during rinse-back or intravenously after rinse-back. When given during rinse-back at least 150 mL of rinse-back volume should be administered after injection. If rinse-back is completed and Parsabiv was not administered, then it may be administered intravenously followed by at least 10 mL sodium chloride 9 mg/mL (0.9%) solution for injection flush volume.

Parsabiv should not be diluted.

Parenteral medicinal products should be inspected visually for particulate matter and change in colour prior to administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Parsabiv should not be initiated if corrected serum calcium is less than the lower limit of the normal range (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

Hypocalcemia

Etelcalcetide treatment should not be initiated in patients if the corrected serum calcium is less than the lower limit of the normal range (see section 4.3).

Potential manifestations of hypocalcemia include paresthesias, myalgias, muscle spasms and seizures.

Since etelcalcetide lowers serum calcium, patients should be advised to seek medical attention if they experience symptoms of hypocalcemia and should be monitored for the occurrence of hypocalcemia (see section 4.2). Serum calcium levels should be measured prior to initiating treatment, within 1-week of initiation or dose adjustment of etelcalcetide and every 4 weeks during treatment. If clinically meaningful decreases in corrected serum calcium levels occur, steps should be taken to increase serum calcium levels (see section 4.2).

Ventricular arrhythmia and QT prolongation secondary to hypocalcemia

Decreases in serum calcium can prolong the QT interval, potentially resulting in ventricular arrhythmia (see section 4.8). Serum calcium levels should be closely monitored in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death and other conditions that predispose to QT prolongation and ventricular arrhythmia while being treated with etelcalcetide.

ECG test should be performed before and during treatment, according to clinical judgment.

Convulsions

Cases of seizures have been reported in patients treated with etelcalcetide (see section 4.8). The threshold for seizures may be lowered by significant reductions in serum calcium levels. Serum calcium levels should be closely monitored in patients with a history of a convulsion disorder while being treated with etelcalcetide.

Worsening heart failure

Decreased myocardial performance, hypotension, and congestive heart failure (CHF) may be associated with significant reductions in serum calcium levels. Serum calcium levels should be monitored in patients with a history of CHF while being treated with etelcalcetide (see section 4.2), which may be associated with reductions in serum calcium levels.

Co-administration with other medicinal products

Administer etelcalcetide with caution in patients receiving any other medicinal products known to lower serum calcium. Closely monitor serum calcium (see section 4.5).

Patients receiving etelcalcetide should not be given cinacalcet. Concurrent administration may result in severe hypocalcemia.

Adynamic bone

Adynamic bone may develop if PTH levels are chronically suppressed below 100 pg/mL. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or etelcalcetide should be reduced or therapy discontinued. After discontinuation, therapy can be resumed at a lower dose to maintain PTH in the target range (see section 4.2).

Immunogenicity

In clinical studies, 7.1% of patients with SHPT treated with etelcalcetide for up to 6 months tested positive for binding antibodies, 80.3% of these had pre-existing antibodies. No evidence of altered pharmacokinetic profile, clinical response or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies.

Upper gastrointestinal bleeding

In clinical studies, two patients treated with Parsabiv in 1,253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to Parsabiv.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting), may be at increased risk for GI bleeding while receiving Parsabiv treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with

Parsabiv and for signs and symptoms of GI bleeding and ulcerations during Parsabiv therapy. Promptly evaluate and treat any suspected GI bleeding.

Excipient with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. There is no known risk of pharmacokinetic interaction with etelcalcetide.

In vitro, etelcalcetide did not inhibit or induce CYP450 enzymes and was itself not a substrate for metabolism by CYP450 enzymes. *In vitro*, etelcalcetide was not a substrate of efflux and uptake transporter proteins; and etelcalcetide was not an inhibitor of common transporter proteins.

Concurrent administration of other medicinal products known to reduce serum calcium (e.g. cinacalcet and denosumab) and etelcalcetide may result in an increased risk of hypocalcemia (see section 4.4). Patients receiving etelcalcetide should not be given cinacalcet (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of etelcalcetide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Parsabiv during pregnancy.

Breast-feeding

It is unknown whether etelcalcetide is present in human milk. Available data in rats have shown that etelcalcetide is excreted in milk (see section 5.3).

