SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

YORVIPATH

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yorvipath consists of PTH(1-34) conjugated to a methoxypolyethylene glycol carrier (mPEG) via a Linker.

Yorvipath 168 micrograms/0.56 mL solution for injection in pre-filled pen

Each pre-filled pen contains palopegteriparatide equivalent to 168 micrograms of PTH(1-34) in 0.56 mL of solvent*. The concentration based on PTH(1-34) is 0.3 mg/mL. Each pre-filled pen delivers doses of 6, 9, or 12 micrograms of PTH(1-34).

Yorvipath 294 micrograms/0.98 mL solution for injection in pre-filled pen

Each pre-filled pen contains palopegteriparatide equivalent to 294 micrograms of PTH(1-34) in 0.98 mL of solvent*. The concentration based on PTH(1-34) is 0.3 mg/mL. Each pre-filled pen delivers doses of 15, 18, or 21 micrograms of PTH(1-34).

Yorvipath 420 micrograms/1.4 mL solution for injection in pre-filled pen

Each pre-filled pen contains palopegteriparatide equivalent to 420 micrograms of PTH(1-34) in 1.4 mL of solvent*. The concentration based on PTH(1-34) is 0.3 mg/mL. Each pre-filled pen delivers doses of 24, 27, or 30 micrograms of PTH(1-34).

*The strength indicates the quantity of the PTH(1-34) moiety without consideration of the mPEG-linker.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear and colourless with a pH of 3.7 - 4.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism.

4.2 Posology and method of administration

Treatment should be initiated and monitored by physicians or qualified healthcare professionals experienced in the diagnosis and management of patients with hypoparathyroidism.

Posology

Dose recommendations of Yorvipath refer to micrograms of PTH(1-34). The dose should be individualised based on serum calcium. The optimal dose after titration is the minimum dose required to prevent hypocalcaemia. This is the dose that maintains serum calcium within the normal range without the need for active forms of vitamin D or calcium supplementation beyond recommended nutritional supplementation for the general population (generally less than 600 mg per day). Doses of active forms of vitamin D and calcium supplements will need to be adjusted prior to initiating and during treatment with Yorvipath based on serum calcium value (see section 4.4).

Patients receiving the maximum Yorvipath dose of 60 mcg per day who experience ongoing hypocalcaemia may require co-administration of therapeutic calcium and/or active forms of vitamin D.

Before initiation of Yorvipath

Serum 25(OH) vitamin D should be within the normal range and serum calcium should be stable within or slightly below the normal range (1.95 - 2.64 mmol/L [7.8 - 10.6 mg/dL]) on at least 1 laboratory value at least two weeks prior to first dose of treatment.

Initiation of Yorvipath

The recommended starting dose is 18 mcg once daily with dose adjustments in 3 mcg increments thereafter every 7 days (see figure 1). The dose range is 6 to 60 mcg per day.

When initiating treatment with Yorvipath, the dose of active vitamin D or calcium supplements should be adjusted:

- If taking active vitamin D:
  - If serum calcium is ≥ 2.07 mmol/L [≥ 8.3 mg/dL], active vitamin D (calcitriol or alfacalcidol) should be discontinued on the same day as the first dose of Yorvipath. Doses of calcium supplements should be maintained.
  - If serum calcium is < 2.07 mmol/L [< 8.3 mg/dL], active vitamin D should be reduced by ≥ 50% on the same day as the first dose of Yorvipath. Doses of calcium supplements should be maintained.
- If not taking active vitamin D:
  - Calcium supplements should be decreased by at least 1 500 mg on the same day as the first dose of Yorvipath. If taking elemental calcium doses ≤ 1 500 mg per day, calcium supplements should be discontinued entirely.
- If calcium supplements are indicated to meet dietary requirements, continuing dietary calcium supplements at doses ≤ 600 mg per day may be considered instead of discontinuing entirely.

Dose adjustment and maintenance of Yorvipath

Serum calcium concentration must be monitored during titration (see section 4.4).
Yorvipath dose may be increased in increments of 3 mcg if at least 7 days have elapsed since a prior dose change (see figure 1). The dose must not be increased more often than every 7 days. Yorvipath may be reduced in increments of 3 mcg no more often than every 3 days in response to hypercalcaemia (see figure 1).

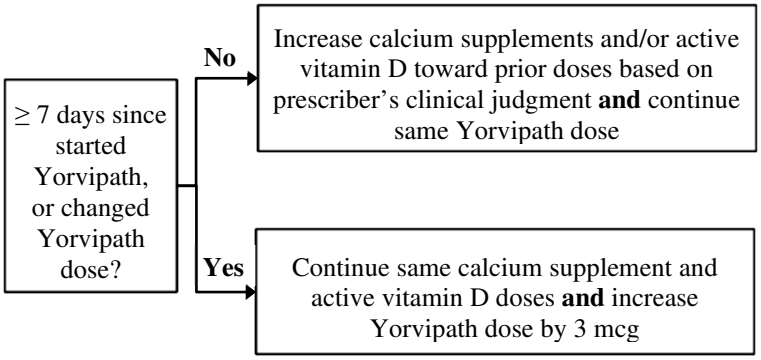
Serum calcium should be measured 7 days after the first dose and figure 1 should be followed for appropriate Yorvipath, active vitamin D, and calcium supplement dosing. After any subsequent dose change in Yorvipath, active vitamin D, or calcium supplements, serum calcium should be measured within 7 to 14 days and patients should be monitored for clinical symptoms of hypocalcaemia or hypercalcaemia. Yorvipath, active vitamin D, and/or calcium supplements should be adjusted as per figure 1. Dose adjustments of Yorvipath, active vitamin D, and calcium

supplements should be made on the same day.

