Product Monograph

Including Patient Medication Information

PrYORVIPATH™

palopegteriparatide injection

Solution, 168 mcg / 0.56 mL, 294 mcg / 0.98 mL, 420 mcg / 1.4 mL for subcutaneous injection in a pre-filled pen

Parathyroid hormones and analogues

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Date of Initial Authorization:
JAN 28, 2026

Submission Control Number: 294475

RECENT MAJOR LABEL CHANGES
Not applicable.

TABLE OF CONTENTS
Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Limited evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness. In the pivotal clinical trial, 8/61 (13%) Yorvipath-treated -participants were 65 years of age or older compared to 2/21 (10%) participants in the placebo group, and 1/61 (2%) of the Yorvipath-treated -participants were 75 years of age or older compared to 1/21 (5%) participants in the placebo group at baseline.

2 CONTRAINDICATIONS

Yorvipath is contraindicated in:

- Patients with hypersensitivity to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been observed with PTH analogs. For a complete listing, see 66 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with pseudohypoparathyroidism.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment should be initiated and monitored by a healthcare professional experienced in the diagnosis and management of patients with hypoparathyroidism.
- Dose recommendations of Yorvipath refer to micrograms of PTH(1-34). The dose should be individualised based on albumin-corrected serum calcium levels. The optimal dose of Yorvipath is the minimum dose required to prevent hypocalcemia, i.e., the dose that maintains albumin-corrected serum calcium levels within the normal range without the need for treatment with active forms of vitamin D or calcium. Calcium supplementation may be continued at doses up to 600 mg daily, which is the recommended amount for general nutritional supplementation.
- Doses of active forms of vitamin D and calcium will need to be adjusted prior to initiating and during treatment with Yorvipath based on albumin-corrected serum calcium level.
- The maximum recommended dosage for Yorvipath is 60 mcg subcutaneously once daily. If an adequate response is not achieved with a maximum Yorvipath dosage of 60 mcg, consider adding or restarting active vitamin D and/or calcium therapy.
- Advise patients to monitor daily for clinical signs and symptoms of hypocalcemia or hypercalcemia.

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of Yorvipath is 18 mcg once daily with dose adjustments in 3 mcg increments or decrements thereafter (see Figure 1). The dose range is 6 to 60 mcg per day.

Laboratory testing Prior to Initiation of Yorvipath

Test serum 25(OH) vitamin D and calcium levels prior to treatment initiation. Serum 25(OH) vitamin D should be within normal range and albumin-corrected serum calcium should be between 1.95 - 2.64 mmol/L, i.e., within or slightly below the normal range on at least one laboratory value obtained within two weeks prior to treatment initiation.

Initiation of Yorvipath

When initiating treatment with Yorvipath, the doses of active vitamin D or calcium should be adjusted as follows:

- If taking active vitamin D:
  - If albumin-corrected serum calcium is ≥ 2.07 mmol/L, active vitamin D should be discontinued on the same day as the first dose of Yorvipath. Calcium dose should be maintained.
  - If albumin-corrected serum calcium is < 2.07 mmol/L, active vitamin D should be reduced by ≥ 50% on the same day as the first dose of Yorvipath. Calcium dose should be maintained.
- If not taking active vitamin D:
  - Calcium dose should be decreased by at least 1500 mg on the same day as the first dose of Yorvipath. If taking elemental calcium doses ≤ 1500 mg per day, calcium 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.

Dosage Adjustment and Maintenance of Yorvipath

Titration Recommendations

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 dose may be decreased in increments of 3 mcg no more often than every 3 days in response to hypercalcemia (see Figure 1).

Serum calcium concentration must be monitored during dose titration and patients should be monitored for clinical symptoms of hypocalcemia or hypercalcemia.

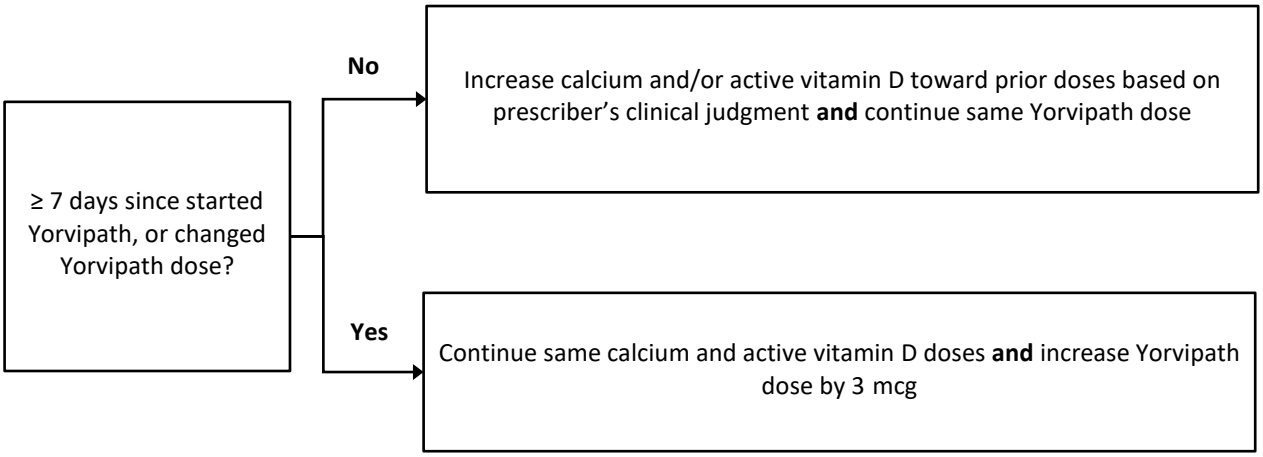
Serum calcium should be measured 7 days after the first dose, and 7 to 14 days after any dose change in Yorvipath, active vitamin D, or calcium. If necessary, the doses of Yorvipath, active vitamin D, and/or calcium should be adjusted as per Figure 1. Adjustments should be made on the same day.