A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or discontinue/abstain from Parsabiv therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available on the effect of etelcalcetide on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Parsabiv has no or negligible influence on the ability to drive and use machines. However, certain potential manifestations of hypocalcemia may affect the ability to drive and use machines (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

Very common adverse reactions with Parsabiv are blood calcium decreased (64%), vomiting (13%), muscle spasms (12%), diarrhea (11%) and nausea (11%). They were mild to moderate in severity and

transient in nature in the majority of patients. Discontinuation of therapy as a result of adverse reactions was mainly due to low blood calcium, nausea, and vomiting.

Tabulated list of adverse reactions

Adverse reactions are listed below using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1 Adverse reactions from controlled clinical studies and post-marketing experience

MedDRA system organ class (SOC)	**Frequency category**	**Adverse reactions**
Immune system disorders	Not known	Hypersensitivity reactions (including anaphylaxis)
Metabolism and nutrition disorders	Very common	Blood calcium decreased[1, 4]
	Common	Hypocalcemia[1, 5] Hyperkalemia[2] Hypophosphatemia
Nervous system disorders	Common	Headache Paresthesia[3]
	Uncommon	Convulsions[6]
Cardiac disorders	Common	Worsening heart failure[1] QT prolongation[1]
Vascular disorders	Common	Hypotension
Gastrointestinal disorders	Very common	Nausea Vomiting Diarrhea
	Uncommon	Upper gastrointestinal bleeding
Musculoskeletal and connective tissue disorders	Very common	Muscle spasms
	Common	Myalgia

[1] See section Description of selected adverse reactions.
[2] Hyperkalemia includes preferred terms of hyperkalemia and blood potassium increased.
[3] Paresthesia includes preferred terms of paresthesia and hypoesthesia.
[4] Asymptomatic reductions in calcium below 7.5 mg/dL (1.88 mmol/L) or clinically significant asymptomatic reductions in serum cCa between 7.5 and < 8.3 mg/dL (1.88 and < 2.08 mmol/L) (that required medical management).
[5] Symptomatic reductions in serum cCa < 8.3 mg/dL (2.08 mmol/L).
[6] See section 4.4.

Description of selected adverse reactions

Hypocalcemia

Most events of asymptomatic blood calcium decreased and symptomatic hypocalcemia were mild or moderate in severity. In the combined placebo-controlled studies, a higher proportion of patients in the Parsabiv group compared with patients in the placebo group developed at least one serum cCa value < 7.0 mg/dL (1.75 mmol/L) (7.6% Parsabiv; 3.1% placebo), < 7.5 mg/dL (1.88 mmol/L) (27.1% Parsabiv; 5.5% placebo), and < 8.3 mg/dL (2.08 mmol/L) (78.6% Parsabiv; 19.4% placebo). In these studies 1% of patients in the Parsabiv group and 0% of patients in the placebo group discontinued treatment due to the adverse event of low serum calcium. For further information regarding potential manifestations of hypocalcemia and serum calcium monitoring see sections 4.4 and 4.2 respectively.

QTc prolongation secondary to hypocalcemia

In the combined placebo-controlled studies, a higher percentage of patients in the Parsabiv group compared with the placebo group had a maximum increase from baseline of > 60 msec in the QTcF

interval (1.2% Parsabiv; 0% placebo). The patient incidence of maximum post-baseline pre-dialysis QTcF > 500 msec in the Parsabiv and placebo groups was 4.8% and 1.9%, respectively.

Worsening heart failure

In the combined placebo-controlled studies, the subject incidence of adjudicated CHF events requiring hospitalization was 2.2% in the Parsabiv treatment group compared to 1.2% in the placebo group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

Overdose of etelcalcetide may lead to hypocalcemia with or without clinical symptoms and may require treatment. In the event of overdose, serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia (see section 4.4) and appropriate measures should be taken (see section 4.2). Although Parsabiv is cleared by dialysis, hemodialysis has not been studied as a treatment for overdose. Single doses up to 60 mg and multiple doses up to 22.5 mg 3 times a week at the end of dialysis in patients receiving hemodialysis were safely administered in clinical studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium homeostasis, anti-parathyroid agents. ATC code: H05BX04

Mechanism of action

The calcium-sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Etelcalcetide is a synthetic peptide calcimimetic agent which reduces PTH secretion through binding and activation of the calcium-sensing receptor. The reduction in PTH is associated with a concomitant decrease in serum calcium and phosphate levels.

