

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Parsabiv 2.5 mg solution for injection
Parsabiv 5 mg solution for injection
Parsabiv 10 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Parsabiv 2.5 mg solution for injection

Each vial contains 2.5 mg of etelcalcetide (as hydrochloride) in 0.5 mL of solution.
Each mL contains 5 mg etelcalcetide.

Parsabiv 5 mg solution for injection

Each vial contains 5 mg of etelcalcetide (as hydrochloride) in 1 mL of solution.
Each mL contains 5 mg etelcalcetide.

Parsabiv 10 mg solution for injection

Each vial contains 10 mg of etelcalcetide (as hydrochloride) in 2 mL of solution.
Each mL contains 5 mg etelcalcetide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear colourless solution.

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 haemodialysis 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 individualised 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) \geq 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 \geq 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 analysers. 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 hypocalcaemia occur, the following management is recommended:

Corrected serum calcium value or clinical symptoms of hypocalcaemia*:	Recommendations
< 8.3 mg/dL (2.08 mmol/L) and \geq 7.5 mg/dL (1.88 mmol/L)	<ul style="list-style-type: none">• If clinically indicated:<ul style="list-style-type: none">- 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 hypocalcaemia	<ul style="list-style-type: none">• Stop Parsabiv until corrected serum calcium levels are \geq 8.3 mg/dL (2.08 mmol/L) and symptoms of hypocalcaemia (if present) have resolved.• If clinically indicated:<ul style="list-style-type: none">- 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 \geq 8.3 mg/dL (2.08 mmol/L) and symptoms of hypocalcaemia (if present) have resolved.

* Total calcium was measured using Roche modular analyser. 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 haemodialysis 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

Hypocalcaemia

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 hypocalcaemia include paraesthesias, myalgias, muscle spasms and seizures.

Since etelcalcetide lowers serum calcium, patients should be advised to seek medical attention if they experience symptoms of hypocalcaemia and should be monitored for the occurrence of hypocalcaemia (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 hypocalcaemia

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.

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 hypocalcaemia.

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.

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 hypocalcaemia (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 hypocalcaemia may affect the ability to drive and use machines (see section 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%), diarrhoea (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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	Hypocalcaemia ^{1,5} Hyperkalaemia ² Hypophosphataemia
Nervous system disorders	Common	Headache Paraesthesia ³
	Uncommon	Convulsions ⁶
Cardiac disorders	Common	Worsening heart failure ¹ QT prolongation ¹
Vascular disorders	Common	Hypotension
Gastrointestinal disorders	Very common	Nausea Vomiting Diarrhoea
Musculoskeletal and connective tissue disorders	Very common	Muscle spasms
	Common	Myalgia

¹ See section Description of selected adverse reactions.

² Hyperkalaemia includes preferred terms of hyperkalaemia and blood potassium increased.

³ Paraesthesia includes preferred terms of paraesthesia and hypoaesthesia.

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

Hypocalcaemia

Most events of asymptomatic blood calcium decreased and symptomatic hypocalcaemia 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 hypocalcaemia and serum calcium monitoring, see sections 4.4 and 4.2 respectively.

QTc prolongation secondary to hypocalcaemia

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 hospitalisation 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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via [the national reporting system](#) listed in [Appendix V](#).

4.9 Overdose

Overdose of etelcalcetide may lead to hypocalcaemia 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 hypocalcaemia (see section 4.4) and appropriate measures should be taken (see section 4.2). Although Parsabiv is cleared by dialysis, haemodialysis 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 haemodialysis 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 haemodialysis 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 haemodialysis 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 haemodialysis 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 $\leq 1,000$ 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 ($\text{Ca} \times \text{P}$).

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 haemodialysis 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 haemodialysis. 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 characterise the long term safety and efficacy of Parsabiv in 891 SHPT patients with CKD on haemodialysis. 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 \times P, and phosphate from baseline.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Parsabiv in one or more subsets of the paediatric population in the treatment of hyperparathyroidism (see section 4.2 for information on paediatric use).

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 [¹⁴C]-etelcalcetide concentrations is approximately 0.6.

Biotransformation

Etelcalcetide is not metabolised by CYP450 enzymes. Etelcalcetide is biotransformed in blood by reversible disulphide 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 haemodialysis 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 haemodialysis, etelcalcetide was predominantly eliminated by haemodialysis. Etelcalcetide was efficiently removed with a haemodialysis clearance value of 7.66 L/hour. Following a single radiolabelled dose of etelcalcetide in CKD patients with secondary

HPT receiving haemodialysis, approximately 60% of dosed [¹⁴C]-etelcalcetide was recovered in dialysate and approximately 7% recovered in urine and faeces 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 haemodialysis. Following 3 times a week intravenous dosing at the end of each 3 to 4 hour haemodialysis 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 characterised in CKD patients receiving haemodialysis. Etelcalcetide is intended for CKD patients receiving haemodialysis.