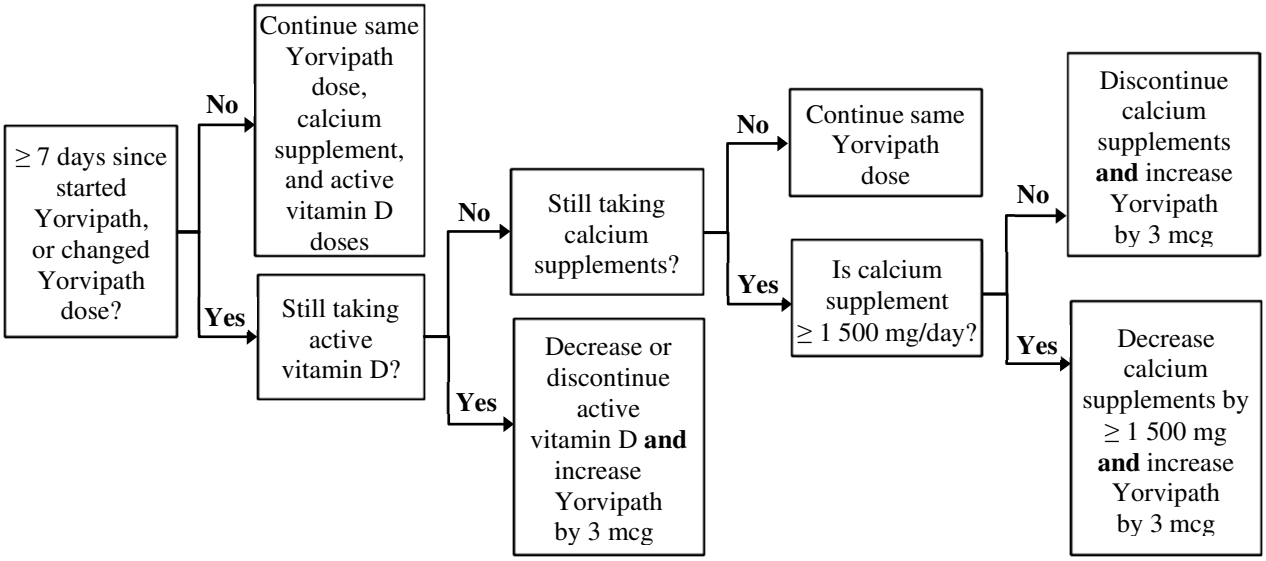
The maintenance dose should be the dose that achieves serum calcium within the normal range, without the need for active vitamin D or therapeutic doses of calcium. Optionally, calcium supplementation sufficient to meet dietary requirements (≤ 600 mg per day) may be continued. Serum calcium and 25(OH) vitamin D should be measured as per standard of care when a maintenance dose is achieved. 25(OH) vitamin D (non-active vitamin D) supplementation may be needed to reach normal serum levels.

Figure 1: Titration of Yorvipath, active vitamin D, and calcium supplements Serum calcium

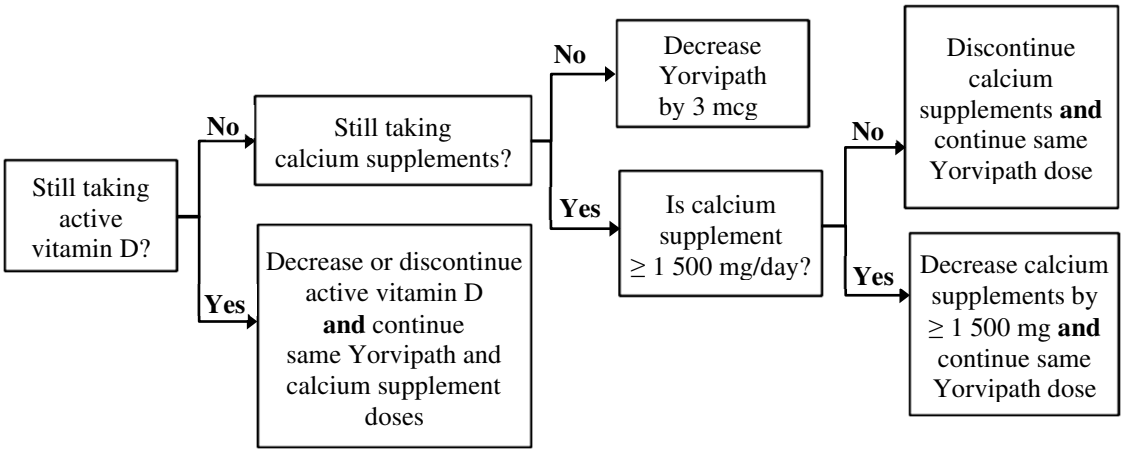
low (< 2.07 mmol/L [< 8.3 mg/dL]):



Serum calcium normal (≥ 2.07 to ≤ 2.64 mmol/L [≥ 8.3 to ≤ 10.6 mg/dL]):



Serum calcium high (≥ 2.65 to < 3.00 mmol/L [≥ 10.7 to < 12.0 mg/dL]):



Serum calcium very high (≥ 3.00 mmol/L [≥ 12 mg/dL]):

Treatment should be withheld for 2 to 3 days and then serum calcium should be rechecked. If subsequent serum calcium is < 3.00 mmol/L [< 12 mg/dL], titration of Yorvipath, active vitamin D, and calcium supplements should be resumed as per the applicable section of figure 1 using the most recent serum calcium value obtained. If serum calcium remains ≥ 3.00 mmol/L [≥ 12 mg/dL], Yorvipath should be withheld for an additional 2 to 3 days and then serum calcium should be rechecked. See section 4.4 for more information on hypercalcaemia.

Missed dose

If a dose is missed by less than 12 hours, it should be administered as soon as possible. If a dose is missed by more than 12 hours, it should be skipped and the next dose should be administered as scheduled.