Pharmacodynamic effects

Following a single intravenous bolus administration of 5 mg etelcalcetide, PTH levels decreased rapidly within 30 minutes post-dose and were maximally decreased for 1 hour, before returning to baseline. The extent and duration of the reduction in PTH increased with increasing dose. Reduction in PTH levels correlated with plasma etelcalcetide concentrations in hemodialysis patients. The effect of reducing PTH levels was maintained throughout the 6-month dosing period when etelcalcetide was administered by intravenous bolus 3 times a week.

Clinical efficacy and safety

Placebo-controlled studies

Two 6-month, double-blind, placebo-controlled clinical studies were conducted in SHPT patients with CKD receiving hemodialysis 3 times per week (N = 1,023). Patients were administered Parsabiv or placebo at a starting dose of 5 mg 3 times per week at the end of hemodialysis and titrated every 4 weeks through week 17 to a maximum dose of 15 mg 3 times per week to achieve target PTH level ≤ 300 pg/mL. The median average weekly dose of Parsabiv during the efficacy assessment period

(EAP) was 20.4 mg (6.8 mg per administration). Patients with lower screening PTH levels typically required lower doses (median average weekly doses of 15.0 mg, 21.4 mg, 27.1 mg, respectively, for patients with screening PTH levels < 600 pg/mL, 600 to ≤ 1,000 pg/mL, and > 1,000 pg/mL). Patients were maintained on dialysate calcium concentration ≥ 2.25 meq/L.

The primary endpoint in each study was the proportion of patients with > 30% reduction from baseline in PTH during the EAP (EAP, defined as weeks 20 to 27 inclusive). The secondary endpoints were the proportion of patients with a mean PTH ≤ 300 pg/mL during the EAP, and percent change from baseline during the EAP for PTH, serum cCa, phosphate and calcium phosphate product (Ca × P).

Demographic and baseline characteristics between the two groups in each study were similar. The mean age of patients across the 2 studies was 58.2 (range 21 to 93) years. Mean (SE) baseline PTH concentrations across the 2 studies were 846.9 (21.8) pg/mL, and 835.9 (21.0) pg/mL for the Parsabiv and placebo groups, respectively with approximately 21% of subjects enrolling across both studies having baseline PTH > 1,000 pg/mL. The average duration of hemodialysis prior to study entry was 5.4 years and 68% of patients were receiving vitamin D sterols at study entry, with 83% receiving phosphate binders.

Both studies demonstrated that Parsabiv reduced PTH, while lowering calcium, phosphate and Ca × P. Results of all primary and secondary endpoints were statistically significant and the results were consistent across both studies as shown in table 2.

Table 2 Effects of Parsabiv on PTH, corrected serum calcium, phosphate and Ca × P in 6 month placebo-controlled studies

	Study 1		**Study 2**	
	Parsabiv (N = 254)	**Placebo (N = 254)**	**Parsabiv (N = 255)**	**Placebo (N = 260)**
PTH				
Patients with > 30% reduction in PTH during the EAP, n (%)	188 (74.0)[a]	21 (8.3)	192 (75.3)[a]	25 (9.6)
Patients with ≤ 300 pg/mL in PTH during the EAP, n (%)	126 (49.6)[a]	13 (5.1)	136 (53.3)[a]	12 (4.6)
Mean percent change during the EAP, % (SE)	-55.11 (1.94)[a]	13.00 (2.81)	-57.39 (1.91)[a]	13.72 (2.50)
Corrected serum calcium				
Mean percent change during the EAP, % (SE)	-7.29 (0.53)[a]	1.18 (0.29)	-6.69 (0.55)[a]	0.58 (0.29)
Phosphate				
Mean percent change during the EAP, % (SE)	-7.71 (2.16)[b]	-1.31 (1.42)	-9.63 (1.61)[a]	-1.60 (1.42)
Ca × P				
Mean percent change during the EAP, % (SE)	-14.34 (2.06)[a]	-0.19 (1.44)	-15.84 (1.57)[a]	-1.06 (1.42)

[a] $p < 0.001$ versus placebo
[b] $p = 0.003$ versus placebo

Parsabiv decreased PTH regardless of baseline PTH, duration of dialysis, and whether or not patients were receiving vitamin D sterols. Patients with lower screening PTH levels were more likely to reach PTH ≤ 300 pg/mL during EAP.