Titration Recommendations when Albumin-Corrected Serum Calcium is Less Than 3 mmol/L

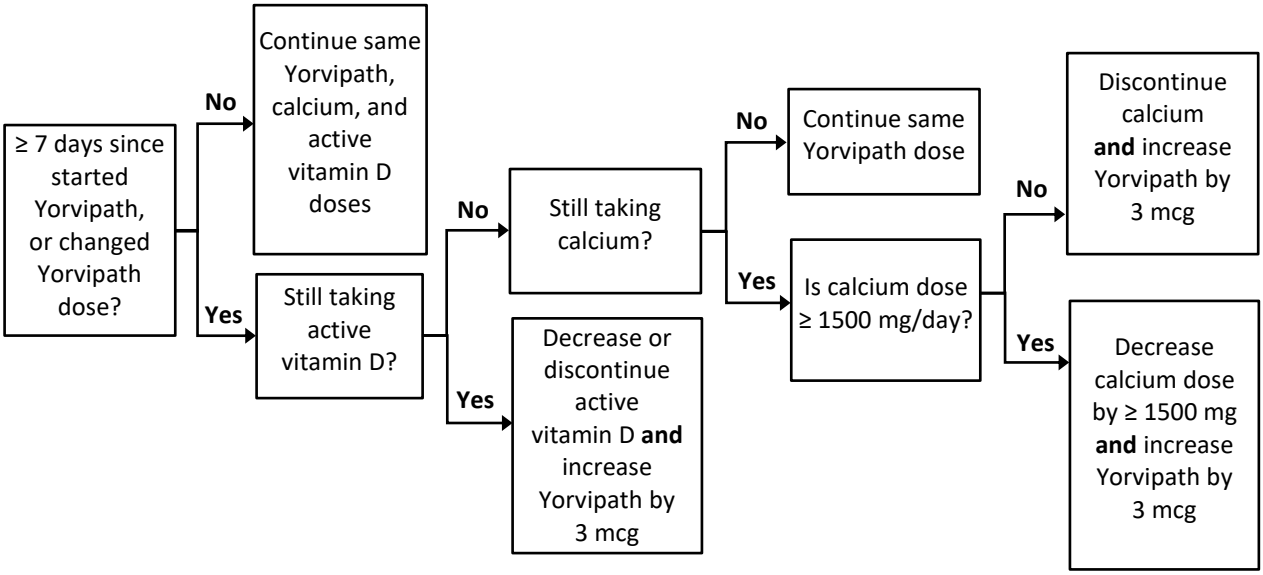
Figure 1 shows dosage titration recommendations for Yorvipath, active vitamin D, and calcium in adults with specific albumin-corrected serum calcium ranges that are less than 3 mmol/L.

Figure 1 - Titration of Yorvipath, Active Vitamin D, and Calcium Doses

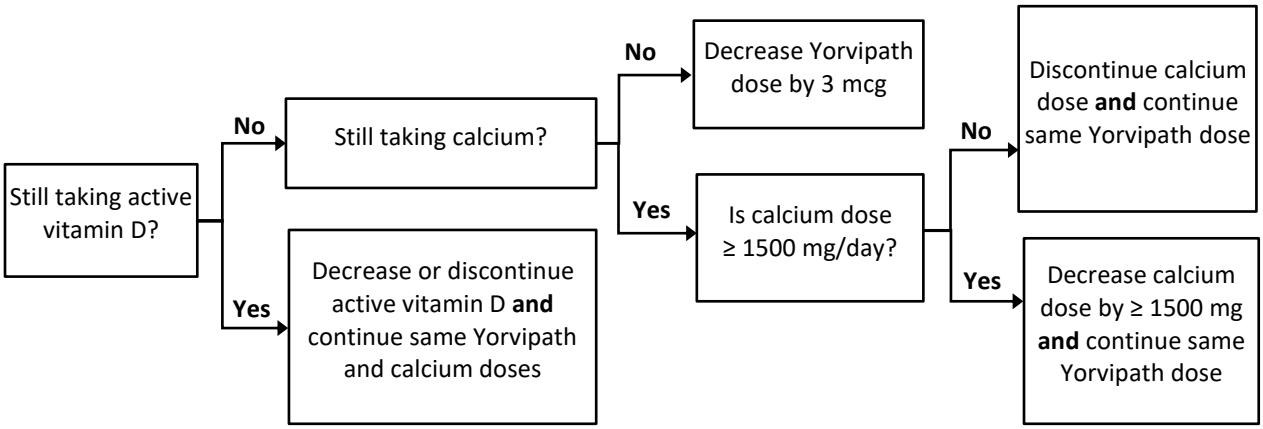
A. Albumin-corrected serum calcium low (< 2.07 mmol/L):



B. Albumin-corrected serum calcium normal (≥ 2.07 to ≤ 2.64 mmol/L):



C. Albumin-corrected serum calcium high (≥ 2.65 to < 3.00 mmol/L):



Titration Recommendations when Albumin-Corrected Serum Calcium is 3 mmol/L or Greater

Withhold treatment with Yorvipath for 2 to 3 days and then reassess serum calcium. If subsequent albumin-corrected serum calcium is < 3.00 mmol/L, resume titration of Yorvipath, active vitamin D, and calcium as per the applicable section of Figure 1 using the most recent serum calcium value obtained.

If albumin-corrected serum calcium remains ≥ 3.00 mmol/L, withhold Yorvipath for an additional 2 to 3 days and then reassess serum calcium and follow the instructions provided above.

Dose Maintenance

The maintenance dose is individualised and should be the dose that achieves albumin-corrected 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. Supplementation with standard (nonactive) vitamin D may be necessary to achieve normal 25(OH) vitamin D concentrations. Serum calcium and 25(OH) vitamin D should be measured as per standard of care when a maintenance dose is achieved.

Interruption or Discontinuation of Yorvipath

Interruption of daily administration of Yorvipath should be avoided to minimise serum PTH fluctuations. Interruption or discontinuation of treatment can result in hypocalcemia. When interrupting or discontinuing treatment for 3 or more consecutive doses, monitor patients for signs and symptoms of hypocalcemia and consider measuring serum calcium. If indicated, resume treatment with calcium and active vitamin D. Resume Yorvipath at the previously prescribed dose as soon as possible after an interruption then measure serum calcium within 7-14 days and adjust doses of Yorvipath, active vitamin D, and calcium as per Figure 1.

Geriatrics (≥ 65 years of age): Dose adjustment is not required based on age (see 10.3 Pharmacokinetics).

Pediatrics (< 18 years of age): The safety and efficacy of Yorvipath in children less than 18 years of age have not yet been established. No data are available. Health Canada has not authorized an indication for pediatric use.

Patients with Hepatic Impairment

Yorvipath has not been studied in patients with severe hepatic impairment and should be used with

caution in these patients (see 10.3 Pharmacokinetics).

Patients with Renal Impairment

Dose adjustment is not required in patients with an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2. Serum calcium levels should be measured more frequently when used in patients with eGFR < 45 mL/min/1.73 m^2. Yorvipath has not been studied in patients with hypoparathyroidism and severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see 10.3 Pharmacokinetics).

4.4 Administration

Patients and caregivers who will administer Yorvipath should receive appropriate training by a healthcare professional prior to first use. Advise patients/caregivers to follow the Instructions for Use on how to administer Yorvipath using the pen and needles:

- Yorvipath must be refrigerated at 2°C to 8°C until first use (see 11 STORAGE, STABILITY AND DISPOSAL).
- Yorvipath should be inspected visually for particulate matter and discoloration prior to administration. Yorvipath is a clear, colorless solution. Do not use if solid particles appear or if the solution is cloudy or colored.
- Pen flow should be tested when a pen is used for the first time.
- The needle has to be pushed straight onto the pen, then screwed until secure.
- 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).
- The initial dose of Yorvipath should be administered when the patient can sit or lie down to prevent orthostatic hypotension.