Interruption or discontinuation of Yorvipath

Interruption of daily administration should be avoided to minimise serum PTH fluctuations. Interruption or discontinuation of treatment can result in hypocalcaemia. When interrupting or discontinuing treatment for 3 or more consecutive doses, patients should be monitored for signs and symptoms of hypocalcaemia and consider to measure serum calcium. If indicated, treatment with calcium supplements and active vitamin D should be resumed. Treatment at the prescribed dose should be resumed as soon as possible after an interruption. When resuming treatment after an interruption, serum calcium should be measured and doses of Yorvipath, active vitamin D, and calcium supplements should be adjusted as per figure 1.

Special populations

Elderly

Dose adjustment is not required based on age (see section 5.2).

Hepatic impairment

Yorvipath has not been studied in patients with hepatic impairment.
Yorvipath should be used with caution in patients with severe hepatic impairment (see section 4.4).
Mild and moderate hepatic impairment is not expected to have a clinically significant impact on the pharmacokinetics of palopegteriparatide

Renal impairment

Dose adjustment is not required in patients with an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min. Serum calcium levels should be measured more frequently when used in patients with eGFR < 45 mL/min (see section 4.4). Yorvipath has not been studied in patients with hypoparathyroidism and severe renal impairment (eGFR < 30 mL/min) (see section 5.2).

Paediatric population

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

Method of administration

Yorvipath must be administered as a subcutaneous injection to the abdomen or front of the thigh. The injection site should be rotated daily between four possible sites; abdomen (left or right) and front of the thigh (left or right).

Doses > 30 mcg per day (sequential injections)

All doses > 30 mcg per day should be administered as two single doses injected sequentially at different injection sites (table 1). It is recommended to use a different Yorvipath pen for the second daily injection, even if the two pens have the same-coloured push button (same strength).

Table 1: Recommended scheme for Yorvipath dosing > 30 mcg/day

Dose	Dosing scheme	Pen combination
33 mcg/day	15 mcg/day + 18 mcg/day	Two pre-filled pens of Yorvipath 294 mcg/0.98 mL (orange push button)*
36 mcg/day	18 mcg/day + 18 mcg/day	
39 mcg/day	18 mcg/day + 21 mcg/day	
42 mcg/day	21 mcg/day + 21 mcg/day	
45 mcg/day	21 mcg/day + 24 mcg/day	One pre-filled pen of Yorvipath 294 mcg/0.98 mL (orange push button) + One pre-filled pen of Yorvipath 420 mcg/1.4 mL (burgundy push button)**
48 mcg/day	24 mcg/day + 24 mcg/day	Two pre-filled pens of Yorvipath 420 mcg/1.4 mL (burgundy push button)
51 mcg/day	24 mcg/day + 27 mcg/day	
54 mcg/day	27 mcg/day + 27 mcg/day	
57 mcg/day	27 mcg/day + 30 mcg/day	
60 mcg/day	30 mcg/day + 30 mcg/day	

*Yorvipath 294 micrograms/0.98 mL delivers doses of 15, 18, or 21 mcg of PTH(1-34) (with orange push button)
**Yorvipath 420 micrograms/1.4 mL delivers doses of 24, 27, or 30 mcg of PTH(1-34) (with burgundy push button)

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with pseudohypoparathyroidism

4.4 Special warnings and precautions for use

Hypercalcaemia

Serious events of hypercalcaemia have been reported with Yorvipath (see section 4.8). The risk is highest when starting or increasing the dose. During treatment, serum calcium should be measured (see section 4.2) and patients should be monitored for signs and symptoms of hypercalcaemia. If severe hypercalcaemia occurs, treatment should be as per clinical guidelines and dose adjustment of Yorvipath should be considered (see section 4.2).

Hypocalcaemia

Serious events of hypocalcaemia have been reported with Yorvipath (see section 4.8). The risk is highest when treatment is abruptly discontinued but may occur at any time. During treatment, serum calcium should be measured and patients should be monitored for signs and symptoms of hypocalcaemia. If severe hypocalcaemia occurs, treatment should be as per clinical guidelines, dose adjustment of Yorvipath should be considered, and dose adjustment of standing or as needed doses of active vitamin D and/or calcium supplements should be considered (see section 4.2).

Concomitant use with cardiac glycosides

Hypercalcaemia of any cause may predispose to digitalis toxicity. In patients using Yorvipath concomitantly with cardiac glycosides (such as digoxin or digitoxin), serum calcium and cardiac glycoside levels should be monitored and patients should be observed for signs and symptoms of digitalis toxicity (see section 4.5).

Severe renal or hepatic disease

No studies have been performed in patients with severe renal impairment and severe hepatic impairment. Use with caution in these patient populations. Patients with eGFR of < 45 mL/min may be more susceptible for hypercalcaemic reactions and transient eGFR decrease, particularly when initiating treatment. If treatment is initiated in these patients, it is recommended to closely monitor serum calcium levels.

Use in patients at increased risk of osteosarcoma

Yorvipath has not been studied in and should be used with caution in patients;
- with skeletal malignancies and bone metastases
- who are receiving or who have received radiation therapy to the skeleton
- with unexplained elevations of bone-specific alkaline phosphatase
- with metabolic bone diseases who are at increased baseline risk for osteosarcoma (e.g., Paget's disease of the bone)

Use in patients with osteoporosis

Screening for and monitoring of osteoporosis should be consistent with local clinical practice for any patient at increased risk of fragility fractures (see section 4.8).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, 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.

Cardiac glycosides (such as digoxin or digitoxin) have a narrow therapeutic index and are affected by calcium. Patients should be monitored for signs and symptoms of digitalis toxicity when taking Yorvipath and cardiac glycosides.

Other medicinal products can exert effects on serum calcium and may alter the therapeutic response to Yorvipath, including but not limited to bisphosphonates, denosumab, romosozumab, thiazide and loop diuretics, systemic corticosteroids, and lithium. Patients should be monitored for changes in serum calcium when treated concomitantly with these medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Yorvipath in pregnant females. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). However, a risk to the pregnant female or developing foetus cannot be excluded. A decision to initiate or discontinue treatment with Yorvipath during pregnancy should take into account the possible risks versus the benefits for the pregnant female. It is recommended to closely monitor maternal serum calcium levels in pregnant females with hypoparathyroidism, including if treated with Yorvipath.