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 tumours 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-foetal 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 hypocalcaemia, tremoring, and reductions in body weight and food consumption at 1.8 times clinical exposure levels.

Studies in rats showed [¹⁴C]-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

4 years.

Once removed from the refrigerator:

- Parsabiv is stable for a maximum of 7 cumulative days if stored in the original carton. No special temperature storage requirements are needed.
- If removed from the original carton Parsabiv is stable for a maximum of 4 hours if protected from direct sunlight.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Parsabiv 2.5 mg solution for injection

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

Parsabiv 5 mg solution for injection

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

Parsabiv 10 mg solution for injection

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

Pack sizes of 1, 6, 12 and 42 vials.

Not all pack sizes may be marketed.

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. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

Parsabiv 2.5 mg solution for injection

EU/1/16/1142/001 - 1 vial

EU/1/16/1142/002 - 6 vials

EU/1/16/1142/003 - 12 vials

EU/1/16/1142/004 - 42 vials

Parsabiv 5 mg solution for injection

EU/1/16/1142/005 - 1 vial

EU/1/16/1142/006 - 6 vials

EU/1/16/1142/007 - 12 vials

EU/1/16/1142/008 - 42 vials

Parsabiv 10 mg solution for injection

EU/1/16/1142/009 - 1 vial

EU/1/16/1142/010 - 6 vials

EU/1/16/1142/011 - 12 vials

EU/1/16/1142/012 - 42 vials

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2016

Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

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

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Parsabiv 2.5 mg solution for injection
etelcalcetide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2.5 mg of etelcalcetide (as hydrochloride).

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, succinic acid, water for injections, hydrochloric acid, sodium hydroxide.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 vial (0.5 mL)

6 vials (0.5 mL)

12 vials (0.5 mL)

42 vials (0.5 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1142/001
EU/1/16/1142/002
EU/1/16/1142/003
EU/1/16/1142/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Parsabiv 2.5 mg solution for injection
etelcalcetide
IV

2. METHOD OF ADMINISTRATION

Intravenous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Parsabiv 5 mg solution for injection
etelcalcetide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5 mg of etelcalcetide (as hydrochloride).

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, succinic acid, water for injections, hydrochloric acid, sodium hydroxide.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 vial (1 mL)

6 vials (1 mL)

12 vials (1 mL)

42 vials (1 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1142/005
EU/1/16/1142/006
EU/1/16/1142/007
EU/1/16/1142/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Parsabiv 5 mg solution for injection
etelcalcetide
IV

2. METHOD OF ADMINISTRATION

Intravenous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Parsabiv 10 mg solution for injection
etelcalcetide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 mg of etelcalcetide (as hydrochloride).

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, succinic acid, water for injections, hydrochloric acid, sodium hydroxide.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 vial (2 mL)

6 vials (2 mL)

12 vials (2 mL)

42 vials (2 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1142/009
EU/1/16/1142/010
EU/1/16/1142/011
EU/1/16/1142/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Parsabiv 10 mg solution for injection
etelcalcetide
IV

2. METHOD OF ADMINISTRATION

Intravenous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Parsabiv 2.5 mg solution for injection Parsabiv 5 mg solution for injection Parsabiv 10 mg solution for injection etelcalcetide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Parsabiv is and what it is used for
2. What you need to know before you use Parsabiv
3. How to use Parsabiv
4. Possible side effects
5. How to store Parsabiv
6. Contents of the pack and other information

1. What Parsabiv is and what it is used for

Parsabiv contains the active substance etelcalcetide, which reduces parathyroid hormone known as PTH.

Parsabiv is used to treat secondary hyperparathyroidism in patients with serious kidney disease who need haemodialysis to clear their blood of waste products.

In secondary hyperparathyroidism too much PTH is produced by the parathyroid glands (four small glands in the neck). “Secondary” means that the hyperparathyroidism is caused by another condition, e.g. kidney disease. Secondary hyperparathyroidism can cause the loss of calcium from the bones, which can lead to bone pain and fractures and problems with blood and heart vessels. By controlling the levels of PTH, Parsabiv helps to control calcium and phosphate in your body.

2. What you need to know before you use Parsabiv

Do not use Parsabiv

- if you are allergic to etelcalcetide or any of the other ingredients of this medicine (listed in section 6).
- if you have very low levels of calcium in your blood. Your doctor will monitor your blood calcium levels.

Warnings and precautions

Before you are given Parsabiv, tell your doctor if you have or have ever had:

- heart problems, such as heart failure or arrhythmias (abnormal heart rhythm);
- seizures (fits or convulsions).