Parsabiv was associated with reductions in bone metabolism markers (bone specific alkaline phosphatase and type I collagen c-telopeptide) and fibroblast growth factor 23 (exploratory endpoints) at the end of the study (week 27), compared with placebo.

Active-controlled study

A 6-month, double-blind, active-controlled study compared the efficacy and safety of Parsabiv with cinacalcet in 683 SHPT patients with CKD on hemodialysis. The dosing regimen for Parsabiv was similar to that in the placebo-controlled studies (starting dose of 5 mg titrated every 4 weeks with 2.5 mg to 5 mg increments to a maximum of 15 mg 3 times a week). The starting dose of cinacalcet was 30 mg daily, titrated every 4 weeks in 30 mg increments or 60 mg for the last uptitration to a maximum dose of 180 mg daily following the cinacalcet prescribing information. The median average

weekly dose of Parsabiv during the EAP was 15.0 mg (5.0 mg per administration) and of cinacalcet was 360.0 mg (51.4 mg per administration). The primary endpoint was non-inferiority for the proportion of patients who achieved > 30% reduction from baseline in mean PTH during the EAP (weeks 20 to 27). Key secondary endpoints were the proportion of patients who achieved > 50% and > 30% reductions from baseline in mean PTH during the EAP and the mean number of days of vomiting or nausea per week in the first 8 weeks, sequentially tested for superiority. Mean (SE) baseline PTH concentrations were 1,092.12 (33.8) and 1,138.71 (38.2) pg/mL for the Parsabiv and cinacalcet groups respectively. Demographics and other baseline characteristics were similar to the placebo-controlled studies.

Parsabiv was non-inferior to cinacalcet for the primary endpoint, and was superior to cinacalcet for the secondary endpoints of proportion of patients achieving > 30% reduction from baseline in mean PTH during the EAP (68.2% Parsabiv versus 57.7% cinacalcet; p = 0.004); and proportion of patients achieving > 50% reduction from baseline in mean PTH during the EAP (52.4% Parsabiv versus 40.2% cinacalcet; p = 0.001). No statistically significant difference between the two groups was observed for the secondary endpoint evaluating the mean number of days of vomiting or nausea per week in the first 8 weeks.

"Switch study"

Results from a study which evaluated changes in corrected serum calcium levels when switching patients from cinacalcet to Parsabiv showed that treatment with Parsabiv, at a starting dose of 5 mg, could be safely initiated after a 7-day discontinuation of cinacalcet, provided that the corrected serum calcium was ≥ 8.3 mg/dL (2.08 mmol/L).

Open-label extension study

A 52-week, single arm extension study to the placebo-controlled and "switch" studies described above was conducted to characterize the long term safety and efficacy of Parsabiv in 891 SHPT patients with CKD on hemodialysis. All subjects received Parsabiv at a starting dose of 5 mg 3 times a week. The dose of Parsabiv could be titrated at weeks 5, 9, 17, 25, 33, 41, and 49 to a maximum dose of 15 mg to achieve target PTH levels ≤ 300 pg/mL while maintaining serum cCa concentrations.

At the end of 52 weeks, Parsabiv was not associated with any new safety findings and demonstrated maintenance of treatment effect as evidenced by a decrease in pre-dialysis PTH by > 30% from baseline in 2/3rd of patients. In addition, Parsabiv decreased pre-dialysis PTH to ≤ 300 pg/mL in more than 50% of patients and decreased mean PTH, cCa, cCa × P, and phosphate from baseline.

5.2 Pharmacokinetic properties

Distribution

In the population pharmacokinetics model, volume of distribution at steady-state was approximately 796 L. Etelcalcetide is predominately bound to plasma albumin by reversible covalent binding. Non-covalent binding of etelcalcetide to plasma proteins is low with a fraction unbound ratio of 0.53. The ratio of blood-to-plasma [^{14}C]-etelcalcetide concentrations is approximately 0.6.