Breast-feeding

It is unknown whether palopegteriparatide is excreted in human milk. As palopegteriparatide is not orally absorbed, it is unlikely to adversely affect the breast-fed child. A decision to discontinue breast-feeding or Yorvipath therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the female. It is recommended to closely monitor maternal serum calcium levels if breast-feeding with hypoparathyroidism, including if treated with Yorvipath.

Fertility

No studies have been performed on the effects of palopegteriparatide on human fertility. Data from animal studies do not indicate that administration of palopegteriparatide impairs fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Yorvipath has no or negligible influence on the ability to drive and use machines. However, dizziness, presyncope, syncope and/or orthostatic hypotension was observed in some patients. These patients should refrain from driving or the use of machines until symptoms have subsided.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions in clinical trials with palopegteriparatide were injection site reactions (21.6%), headache (18.7%), and paraesthesia (13.7%). The most serious adverse reaction reported in clinical trials was hypercalcaemia (1.40%).

Tabulated list of adverse reactions

Table 2 presents the adverse reactions for palopegteriparatide-treated patients identified in all phase 2 and phase 3 placebo-controlled studies within the MedDRA system organ class. The adverse reactions listed in the table below are presented by system organ class and frequency categories, defined 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), and frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2. Frequency of adverse reactions of palopegteriparatide

MedDRA system organ class	Frequency	Adverse reaction
Metabolism and nutrition disorders	Common	Hypercalcaemia[a], Hypocalcaemia
Nervous system disorders	Very common	Headache[d], Paraesthesia[a]
	Common	Dizziness[a, c, d], Syncope[d], Presyncope[d]
Cardiac disorders	Common	Palpitations[d], Postural orthostatic tachycardia syndrome[d]
Vascular disorders	Common	Orthostatic hypotension[d]
	Uncommon	Hypertension[e]
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain
Gastrointestinal disorders	Very common	Nausea[a]
	Common	Diarrhoea[a], Constipation, Vomiting, Abdominal discomfort, Abdominal pain
Skin and subcutaneous tissue disorders	Common	Rash, Photosensitivity reaction
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Myalgia, Muscle twitching[f], Musculoskeletal pain[f]
Renal and urinary disorders	Uncommon	Nocturia[e]
	Frequency not known	Polyuria[e]
General disorders and administration site conditions	Very common	Injection site reactions[a, b], Fatigue
	Common	Asthenia, Thirst
	Uncommon	Chest discomfort[f], Chest pain[f]
Investigations	Frequency not known	Bone density decreased

[a] For these adverse reactions, the first occurrence was almost exclusively within the first 3 months of treatment (titration period).
[b] Injection site reactions include injection site reaction, injection site erythema, injection site bruising, injection site pain, injection site haemorrhage, injection site rash, and injection site swelling.
[c] Dizziness includes dizziness and dizziness postural.
[d] Vasodilatory symptoms include dizziness postural, headache, palpitations, Postural orthostatic tachycardia syndrome, orthostatic hypotension, Blood pressure orthostatic decreased and syncope. Vasodilatory symptoms (as identified in clinical trials) occurred more frequently in the first 3 months of treatment and constituted a subset of total events reported as adverse reactions. A total of 3 events (in 2 patients) considered related to palopegteriparatide occurred within the first 3 months in TCP-304: dizziness postural (n=1), and headache and palpitations (n=1).
[e] These signs and symptoms are potentially associated with hypercalcaemia, as observed in clinical trials.
[f] These signs and symptoms are potentially associated with hypocalcaemia, as observed in clinical trials.

Description of selected adverse reactions

Hypercalcaemia

Serious events of hypercalcaemia have been reported with Yorvipath. The incidence of hypercalcemia was greater in patients treated with Yorvipath compared to placebo. During the blinded period, symptomatic hypercalcemia was reported in 8.6% of patients treated with Yorvipath, and all occurred within the first 3 months after initiation of Yorvipath.

Immunogenicity

Patients may develop antibodies to palopegteriparatide. The proportion of patients testing positive for binding antibodies at any time during treatment was low, with 0.7% having low titre, non-neutralising antibodies towards PTH and 5% having low titre treatment-emergent antibodies against PEG. In 2.2% of the palopegteriparatide-treated patients with pre-existing PEG antibodies, a transient impact on PK (increased clearance of total PTH, mPEG and decreased PTH concentrations) with decreasing serum calcium was observed. However, therapeutic effectiveness was maintained by appropriate dose adjustment of palopegteriparatide according to the trial titration algorithm.

Injection site reactions

Injection site reactions were the most common adverse reactions reported in clinical trials (median onset was 2.5 days; incidence of 21.6%). The most common injection site reactions were localised erythema (all < 5 cm with the majority 0 to < 2 cm) and were mild or moderate (grade 1 or 2) in severity with median duration of 72 hours. All injection site reactions resolved without treatment; none were serious or led to discontinuation.

Vasodilatory symptoms

Vasodilatory symptoms have been reported with Yorvipath. These symptoms are usually transient and resolved without treatment; none were serious or led to discontinuation. If symptoms occur, dosing at bedtime while reclining is recommended.

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.
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/

and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

In the event of overdose, the patient should be carefully monitored by a medical professional.

Overdose can cause hypercalcaemia, the manifestations of which may include dehydration, heart palpitations, ECG changes, hypotension, nausea, vomiting, dizziness, muscle weakness, and confusion. Severe hypercalcaemia may require medical care and careful monitoring (see section 4.4).