Doses > 30 mcg per day (sequential injections)

All daily doses greater than 30 mcg should be administered as two separate injections given sequentially at different injection sites (see Table 1). During development, it was determined that doses above 30 mcg must be delivered using two pens in sequence. This approach ensures that every pen, regardless of the prescribed daily dose, maintains a consistent 14-day in-use period, thereby simplifying product handling for patients.

This dosing configuration has been evaluated in the risk management file and validated in the usability/HFE study. Therefore, it is recommended to use a second Yorvipath pen for the additional daily injection, even when both pens have push buttons of the same colour (indicating the same strength).

Table 1 - Recommended scheme for Yorvipath dosing above 30 mcg/day

Total Dose	First pen turn dial to dose of:	Second pen turn dial to dose of:		Which Yorvipath pen to use?
	Orange pen (294 mcg / 0.98 mL)	Orange pen (294 mcg / 0.98 mL)		
33 mcg/day	15 mcg	+	18 mcg	Use 2 separate orange pens one after the other in 2 separate injection sites
36 mcg/day	18 mcg	+	18 mcg	
39 mcg/day	18 mcg	+	21 mcg	
42 mcg/day	21 mcg	+	21 mcg	
	Orange pen (294 mcg / 0.98 mL)	Burgundy pen (420 mcg / 1.4 mL)		ATTENTION: for this dose, you must use two different strength pens one after the other, in separate injection sites
45 mcg/day	21 mcg	+	24 mcg	First injection: Use 1 orange pen (294 mcg / 0.98 mL pen) + Second injection: Use 1 burgundy pen (420 mcg / 1.4 mL pen)
	Burgundy pen (420 mcg / 1.4 mL)	Burgundy pen (420 mcg / 1.4 mL)		
48 mcg/day	24 mcg	+	24 mcg	Use 2 separate burgundy pens one after the other in 2 separate injection sites
51 mcg/day	24 mcg	+	27 mcg	
54 mcg/day	27 mcg	+	27 mcg	
57 mcg/day	27 mcg	+	30 mcg	
60 mcg/day	30 mcg	+	30 mcg	

Yorvipath 294 mcg / 0.98 mL pen delivers doses of 15, 18, or 21 mcg (with orange push button).
Yorvipath 420 mcg / 1.4 mL pen delivers doses of 24, 27, or 30 mcg (with burgundy push button).

4.5 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.

5 OVERDOSAGE

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

Overdose can cause hypercalcemia, the manifestations of which may include dehydration, heart palpitations, ECG changes, hypotension, nausea, vomiting, dizziness, muscle weakness, and confusion. Severe hypercalcemia may require medical care and careful monitoring (see 7 WARNINGS AND PRECAUTIONS).

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 4.017 mmol/L. The participant was symptomatic and required medical intervention. After withholding Yorvipath, calcium, and active vitamin D, the participant recovered and restarted on the correct dose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Injection, single use pre-filled pen: • 168 mcg / 0.56 mL pen, labeled doses of 6, 9, or 12 mcg • 294 mcg / 0.98 mL pen, labeled doses of 15, 18, or 21 mcg • 420 mcg / 1.4 mL pen, labeled doses of 24, 27, or 30 mcg	Hydrochloric acid, mannitol, metacresol, sodium hydroxide, succinic acid, water for injection

Yorvipath is a clear and colourless solution for injection in a pre-filled pen. Do not inject the medicinal product if it is cloudy or contains particulate matter.

Yorvipath is available in packs containing 2 pre-filled pens with 30 disposable needles for 28 days of treatment. Each pre-filled pen is for 14 days of treatment.

Strength colours are indicated on the outer and inner cartons, on the label and push button of the pre-filled pen, as follows:

Colour	Presentation	Delivered Doses
Blue	Yorvipath 168 mcg / 0.56 mL	6 mcg, 9 mcg, 12 mcg
Orange	Yorvipath 294 mcg / 0.98 mL	15 mcg, 18 mcg, 21 mcg
Burgundy	Yorvipath 420 mcg / 1.4 mL	24 mcg, 27 mcg, 30 mcg

7 WARNINGS AND PRECAUTIONS

General

Risk of Digoxin Toxicity with Concomitant Use of Digitalis Compounds

Yorvipath increases serum calcium. Concomitant use with digoxin (which has a narrow therapeutic index) may predispose patients to digitalis toxicity if hypercalcemia develops. Digoxin efficacy may be reduced if hypocalcemia is present. When Yorvipath is used concomitantly with digoxin, measure serum calcium and digoxin levels routinely, and monitor for signs and symptoms of digoxin toxicity. Refer to the digoxin prescribing information for dose adjustments, if needed (see 9.4 Drug-Drug Interactions).

Risk of Unintended Changes in Serum Calcium Levels Related to Number of Daily Injections

Using two Yorvipath injections to achieve the recommended daily dosage increases the variability of the total delivered dose, which can cause unintended changes in serum calcium levels, including hypercalcemia and hypocalcemia. Provide patient education on the clinical manifestations of hypercalcemia and hypocalcemia, with instructions to monitor for and report relevant symptoms.

Hypersensitivity

Post-marketing reports of hypersensitivity reactions, including anaphylaxis have been reported with palopegteriparatide. If a hypersensitivity reaction occurs, discontinue palopegteriparatide and seek medical attention.

Carcinogenesis and Genotoxicity

Based on the non-clinical data, Yorvipath is not genotoxic (see 16 Non-Clinical Toxicology).

Use in patients at increased risk of osteosarcoma

Yorvipath is a PTH analog. An increased incidence of osteosarcoma has been reported in male and female rats treated with short-lived PTH analogs, including teriparatide. Osteosarcoma occurrence in rats is dependent on teriparatide or PTH dose and treatment duration. Osteosarcoma has been reported in patients treated with teriparatide in the postmarketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of teriparatide use.

Yorvipath is not recommended in patients who are at increased risk of osteosarcoma, such as patients:

- With skeletal malignancies and bone metastases
- Who are receiving or who have received external beam or implant radiation therapy to the skeleton
- With unexplained elevations of bone specific alkaline phosphatase
- With hereditary disorders predisposing to osteosarcoma
- With metabolic bone diseases other than hypoparathyroidism, including Paget's disease of bone.