Parsabiv reduces calcium levels. Please tell your doctor if you have spasms, twitches, or cramps in your muscles, or numbness or tingling in your fingers, toes or around your mouth or seizures, confusion or loss of consciousness while being treated with Parsabiv. For additional information see section 4.

Low calcium levels can cause abnormal heart rhythm. Tell your doctor if you experience an unusually fast or pounding heartbeat, if you have heart rhythm problems or heart failure or if you take medicines that can cause heart rhythm problems, while receiving Parsabiv. For additional information see section 4.

Very low levels of PTH over long periods can result in a type of abnormal bone structure known as adynamic bone which can only be diagnosed by biopsy. Your PTH levels will be monitored during treatment with Parsabiv and your dose of Parsabiv may be reduced if your PTH levels become very low.

Children and adolescents

It is not known whether Parsabiv is safe and effective in children less than 18 years of age as it has not been studied in these patients.

Other medicines and Parsabiv

Tell your doctor if you are taking, have recently taken or might take any other medicines, including those medicines obtained without a prescription, or any other medicines that lower serum calcium (e.g. cinacalcet and denosumab).

You should not receive Parsabiv together with cinacalcet. Tell your doctor if you are taking cinacalcet or have recently taken cinacalcet.

Pregnancy

Parsabiv has not been tested in pregnant women. It is not known whether Parsabiv can harm your unborn baby. Tell your doctor if you are pregnant, think you may be pregnant, or plan to get pregnant when taking Parsabiv. As a precautionary measure, it is preferable to avoid the use of Parsabiv during pregnancy.

Breast-feeding

It is not known whether Parsabiv can pass into breast milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Parsabiv, considering the benefit of breast-feeding to the baby and the benefit of Parsabiv to the mother.

Driving and using machines

Parsabiv has no or negligible influence on the ability to drive and use machines. However certain symptoms of low calcium levels (such as fits or convulsions) can affect your ability to drive or operate machinery.

Parsabiv contains sodium

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

3. How to use Parsabiv

The recommended starting dose for Parsabiv is 5 mg. It will be given by a doctor or nurse at the end of your haemodialysis treatment through the tube (bloodline) that connects you to the haemodialysis machine. Parsabiv will be given 3 times per week. The dose may be increased up to 15 mg or lowered down to 2.5 mg depending on your response.

You may need to take calcium and vitamin D supplements while being treated with Parsabiv. Your doctor will discuss this with you.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Low calcium levels in blood (hypocalcaemia) have been reported commonly (may affect up to 1 in 10 people). If you feel numbness or tingling around your mouth or in your extremities, muscle aches or cramps and seizures (fits), you should tell your doctor immediately. These may be signs that your calcium levels are too low.

Very common: may affect more than 1 in 10 people

- Nausea
- Vomiting
- Diarrhoea
- Muscle spasms
- Low calcium levels in blood with no symptoms

Common: may affect up to 1 in 10 people

- High potassium levels in blood
- Low phosphate levels in blood
- Headache
- Numbness or tingling sensation
- Worsening heart failure
- Disturbances in the heart's electrical activity seen as QT prolongation on electrocardiogram
- Low blood pressure
- Muscle pain

Uncommon: may affect up to 1 in 100 people

- Seizures (fits or convulsions); for additional information see section 2

Not known: frequency cannot be estimated from the available data

- Allergic reactions (including anaphylactic reactions)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Parsabiv

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Keep the vial in the outer carton in order to protect from light.

Once removed from the refrigerator:

- Parsabiv is stable for a maximum of 7 cumulative days if stored in the original carton. No special temperature storage requirements are needed.
- If removed from the original carton Parsabiv is stable for a maximum of 4 hours if protected from direct sunlight.

Do not use this medicine if you notice it has particles or it has changed colour.

For single use only.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Parsabiv contains

- The active substance is etelcalcetide.
Parsabiv 2.5 mg solution for injection: Each vial contains 2.5 mg of etelcalcetide in 0.5 mL solution (5 mg/mL).
Parsabiv 5 mg solution for injection: Each vial contains 5 mg of etelcalcetide in 1 mL solution (5 mg/mL).
Parsabiv 10 mg solution for injection: Each vial contains 10 mg of etelcalcetide in 2 mL solution (5 mg/mL).
- The other ingredients are sodium chloride, succinic acid, water for injections, hydrochloric acid, and sodium hydroxide (refer to section 2: Parsabiv contains sodium).

What Parsabiv looks like and contents of the pack

Parsabiv is a clear and colourless liquid.

Parsabiv is a solution for injection in a vial.

Pack sizes of 1, 6, 12 and 42 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

Marketing Authorisation Holder

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Minervum 7061
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The Netherlands

Manufacturer

Amgen NV
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>