One instance of accidental overdose of approximately 3-fold the prescribed dose lasting more than 7 consecutive days resulted in serum calcium as high as 16.1 mg/dL, the patient was symptomatic and required medical intervention. After withholding palopegteriparatide, calcium, and active vitamin D, the patient recovered and restarted on the correct dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium homeostasis, parathyroid hormones and analogues, ATC code: H05AA05

Mechanism of action

Endogenous parathyroid hormone (PTH) is secreted by the parathyroid glands as a polypeptide of 84 amino acids. PTH exerts its action via cell-surface parathyroid hormone receptors, for example, expressed in bone, kidney and nerve tissue. Activation of PTH1R stimulates bone turnover, increases renal calcium reabsorption and phosphate excretion and facilitates synthesis of active vitamin D.

Palopegteriparatide is a prodrug, consisting of PTH(1-34) conjugated to a methoxypolyethylene glycol carrier (mPEG) via a proprietary TransCon Linker. PTH(1-34) and its main metabolite, PTH(1-33), have similar affinity to and activation of PTH1R as endogenous PTH. At physiological

conditions, PTH is cleaved from palopegteriparatide in a controlled manner to provide a continuous systemic exposure of active PTH.

Clinical efficacy and safety

Study in patients with established hypoparathyroidism

The pivotal phase 3 PaTHway clinical trial (TCP-304) assessed the efficacy and safety of Yorvipath as PTH replacement therapy for adults with hypoparathyroidism. The 26-week double-blind, placebo-controlled period of the clinical trial included patients randomised (3:1) to Yorvipath at a starting dose of 18 micrograms/day or placebo, co-administered with conventional therapy (calcium supplement and active vitamin D). Randomisation was stratified by aetiology of hypoparathyroidism (i.e., postsurgical vs. all other causes). Study treatment (palopegteriparatide or placebo) and conventional therapy were subsequently titrated according to a dosing algorithm guided by albumin-adjusted serum calcium levels.

Patients' mean age at recruitment was 49 years (19 to 78 years of age; 12% were ≥ 65 years old), and the majority of patients were female (78%) and Caucasian (93%). Eighty-five percent (85%) of patients had hypoparathyroidism acquired from neck surgery. Of the patients with other aetiologies of hypoparathyroidism, 7 (8.5%) patients had idiopathic disease, 2 had autoimmune polyglandular syndrome type 1 (APS-1), 1 had autosomal dominant hypocalcaemia type 1 (ADH1, CaSR mutation), 1 had DiGeorge Syndrome, and 1 had hypoparathyroidism, sensorineural deafness and renal dysplasia (HDR) syndrome (GATA3 mutation).

Prior to randomisation, all patients underwent an approximate 4-week screening period in which calcium and active vitamin D supplements were adjusted to achieve an albumin-adjusted serum calcium concentration between 1.95 to 2.64 mmol/L (7.8 to 10.6 mg/dL), a magnesium concentration ≥ 0.53 mmol/L (≥ 1.3 mg/dL) and below the upper reference range of normal, and a 25(OH) vitamin D concentration between 50 to 200 nmol/L (20 to 80 ng/mL). For conventional therapy, patients were treated with mean baseline doses of calcium (elemental) of 1 839 mg/day. Mean baseline doses of active vitamin D were 0.75 micrograms/day in calcitriol-treated patients (n=70), and 2.3 micrograms/day in alfacalcidol-treated patients (n=12). Baseline mean albumin-adjusted serum calcium and mean 24-hour urine calcium were similar in both treatment groups: mean serum calcium was 2.2 mmol/L (8.8 mg/dL) and 2.15 mmol/L (8.6 mg/dL) and mean 24-hour urine calcium was 392 mg/day and 329 mg/day, for Yorvipath and placebo,respectively.

Primary endpoint

The composite primary efficacy endpoint was defined as the proportion of patients at week 26 who achieved: serum calcium levels in the normal range (2.07 to 2.64 mmol/L [8.3 to 10.6 mg/dL]), independence from conventional therapy defined as requiring no active vitamin D and ≤ 600 mg/day of calcium supplementation, and no increase in prescribed study treatment within 4 weeks prior to week 26. Key secondary endpoints included a subset of Hypoparathyroidism Patient Experience Scale (HPES) domain scores and 36-Item Short Form Survey (SF-36) subscale scores.

The number of patients meeting the composite primary endpoint compared with the placebo group and each component of the primary endpoint at week 26 is presented in table 3.

Table 3: TCP-304: Response rate based on primary endpoint at week 26

	Yorvipath (N=61) (n, %)	Placebo (N=21) (n, %)	Response rate difference (95% CI)
Response at week 26	48 (78.7%)	1 (4.8%)	74.0% (60.4%, 87.6%) p < 0.0001
Response for each component			
Albumin-adjusted serum calcium within normal range[a]	49 (80.3%)	10 (47.6%)	32.7% (9.2%, 56.3%)
Independence from active vitamin D[b]	60 (98.4%)	5 (23.8%)	74.6% (56.1%, 93.1%)
Independence from therapeutic doses of calcium[c]	57 (93.4%)	1 (4.8%)	88.7% (77.7%, 99.7%)
No dose increase in Yorvipath[d]	57 (93.4%)	12 (57.1%)	36.4% (14.2%, 58.5%)

[a] The normal range for albumin-adjusted serum calcium was 2.07 to 2.64 mmol/L (8.3 to 10.6 mg/dL).
[b] All daily standing doses of active vitamin D equal to zero AND use of PRN doses for ≤ 7 days within 4 weeks prior to week 26 visit.
[c] Average daily standing doses of elemental calcium ≤ 600 mg AND use of PRN doses on ≤ 7 days within 4 weeks prior to week 26 visit.
[d] No dose increase in Yorvipath within 4 weeks prior to week 26 visit.
Abbreviations: CI: confidence interval; PRN: pro re nata.