- With open epiphyses. Yorvipath is not approved in pediatric patients (see 7.1.3 Pediatrics)

Cardiovascular

Hypotension

Orthostatic hypotension has been reported with Yorvipath. Associated signs and symptoms may include decreased blood pressure, dizziness (including postural dizziness), palpitations, tachycardia, presyncope, or syncope. Such symptoms can be managed by dosing at bedtime, while reclining. Yorvipath should be administered initially when the patient can sit or lie down due to the potential of orthostatic hypotension.

Endocrine and Metabolism

Serious Hypercalcemia

Serious events of hypercalcemia have been reported with Yorvipath (see 8.2 Clinical Trial Adverse Reactions). The risk is highest when starting treatment or increasing the dose, or when using two separate pens to achieve the daily dose. During treatment, serum calcium should be measured (see 4 DOSAGE AND ADMINISTRATION) and patients should be monitored for signs and symptoms of hypercalcemia. If severe hypercalcemia occurs, treatment should be as per clinical guidelines, and dose adjustment of Yorvipath should be considered (see 4 DOSAGE AND ADMINISTRATION).

Serious Hypocalcemia

Serious events of hypocalcemia have been reported with Yorvipath (see 8.2 Clinical Trial Adverse Reactions). The risk is highest when treatment is abruptly discontinued or when two separate pens are used to achieve the daily dose but may occur at any time. During treatment, serum calcium should be measured and patients should be monitored for signs and symptoms of hypocalcemia. If severe hypocalcemia 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 4 DOSAGE AND ADMINISTRATION).

Musculoskeletal

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.

Reproductive Health

- **Fertility**

No studies have been performed on the effects of Yorvipath on human fertility. Data from animal studies do not indicate that administration of Yorvipath impairs fertility (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnancy

There are no adequate and well-controlled studies with Yorvipath in pregnancy. In embryo-fetal development studies, subcutaneous administration of palopegteriparatide to pregnant rats and rabbits during organogenesis resulted in no adverse developmental effects (see 16 NON-CLINICAL TOXICOLOGY NON-CLINICAL TOXICOLOGY).

A decision to initiate or discontinue treatment with Yorvipath during pregnancy should take into account the possible risks versus the benefits for the pregnant individual. It is recommended to closely monitor serum calcium levels in pregnant patients with hypoparathyroidism treated with Yorvipath.

7.1.2 Breastfeeding

It is unknown whether Yorvipath is excreted in human milk. As Yorvipath is not orally absorbed, it is unlikely to adversely affect the breastfed child. A decision to discontinue breastfeeding or Yorvipath therapy should take into account the benefit of breastfeeding for the child and the benefit of therapy for the parent. It is recommended to closely monitor serum calcium levels when the patient with hypoparathyroidism is breastfeeding during treatment with Yorvipath.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies did not include a sufficient number of -participants 65 years of age or older to determine any differences in response from younger adult -participants.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported adverse reactions (≥ 10%) in Yorvipath-treated -participants in the 26-week blinded period of the pivotal Phase 3 trial (TCP-304) were injection site reactions (39%), vasodilatory signs and symptoms (28%), and headache (21%). A serious adverse reaction of hypercalcemia (1.60%) was reported in a participant receiving Yorvipath.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table **3**4 below presents the most common adverse reactions in the 26-week blinded period of the pivotal Phase 3 Trial (TCP-304), that occurred in ≥ 5% of participants treated with Yorvipath, and with ≥ 2% higher frequency when compared to placebo.

Table 3 - Adverse Reactions in ≥ 5% of Participants with Hypoparathyroidism Treated with Yorvipath and with ≥ 2% Higher Frequency Compared to Placebo in Study TCP-304

Adverse Reaction	Yorvipath n = 61 n (%)	Placebo n = 21 n (%)
General disorders and administration site conditions		
Injection site reactions[a]	24 (39)	1 (5)
Nervous system disorders		
Vasodilatory signs and symptoms[b]	17 (28)	2 (10)
Headache	13 (21)	2 (10)
Gastrointestinal disorders		
Diarrhea	6 (10)	1 (5)
Metabolism and nutrition disorders		
Hypercalcemia	6 (10)	0
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	4 (7)	0

Abbreviations: N, total number of participants in the treatment arm; n, number of participants with the adverse reaction; %, percent of participants with the adverse reaction.

[a] Injection site reactions includes the preferred terms injection site bruising, injection site erythema, injection site rash, and injection site reaction.

[b] Vasodilatory signs and symptoms includes the preferred terms blood pressure orthostatic decreased, dizziness, dizziness postural, nausea, orthostatic hypotension, palpitations, postural orthostatic tachycardia syndrome, presyncope, syncope, and vertigo.

Injection Site Reactions

Injection site reactions were the most common adverse reactions reported in clinical trials (incidence of 21.6%; median onset of 2.5 days). The most common injection site reactions were localized 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 Signs and 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.

8.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hypercalcaemia

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

Table 4 – Incidence of Elevated Albumin-Corrected Serum Calcium (> 2.65 mmol/L or > 3 mmol/L Post-Baseline in Participants with Hypoparathyroidism Treated with Yorvipath or Placebo in Study 304

	Yorvipath N = 61	Placebo N = 21
Albumin-Corrected Serum Calcium > 2.65 mmol/L, n (%)	33 (54.1)	2 (9.5)
Albumin-Corrected Serum Calcium > 3 mmol/L, n (%)	8 (13.1)	0 (0)

8.4 Post-Market Adverse Reactions

No new adverse drug reactions in the post-market setting have been observed.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been performed with Yorvipath.

9.4 Drug-Drug Interactions

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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Endogenous parathyroid hormone (PTH) is secreted by the parathyroid glands as a polypeptide of 84 amino acids. Endogenous PTH maintains extracellular calcium and phosphate homeostasis by

increasing serum calcium and decreasing serum phosphate. These effects are mediated by stimulating bone turnover to mobilize calcium and phosphate from bone, promoting renal calcium reabsorption and phosphate excretion and facilitating 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. At physiological conditions, palopegteriparatide releases PTH(1-34) and its main metabolite PTH(1-33) via autocleavage of the TransCon Linker to maintain continuous systemic exposure of active PTH.