Biotransformation

Etelcalcetide is not metabolized by CYP450 enzymes. Etelcalcetide is biotransformed in blood by reversible disulfide exchange with endogenous thiols to predominantly form conjugate with serum albumin. The plasma exposure of biotransformation products was approximately 5-fold higher than that of etelcalcetide and their concentration-time course parallels that of etelcalcetide. The predominant biotransformation product (albumin bound) was minimally active *in vitro*.

Elimination

Intravenous administration 3 times per week at the end of a hemodialysis session resulted in an effective half-life of 3 to 5 days. Etelcalcetide is rapidly cleared in subjects with normal renal function, whilst in CKD patients requiring hemodialysis, etelcalcetide was predominantly eliminated by hemodialysis. Etelcalcetide was efficiently removed with a hemodialysis clearance value of 7.66 L/hour. Following a single radiolabeled dose of etelcalcetide in CKD patients with secondary HPT receiving hemodialysis, approximately 60% of dosed [^{14}C]-etelcalcetide was recovered in dialysate and approximately 7% recovered in urine and feces combined over 175 days of collection period. The inter-subject variability of the system clearance in the patient population is approximately 70%.

Linearity/non-linearity

The pharmacokinetics of etelcalcetide is linear and does not change over time following single (5 to 60 mg) and multiple intravenous doses (2.5 to 20 mg) in CKD patients with secondary HPT receiving hemodialysis. Following 3 times a week intravenous dosing at the end of each 3 to 4 hour hemodialysis session in CKD patients, etelcalcetide plasma levels reached near steady-state 4 weeks after dosing with an observed accumulation ratio of 2- to 3-fold.

Renal impairment

No specific pharmacokinetic studies of etelcalcetide have been conducted in patients with mild to severe kidney impairment. The pharmacokinetics of etelcalcetide was characterized in CKD patients receiving hemodialysis. Etelcalcetide is intended for CKD patients receiving hemodialysis.

Hepatic impairment

No specific study in patients with hepatic impairment was performed.

Body weight, gender, age, race

No body weight, gender, age, or race-related pharmacokinetic differences have been observed in adult patients studied.

5.3 Preclinical safety data

The expected pharmacological effect of decreased PTH and calcium in blood were observed in animal studies at clinical exposure levels. Reductions in serum calcium associated with tremoring, convulsions and stress-related findings were observed at clinical exposure levels. All effects were reversible upon cessation of treatment.

Etelcalcetide was mutagenic in some strains of bacteria (Ames), however was not genotoxic in *in vitro* and *in vivo* mammalian genotoxicity assays and therefore is considered non-genotoxic in humans. In mouse and rat carcinogenicity studies, there were no etelcalcetide-related tumors up to exposure of 0.4-fold clinical exposure levels.

There was no effect on male or female fertility when etelcalcetide was administered to rats at exposure levels up to 1.8-fold higher than clinical exposures levels achieved in patients receiving etelcalcetide at 15 mg three times per week.

There were no effects on embryo-fetal development in rats and rabbits when exposed to up to 1.8 to 4.3 times clinical exposure levels during organogenesis. In a pre- and post-natal development study in rats there was a minimal increase in perinatal pup mortality, delay in parturition and transient reductions in post-natal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption at 1.8 times clinical exposure levels.

Studies in rats showed [^{14}C]-etelcalcetide was excreted in the milk at concentrations similar to plasma.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Succinic acid
Water for injections
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Once removed from the refrigerator:

- Parsabiv is stable for up to 7 days in the original carton.
- If removed from the original carton Parsabiv is stable for up to 4 hours if protected from direct sunlight.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Single use vial (type I glass) with stopper (fluoropolymer laminated elastomeric) and an aluminum seal with flip-off dust cover.
Each vial contains 0.5 / 1 / 2 mL solution for injection.

Pack sizes of 6 vials.

6.6 Special precautions for disposal and other handling

For single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

8. LICENSE HOLDER

Amgen Europe B.V.
P.O. BOX 53313
Tel – Aviv
6153201

9. LICENSE NUMBER

161-94-35289

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