Secondary endpoints

Conventional therapy intake: calcium and active vitamin D doses

In the phase 3 PaTHway trial, at week 26, 93% (57/61) of patients in the Yorvipath group were able to discontinue conventional therapy (i.e., discontinue active vitamin D and therapeutic doses of calcium). All patients in the Yorvipath group discontinued active vitamin D by week 8 and had sustained reduction in therapeutic doses of calcium. There was a significant reduction in conventional therapy intake in the Yorvipath group from baseline to week 26 compared with placebo: active vitamin D (nominal p-value < 0.0001), calcium dose (nominal p-value = 0.0003), and daily pill burden (nominal p-value < 0.0001) (table 4).

Table 4: Secondary endpoints: conventional therapy intake at week 26 - blinded period (ITT population)

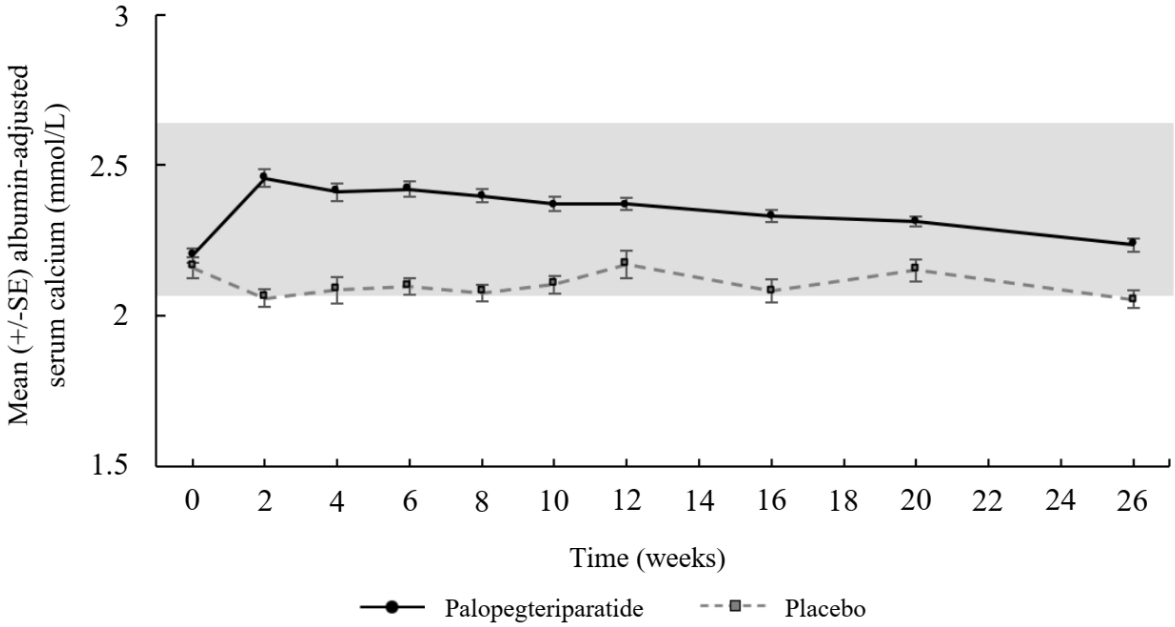
	Yorvipath (n/N=60/61)[a]		Placebo (n/N=19/21)[a]		Nominal p-value
	Baseline	Week 26	Baseline	Week 26	
Supplemental active vitamin D dose (mcg), mean (SD)	1.0 (0.7)	0.0 (0.0)	1.0 (0.6)	0.6 (0.7)	< 0.0001
Supplemental calcium dose (mg), mean (SD)	1 737 (907)	274 (177)	2 089 (1 448)	1 847 (1 326)	0.0003
Daily pill burden (number of conventional therapy pills), mean (SD)	6.6 (2.1)	0.5 (1.7)	6.3 (2.8)	5.4 (3.2)	< 0.0001

Nominal p-value from testing the differences in change from baseline to week 26 between Yorvipath and placebo.
[a] N is the number of patients in the ITT population; n is the number of patients with data at both baseline and week 26.

Serum biochemistries

Mean serum calcium initially increased and stayed within the normal range in palopegteriparatide-treated patients (figure 2). In placebo patients, serum calcium levels decreased slightly, falling below normal range at week 2 (mean observed value: 2.06 mmol/L) and at week 26 (mean observed value: 2.06 mmol/L). The LS mean treatment difference between Yorvipath and placebo was 0.17 mmol/L (95% CI: 0.100, 0.247; nominal p < 0.0001) at week 26.

Figure 2: **Serum calcium (mean ± SE) by visit - blinded period (ITT population)**



Mean serum phosphate levels for palopegteriparatide-treated patients were in the normal range at baseline and fell within the normal range through week 26 (Mean change from baseline to week 26 was -0.13 mmol/L). Mean serum calcium x phosphate product decreased in patients treated with Yorvipath and remained stable within the normal range through week 26.

24-hour urine calcium excretion

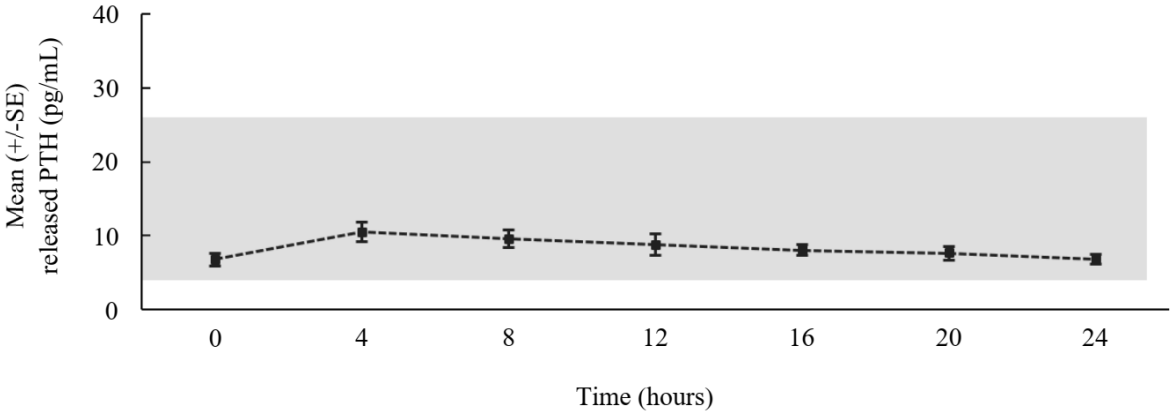
Yorvipath therapy normalised mean 24-hour urine calcium excretion and showed greater reduction in 24-hour urine calcium versus placebo.