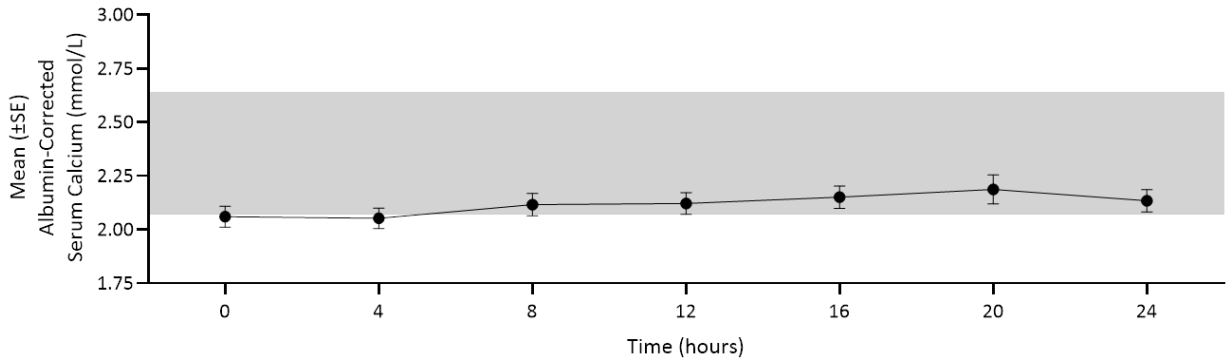
Similar to endogenous PTH, PTH(1-34) and PTH(1-33) released from palopegteriparatide exert their effects through binding to the parathyroid hormone 1 receptor (PTH1R), which is expressed in bone, kidney and nerve tissue.

10.2 Pharmacodynamics

PTH released from palopegteriparatide and serum calcium concentrations increased in a dose-related manner when palopegteriparatide was administered to healthy volunteers. Exposure-response was not established in participants with hypoparathyroidism.

In a pharmacodynamic/pharmacokinetic sub-study in hypoparathyroid participants, daily subcutaneous administration of palopegteriparatide increased serum calcium levels to within the normal range. Mean steady state concentration-time profile of albumin-corrected serum calcium concentrations over 24-hours following administration of palopegteriparatide is presented in Figure 2.

Figure 2 - Mean Steady-State Albumin-Corrected Serum Calcium Concentrations Following Subcutaneous Administration of Palopegteriparatide in Participantswith Hypoparathyroidism



The normal range for albumin-corrected serum calcium in clinical trials was considered to be 2.07 to 2.64 mmol/L as denoted by the grey shading. Mean palopegteriparatide dose (range): 22.3 (12 - 33) mcg/day, n = 7.

10.3 Pharmacokinetics

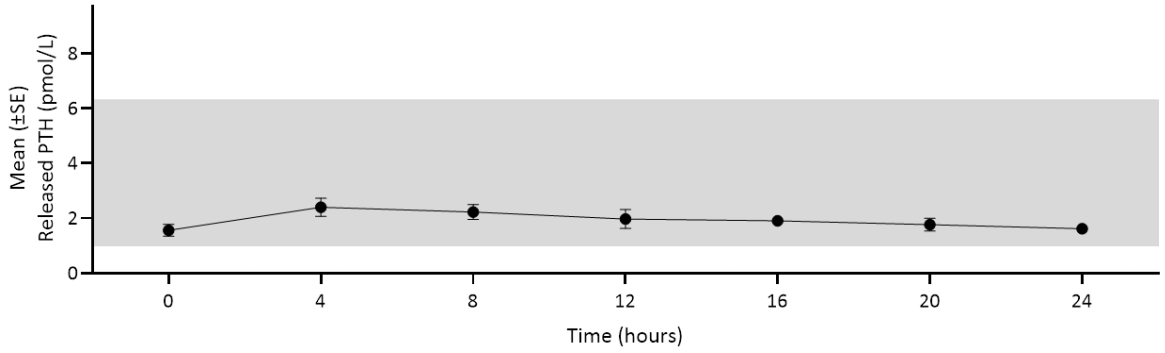
Yorvipath is a prodrug that releases PTH(1-34) via autocleavage of the TransCon linker with first-order kinetics.

Absorption

In healthy participants, following multiple subcutaneous doses of palopegteriparatide in the range of 12 to 24 mcg PTH(1-34)/day, released Free PTH concentrations increased in a dose-proportional manner and reached steady-state by approximately Day 8. The median (range) time to reach maximum concentrations (Tmax) of Free PTH is 4 (4 to 8) hours.

Figure 3 Mean steady state concentration-time profile of released PTH over 24 hours following daily subcutaneous administration of palopegteriparatide in participants with hypoparathyroidism is presented in Figure 3. At steady-state, administration of palopegteriparatide resulted in continuous exposure to released PTH over the 24-hour dosing period.

Figure 3 - Mean released PTH* Following Subcutaneous Administration of palopegteriparatide at Steady State in Participantswith Hypoparathyroidism



The estimated normal range for PTH(1-34) is approximately 0.42 -2.76 pmol/L (4 to 26 pg/mL) as denoted by the grey shading. This is calculated based on PTH(1-34) constituting 40% of the molecular weight of PTH(1-84)** and the normal range of 1.06 - 6.9 pmol/L (10 to 65 pg/mL) for PTH(1-84).

* Mean palopegteriparatide dose (range): 22.3 (12-33) mcg /day, n=7, released PTH: sum of PTH(1-34) and active metabolite PTH(1-33).

** PTH(1-84) = endogenous parathyroid hormone.

Distribution

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

Metabolism

PTH released from palopegteriparatide is composed of PTH(1-34) and the metabolite PTH(1-33). Peripheral metabolism of PTH occurs in the liver and kidneys.

Elimination

The apparent half-life of PTH released from palopegteriparatide is approximately 60 hours. The estimated clearance (CV%) of palopegteriparatide at steady state is 0.58 L/day (52%) in healthy participants.

No metabolism or excretion studies have been performed with palopegteriparatide.

Peripheral metabolism of PTH occurs via enzymatic cleavage in the liver followed by excretion via the kidneys.

Special Populations and Conditions

- **Geriatrics:** The pharmacokinetics of palopegteriparatide was not influenced by age (19 to 76 years old).
- **Sex:** The pharmacokinetics of palopegteriparatide was not influenced by sex.
- **Ethnic origin:** The pharmacokinetic data of palopegteriparatide for race and ethnicity did not show any trends indicating differences, but the available data are too limited to make definitive conclusions.
- **Hepatic Insufficiency**: No dedicated hepatic impairment study was conducted. Mild and moderate hepatic impairment is not expected to have a clinically significant impact on the pharmacokinetics of palopegteriparatide.
- **Renal Insufficiency:** Palopegteriparatide has been administered to participantswith hypoparathyroidism with an eGFR of ≥ 30 mL/min/1.73 m^2 in long-term clinical trials without the need for dose adjustment beyond the trial titration algorithm. No clinical studies were conducted in participantswith hypoparathyroidism who have severe renal impairment. In a study where palopegteriparatide was administered as a single 50 mcg subcutaneous dose to non-hypoparathyroid participants with renal impairment, palopegteriparatide exposure was similar in participants with mild, moderate, and severe renal impairment as compared to participants without renal impairment.
- **Obesity:** The pharmacokinetics of palopegteriparatide was not influenced by body weight.

10.4 Immunogenicity

Patients may develop antibodies to Yorvipath. The proportion of participantstesting 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 Yorvipath treated participantswith pre-existing and treatment-induced anti-PEG antibodies, a transient impact on PK with decreasing serum calcium was observed. However, therapeutic effectiveness was maintained by dose adjustment of Yorvipath according to the trial titration algorithm.

11 STORAGE, STABILITY AND DISPOSAL

Do not freeze. Store away from heat. Keep Yorvipath in the packaging to protect from light.

Until first use, store Yorvipath in the refrigerator between 2°C to 8°C.

After first use, store Yorvipath for 14 days at room temperature below 30°C. After each use, remove the needle and put the pen cap on to protect from light. Discard the pre-filled pen 14 days after first use.

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

12 SPECIAL HANDLING INSTRUCTIONS

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.

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

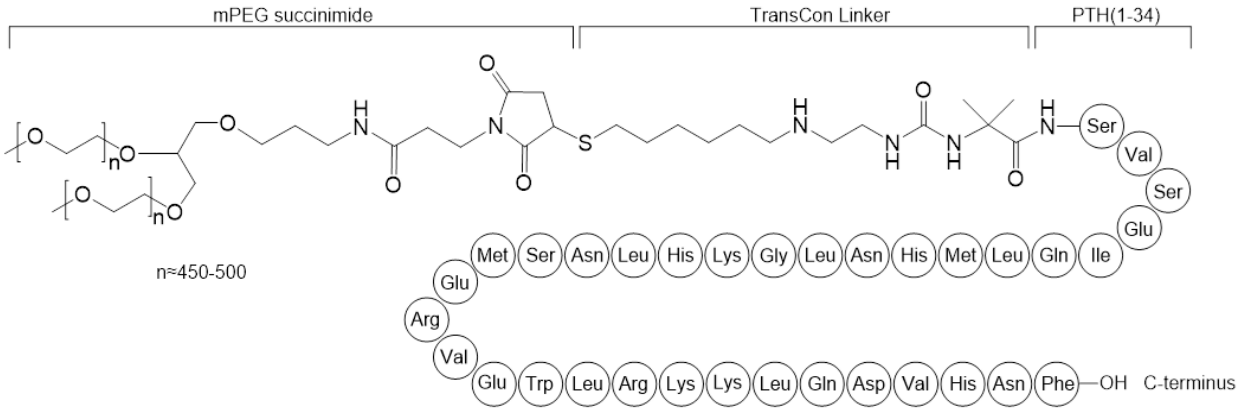
Drug Substance

Proper name: palopegteriparatide

Chemical name: 2-[6-[1-[3-[3-[2,3-Bis[methyl-poly(oxyethylen)-oxy)propyloxy]propylamino]-3-oxo-propyl]-2,4-dioxo-pyrrolidin-3yl]sulfanylhexylamino]ethylcarbamoyl-alpha-aminoisobutyryl-L-seryl-L-valyl-L-seryl-L-glutamyl-L-isoleucyl-L-glutaminyl-L-leucyl-L-methionyl-L-histidyl-L-asparaginyl-L-leucyl-glycyl-L-lysyl-L-histidyl-L-leucyl-L-asparaginyl-L-seryl-L-methionyl-L- glutamyl-L-arginyl-L-valyl-L-glutamyl-L-tryptophyl-L-leucyl-L-arginyl-L-lysyl-L-lysyl-L-leucyl-L-glutaminyl-L-aspartyl-L-valyl-L-histidyl-L-asparaginyl-L-phenylalanine

Molecular formula and molecular mass: The theoretical molecular formula is $C_{209}H_{340}N_{60}O_{59}S_3$ + 2 × $(C_2H_4O)n$, where n is between approximately 450 and 500. The average molecular weight of palopegteriparatide is approximately 47.4 kDa.

Structural formula:



Physicochemical properties: Palopegteriparatide is a white to off-white solid. pH in a 5% w/w aqueous solution of palopegteriparatide drug substance is approximately 7.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Hypoparathyroidism

Table 5- Summary of Participant Demographics for Study TCP-304 in Participants with Hypoparathyroidism

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
TCP-304	Phase 3, 26-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group trial	Participants randomized 3:1 to starting dose of Yorvipath 18 mcg/day or placebo. Dose was individually and progressively titrated to an optimal dose in increments/ decrements of 3 mcg/day. **Yorvipath:** (range: 6 to 60 mcg/day) via subcutaneous (SC) injection, once daily (QD) **Placebo:** SC, QD	**Yorvipath:** n = 61 **Placebo:** n = 21	49 years (19-78 years)	64 females 18 males

The pivotal phase 3 PaTHway clinical trial (TCP-304) assessed the efficacy and safety of Yorvipath as PTH replacement therapy for adults with postsurgical chronic hypoparathyroidism, or auto-immune, genetic, or idiopathic hypoparathyroidism for at least 26 weeks, treated with active vitamin D (calcitriol ≥ 0.5 mcg/day or alfacalcidol ≥1.0 mcg/day) and elemental calcium ≥800 mg/day for at least 12 weeks prior to Screening.

Study Design

This was a 26-week double blind, placebo controlled clinical trial which included participants randomised (3:1) to Yorvipath or placebo, co-administered with conventional therapy (calcium and active vitamin D treatment). Randomisation was stratified by aetiology of hypoparathyroidism (i.e., postsurgical vs. all other causes).

The starting dose of Yorvipath was 18 mcg/day, with dose adjustments in 3 mcg increments or decrements, and a dose range of 6 to 60 mcg per day. Study treatment (Yorvipath or placebo) and conventional therapy were titrated according to a dosing algorithm guided by albumin-corrected serum calcium levels.

The 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 participants

had hypoparathyroidism acquired from neck surgery. Of the participants with other aetiologies of hypoparathyroidism, 7 (8.5%) had idiopathic disease, 2 had autoimmune polyglandular syndrome type 1 (APS 1), 1 had autosomal dominant hypocalcemia type 1 (ADH1, CaSR mutation), 1 had DiGeorge Syndrome, and 1 had hypoparathyroidism, sensorineural deafness and renal dysplasia (HDR) syndrome (GATA3 mutation). At baseline, the median duration of hypoparathyroidism was 8.5 years (range: 1 to 56 years).

Prior to randomisation, all participants underwent an approximate 4 week screening period in which calcium and active vitamin D treatments were adjusted to achieve an albumin-corrected 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, participants were treated with mean baseline doses of elemental calcium of 1839 mg/day. Mean baseline doses of active vitamin D were 0.75 micrograms/day in calcitriol treated participants (n=70), and 2.3 micrograms/day in alfacalcidol-treated participants (n = 12).