5.2 Pharmacokinetic properties

Absorption

Following daily subcutaneous administration, palopegteriparatide releases PTH via autocleavage of the TransCon Linker with first-order kinetics, resulting in continuous exposure over 24 hours within the estimated normal range (figure 3).

Figure 3: Mean released PTH* following subcutaneous administration of palopegteriparatide at steady state in patients with hypoparathyroidism



The estimated normal range for PTH(1-34) is approximately 4 to 26 pg/mL. This is calculated based on PTH(1-34)

constituting 40% of the molecular weight of PTH(1-84)** and the normal range (10 to 65 pg/mL) for PTH(1-84).
* Mean palopegteriparatide dose (range): 22.3 (12-33) mcg PTH(1-34)/day, n=7, released PTH: sum of PTH(1-34) and PTH(1-33).
** PTH(1-84) = endogenous parathyroid hormone.

In patients with hypoparathyroidism administered palopegteriparatide corresponding to 18 mcg of PTH(1-34)/day, the predicted maximum plasma concentration (C_{max}) (CV%) of palopegteriparatide was 5.18 ng/mL (36%) and the predicted C_{max} (CV%) for released PTH was 6.9 pg/mL (22%) with a median time to reach maximum concentrations (T_{max}) of 4 hours. The predicted exposure over the 24-hour dosing interval (area under the curve, AUC) (CV%) for released PTH was 150 pg*h/mL (22%).

Following multiple subcutaneous doses of palopegteriparatide in the range of 12 to 24 mcg PTH(1-34)/day, the palopegteriparatide and released PTH concentrations increased in a dose-proportional manner reaching steady-state within approximately 10 and 7 days, respectively. The peak-to-trough ratio was low, approximately 1.1 and 1.5 over 24 hours at steady state for palopegteriparatide and released PTH, respectively. Palopegteriparatide accumulated after multiple dosing by up to 18-fold for AUC.

Distribution

The apparent volume of distribution (CV%) of palopegteriparatide is estimated to 4.8 L (50%) and to 8.7 L (18%) for released PTH.

Biotransformation

PTH released from palopegteriparatide is composed of PTH(1-34) and the metabolite PTH(1-33). PTH is renally metabolised and cleared.

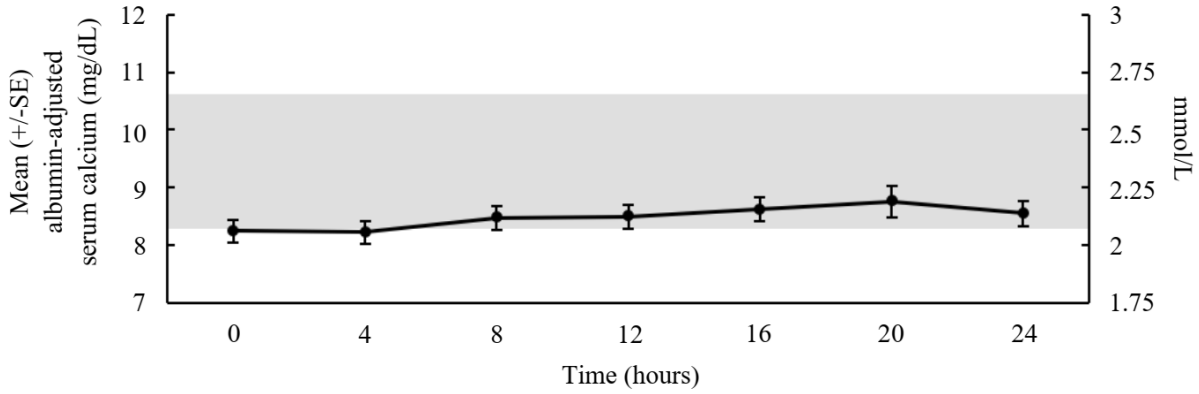
Elimination

In healthy adults, the clearance (CV%) of palopegteriparatide at steady state is estimated to be 0.58 L/day (52%) with a predicted half-life of 70 hours. The apparent half-life of PTH released from palopegteriparatide is approximately 60 hours. In the liver, most of the PTH is cleaved by cathepsins. In the kidney, a small amount of PTH binds to PTH1R, but most is excreted by glomerular filtration.

Pharmacokinetic/pharmacodynamic relationship

In a pharmacodynamic/pharmacokinetic sub-study in hypoparathyroid patients, daily subcutaneous administration of palopegteriparatide (mean dose (range): 22.3 (12-33) mcg PTH(1-34)/day) increased serum calcium levels to within the normal range (see figure 4). The increase in serum calcium levels occurred in a dose-related manner, supporting the ability to titrate palopegteriparatide according to measured serum calcium values in the individual patient.

Figure 4: Mean albumin-adjusted serum calcium concentrations following subcutaneous administration of palopegteriparatide at steady state in patients with hypoparathyroidism



The normal range for albumin-adjusted serum calcium is 2.07 to 2.64 mmol/L (8.3 to 10.6 mg/dL) as denoted by the grey shading. Mean palopegteriparatide dose (range): 22.3 (12-33) mcg PTH(1-34)/day, n=7.

Special populations

The pharmacokinetics of released PTH was not influenced by sex or body weight. The data for race and ethnicity did not show any trends indicating differences, but the available data are too limited to make definitive conclusions.

Elderly

The pharmacokinetics of released PTH was not influenced by age (19 to 76 years old).