Baseline mean albumin-corrected serum calcium and mean 24-hour urine calcium were similar in both treatment groups: mean albumin-corrected 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 participants at Week 26 who achieved the following:

- Albumin-corrected serum calcium measured within 4 weeks prior to and on Week 26 visit within the normal range (2.07 to 2.64 mmol/L [8.3 to 10.6 mg/dL]), AND
- Independence from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of pro re nata [PRN] ≤7 days during the 4 weeks) AND
- Independence from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND use of PRN doses ≤7 days during the 4 weeks) AND
- No increase in prescribed study treatment within 4 weeks prior to week 26 visit.

Key Secondary Endpoints

The 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 Cochran–Mantel–Haenszel (CMH) test controlling for randomization stratification factor (etiology of hypoparathyroidism: post-surgical versus other) was used for the primary analysis. Sensitivity analyses were also conducted.

14.2 Study Results

The number of Yorvipath-treated participants meeting the composite primary endpoint and each of its components at week 26 compared with the participants from the placebo group is presented in Table 6. **Table** In the Yorvipath group, 78.7% (48/61) of participants met the composite primary endpoint compared with 4.8% (1/21) of participants in the placebo group (p-value for difference between groups

<0.0001).

Table 6 – Results of Study TCP-304 in Patients with Hypoparathyroidism

Primary Endpoint	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-corrected 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%)

Abbreviations: CI: confidence interval; PRN: pro re nata.

[a] The normal range for albumin-corrected 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.

Key-Secondary Endpoints

Patient-reported Outcomes

Treatment with Yorvipath resulted in statistically significant improvements from baseline to Week 26 in HPES-Symptom – Physical and Cognitive domain scores, HPES-Impact – Physical Functioning and Daily Life domain scores, and SF-36 Physical Functioning subscale score compared to placebo (Table 7). Improvements in patient-reported outcomes were generally observed as early as Week 10 (the time of first assessment on palopegteriparatide) and were sustained through Week 26.

Table 7 - Change from Baseline to Week 26 in HPES-Symptom, HPES-Impact, and SF-36v2®

	Yorvipath (n = 59)	Placebo (n = 19)	Difference	P-value
HPES-Symptom				
Physical domain score, LS mean (SE)	-21.0 (2.2)	-4.8 (5.0)	-16.2 (5.0)	0.0038
Cognitive domain score, LS mean (SE)	-20.5 (2.6)	-6.2 (4.7)	-14.3 (4.7)	0.0055
HPES-Impact				
Physical Functioning domain score, LS mean (SE)	-18.3 (2.7)	-1.0 (5.5)	-17.3 (5.5)	0.0046
Daily Life domain score, LS mean (SE)	-17.7 (2.4)	-0.4 (5.7)	-17.3 (5.7)	0.0061
SF-36v2®				
Physical Functioning subscale score, LS mean (SE)	5.3 (0.9)	0.1 (2.3)	5.2 (2.3)	0.0347

Summary statistics at baseline and post-baseline visits are calculated from participants with data at both baseline

and post-baseline visits.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In a 26-week rat study, daily subcutaneous administration of palopegteriparatide resulted in increased bone turnover in healthy euparathyroid rats. In both sexes treated at the low dose of 5 mcg/kg/day (2-fold the maximum recommended human dose (MRHD), based on AUC of PTH(1-34) and active metabolite PTH(1-33)) and in females treated at 10 mcg/kg/day (5-fold the MRHD, based on AUC of PTH(1-34) and PTH(1-33)), the increased bone turnover tended towards a net catabolic effect (bone resorption). The net catabolic bone phenotype was characterized by a decrease in proximal tibial bone mass and bone mineral density (BMD). In males treated at 10 mcg/kg/day (5-fold the MRHD, based on AUC of PTH(1-34) and PTH(1-33)) and in both sexes treated at the high dose of 20 mcg/kg/day (9-fold the MRHD, based on AUC of PTH(1-34) and PTH(1-33)), the increased bone turnover resulted in a net anabolic bone effect (bone formation). The net anabolic phenotype was characterized by an increase in proximal tibial bone mass and density. The increase in bone formation was accompanied by an increase in osteoblast cellularity, peritrabecular fibrosis and unmineralized bone matrix, and physeal dysplasia at the highest dose level. The relevance of these effects remains unclear in a clinical setting where palopegteriparatide doses are individually adjusted.

Carcinogenicity

No long-term animal studies have been performed to evaluate the carcinogenic potential of palopegteriparatide.

Genotoxicity

Palopegteriparatide demonstrated no genotoxic potential at maximum tested limits in the standard battery of genotoxicity studies. Palopegteriparatide was non-mutagenic in an *in vitro* bacterial reverse-mutation assay (Ames test). Additionally, it was non-clastogenic in both the *in vitro* human lymphocyte chromosome aberration assay at concentrations up to 500 mcg/mL and the *in vivo* rat bone marrow micronucleus assay at subcutaneous doses up to 60 mcg/kg/day.

Reproductive and Developmental Toxicology

Two fertility and early embryonic development (FEED) studies were conducted in male and female rats, where palopegteriparatide was administered by subcutaneous injection at 2, 6, and 20 mcg/kg/day. No effect on fertility and reproductive function of male and female rats was observed up to the highest tested dose.

In an embryo-fetal developmental toxicity study in rats, palopegteriparatide was administered subcutaneously during the period of organogenesis (gestation days (GD) 6 to 17) at doses of 2, 8, and 30 mcg/kg/day. In pregnant rats, there was no evidence of embryo-lethality, fetotoxicity, or fetal

malformations up to the highest dose tested corresponding to 8-fold the MRHD, based on the AUCs of PTH(1-34) and active metabolite PTH(1-33).

In an embryo-fetal developmental toxicity study in rabbits, palopegteriparatide was administered subcutaneously to pregnant female rabbits during the period of organogenesis (GD 7 to 19) at doses of 1, 3, and 6 mcg/kg/day. There was no evidence of any palopegteriparatide-related embryo-lethality, fetotoxicity, or fetal malformations at any dose level up to 7-fold the MRHD, based on the AUC of PTH(1-34).

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.

In the pre- and post-natal development (PPND) study in rats, palopegteriparatide was injected subcutaneously at doses of 5, 10, and 20 mcg/kg/day to pregnant rats from GD 6 to lactation day 21. Palopegteriparatide did not induce adverse effects on maternal reproductive function or on developmental parameters of male and female offspring of pregnant and lactating female rats at doses up to 20 mcg/kg/day (4-fold the MRHD, based on C_{max} of PTH(1-34) and active metabolite PTH(1-33)). Non-adverse dose-related decrease in reproductive performance was observed in the F1 generation with differences reaching statistical significance compared to controls at the highest dose.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrYorvipath™

palopegteriparatide injection

Read this carefully before you start taking **Yorvipath** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Yorvipath**.

What is Yorvipath used for?

Yorvipath is used to treat adults with chronic low parathyroid hormone levels (hypoparathyroidism).

How does Yorvipath work?