Renal impairment

Yorvipath has been administered to patients with hypoparathyroidism with an eGFR of ≥ 30 mL/min in long-term clinical trials without the need for dose adjustment beyond the trial titration algorithm. No clinical trials were conducted in patients with hypoparathyroidism with severe renal impairment (< 30 mL/min) or on dialysis. In a trial where Yorvipath was administered as a single dose to non-hypoparathyroid subjects with renal impairment, palopegteriparatide exposure and resulting serum calcium levels were similar in subjects with mild, moderate, and severe renal impairment as compared to subjects without renal impairment.

5.3 Preclinical safety data

No special hazard for humans were revealed in the conventional studies of safety pharmacology, genotoxicity, and local tolerance conducted with palopegteriparatide.

At the highest dose levels in all animal species employed, repeated dosing resulted in adverse persistent hypercalcemia, which in some studies led to premature death/euthanasia, clinical signs, body weight loss and/or soft tissue mineralisation observed mainly in the kidneys. These findings are considered results of persistent exaggerated PTH pharmacology and of no relevance in a clinical setting where dose adjustments are performed to ensure normalised serum calcium.

In accordance with the expected pharmacological effects, repeated daily administration of palopegteriparatide increased bone turnover in rats. At low dose levels (2-fold the maximum recommended human dose (MRHD), based on exposure to released PTH by AUC) in rats, the increased bone turnover induced overall net catabolic bone effects. At high dose levels (5-fold the MRHD, based on exposure to released PTH by AUC) in rats, the increased bone turnover resulted in a net anabolic bone effect. Physeal dysplasia was observed at the highest dose level (9-fold the

MRHD, based on exposure to released PTH by AUC) in rats. These effects are of no relevance in a clinical setting where Yorvipath doses are individually adjusted.

There were no cardiovascular findings in monkeys up to and including the highest dose tested in single- (3-fold the MRHD, based on exposure to released PTH by C_{max}) or repeat-dose studies (0.98- fold the MRHD, based on exposure to released PTH by C_{max}).

Increased occurrence of osteosarcomas has been observed in carcinogenicity studies with short-lived PTH analogues in rats, but there is no evidence of increased risk of osteosarcoma in patients treated with short-lived PTH analogues. No carcinogenicity study has been conducted with palopegteriparatide.

In animal reproduction studies, administration of palopegteriparatide to pregnant rats and rabbits during the period of organogenesis resulted in no evidence of embryo-lethality, foetotoxicity or dysmorphogenesis up to and including the highest doses tested (8- and 7-fold, respectively, the MRHD, based on exposure to released PTH by AUC). Exaggerated PTH pharmacological effects were observed at the highest doses tested in the pregnant rats and rabbits (increased serum calcium levels, decreased body weight, decreased food consumption and/or clinical signs). The exposures at the no observed adverse effect level (NOAEL) for maternal toxicity were 2- and 3- fold the MRHD, based on exposure to released PTH by AUC in pregnant rats and rabbits, respectively.

Palopegteriparatide did not adversely affect pre- and post-natal development in offspring from pregnant and lactating rats up to and including the highest dose tested (4-fold the MRHD, based on exposure to released PTH by C_{max}).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, 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.

<u>After first opening:</u>

Store below 30 °C.
Keep the pen cap on the pre-filled pen in order to protect from light. Yorvipath must be discarded after 14 days.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Do not freeze.

Store in the original package with the pen cap on in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

A cartridge (type 1 glass) with a plunger (halobutyl) and a laminate rubber sheet (halobutyl/isoprene) contained in a pre-filled multidose disposable pen made of polypropylene.

Packs of two pre-filled pens and 30 disposable needles for 28 days of treatment (co-packaged in two inner cartons). Each inner carton contains one pre-filled pen and 15 needles for 14 days of treatment.

Not all pack sizes may be marketed.

Yorvipath 168 micrograms/0.56 mL solution for injection in pre-filled pen

- Each pre-filled pen contains palopegteriparatide equivalent to 168 micrograms of PTH(1-34) in 0.56 mL of solvent.
- Pre-filled pen delivering doses of 6, 9, or 12 micrograms
- The strength colour on the outer carton, pen label and push button is blue

Yorvipath 294 micrograms/0.98 mL solution for injection in pre-filled pen

- Each pre-filled pen contains palopegteriparatide equivalent to 294 micrograms of PTH(1-34) in 0.98 mL of solvent.
- Pre-filled pen, delivering doses of 15, 18, or 21 micrograms
- The strength colour on the outer carton, pen label and push button is orange

Yorvipath 420 micrograms/1.4 mL solution for injection in pre-filled pen

- Each pre-filled pen contains palopegteriparatide equivalent to 420 micrograms of PTH(1-34) in 1.4 mL of solvent.
- Pre-filled pen, delivering doses of 24, 27, or 30 micrograms
- The strength colour on the outer carton, pen label and push button is burgundy

6.6 Special precautions for disposal and other handling

Dose preparation

A new Yorvipath pen should be taken out of the refrigerator 20 minutes before first opening.

The solution should appear clear, colourless and free of visible particles. Do not inject the medicinal product if it is cloudy, or contains particulate matter.

Each pre-filled pen is for use by a single patient. A pre-filled pen must never be shared between patients, even if the needle is changed.

If a pre-filled pen has been frozen or exposed to heat, it must be discarded.

Every time a pre-filled pen is prepared for administration, a new needle must be attached.

Needles must not be re-used. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing. The injection needle should be removed after each injection and the pen should be stored without a needle attached. Discard the needles after each injection.

Instructions for the preparation and administration of Yorvipath are given in the package leaflet and instructions for use.

Disposal

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

7. REGISTRATION HOLDER

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8. MANUFACTURER

Ascendis Pharma A/S
Tuborg Boulevard 12, 2900 Hellerup Denmark

9. MARKETING AUTHORISATION NUMBER(S)

38127

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