In people with hypoparathyroidism, the body produces no or too little parathyroid hormones (PTH). Because of this, they cannot keep the levels of calcium and phosphate within a normal range, and this leads to the symptoms of the condition, such as muscle spasms, twitching, and tingling in your fingertips, toes and lips. Yorvipath replaces the missing PTH to help control the levels of calcium and phosphate.

What are the ingredients in Yorvipath?

Medicinal ingredients: Palopegteriparatide

Non-medicinal ingredients: Hydrochloric acid, mannitol, metacresol, sodium hydroxide, succinic acid, water for injection

Yorvipath comes in the following dosage forms:

Solution for injection in pre-filled pens, available as:

Pre-filled Pen	Doses delivered	Push button colour
168 mcg / 0.56 mL	6 mcg, 9 mcg, 12 mcg	blue
294 mcg / 0.98 mL	15 mcg, 18 mcg, 21 mcg	orange
420 mcg / 1.4 mL	24 mcg, 27 mcg, 30 mcg	burgundy

Each package contains 2 inner boxes. Each inner box contains 1 Yorvipath pen and 15 disposable needles (including 1 spare needle). Thus, each package contains a total of 2 Yorvipath pens and 30 disposable needles.

Do not use Yorvipath if:

- you are allergic to palopegteriparatide or any of the other ingredients in Yorvipath.
- you have pseudohypoparathyroidism, a condition in which the body does not adequately respond to the parathyroid hormone produced by the body.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Yorvipath. Talk about any health conditions or problems you may have, including if you:

- are at higher risk of a type of bone cancer called osteosarcoma. This is especially important:
  - if you have a bone disease that increases your risk of developing osteosarcoma (including if you have Paget's disease of the bone).
  - if a blood test shows that you have unexplained increases in bone alkaline phosphatase.
  - if you have cancer of the bones or other cancer that has spread to your bones.

- if you are having or have had radiation therapy to the skeleton.
- if you are affected with a condition that runs in your family that can increase your chance of getting cancer in your bones.

- are taking digoxin or digitoxin, which is prescribed for heart failure, fast heart rate, or irregular heart rhythm
- have or have had problems with your kidneys
- have or have had problems with your liver

Other warnings you should know about:

- **High levels of calcium in your blood (hypercalcemia)**
  - You may experience increased levels of calcium in your blood, especially when starting or increasing your dose of Yorvipath, or if you have to use 2 pens to make up your daily dose.
  - Contact your healthcare professional if you experience nausea, dizziness, vomiting, constipation, lethargy, or muscle weakness that do not go away.

- **Low levels of calcium in your blood (hypocalcemia)**
  - You may experience decreased levels of calcium in your blood if you suddenly discontinue Yorvipath, or if you have to use 2 pens to make up your daily dose.
  - Contact your healthcare professional if you experience confusion, memory loss, depression, hallucinations, muscle spasms, muscle cramps, numbness or tingling in the hands, feet, or face.

- **Check-up and testing:** You will have regular visits with your healthcare professional during your treatment with Yorvipath. They will:
  - Do a blood test to check your calcium and vitamin D levels before you start treatment with Yorvipath.
  - Check how you respond to the Yorvipath treatment:
    - 7 days after starting treatment and
    - 7 to 14 days after your dose is changed

    This will be done using tests to measure the level of calcium in your blood or urine. Your healthcare professional may tell you to change the amount of calcium or vitamin D you take (in any form, including foods rich in calcium).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Yorvipath:

- Cardiac glycosides (such as digoxin or digitoxin), which are used to treat heart conditions
- Medicines used to treat osteoporosis and other conditions that affect the density and strength of bones such as bisphosphonates, denosumab, or romosozumab
- A type of water pills, called thiazide or loop diuretics used to treat high blood pressure
- Systemic corticosteroids used to treat inflammation
- Lithium which is used to treat mental illnesses such as bipolar disorder

How to take Yorvipath:

- Before you use the pen for the first time, your healthcare professional will show you how to inject Yorvipath. Use exactly as your healthcare professional tells you to use it.
- Yorvipath is an injection given under the skin ('subcutaneous injection'). This means that it is injected with a short needle into the fatty tissue under the skin.
- Inject Yorvipath once per day. Set a reminder on a calendar to remind yourself of your daily injection.
- Some people may feel dizzy, get a fast heartbeat, or feel light-headed right after injecting Yorvipath. For the first few doses, give your injection of Yorvipath in a place where you can sit or lie down right away if you get these symptoms. If your symptoms get worse or do not go away, contact your healthcare professional before you continue using Yorvipath.
- Yorvipath should be injected into the belly (abdomen) or front of the thigh, and it is important to inject into a different area every day to help avoid damaging your skin. You can change between the left and right side of the belly and between the left and right front of the thigh.
- See INSTRUCTIONS FOR USE for full administration instructions. You should always use the pen as described in the INSTRUCTIONS FOR USE.

Usual dose:

- Your healthcare professional will decide the best dosage for you based on your condition.
- The recommended starting dose of Yorvipath is 18 mcg once daily.
- Your healthcare professional may advise you to gradually change your dose based on your response to the medicine. Your dosage will be adjusted until you are using a dose that keeps the amount of calcium in your body within the normal range without the need for active vitamin D or calcium treatments.
- Initially, you will take Yorvipath with calcium and active vitamin D. During treatment, your healthcare professional may change your doses of calcium and active vitamin D.

If your dose is **above 30 mcg** per day:

- Your healthcare professional will explain how to take your dose.
- You will need to administer two injections, one after the other, in separate injection sites.
- **You should use a different Yorvipath pen for the second daily injection, even if the two pens have the same-coloured push button (same strength).**
- Using two separate pens will increase your risk of having high or low levels of calcium in your blood. Be aware of the symptoms and contact your healthcare professional right away if you develop signs of high or low levels of calcium.
- Refer to the table below for which pens to use. Always check with your healthcare professional if you are not sure.

Recommended scheme for Yorvipath dosing above 30 mcg/day

Total Dose	First pen turn dial to dose of:		Second pen turn dial to dose of:	Which Yorvipath pen to use?
	Orange pen (294 mcg / 0.98 mL)		**Orange pen (294 mcg / 0.98 mL)**	Use **2 separate orange pens** one after the other in 2 separate injection sites
33 mcg/day	15 mcg	+	18 mcg	
36 mcg/day	18 mcg	+	18 mcg	
39 mcg/day	18 mcg	+	21 mcg	
42 mcg/day	21 mcg	+	21 mcg	
	Orange pen (294 mcg / 0.98 mL)		**Burgundy pen (420 mcg / 1.4 mL)**	**ATTENTION**: for this dose, you must use two different strength pens one after the other, in separate injection sites
45 mcg/day	21 mcg	+	24 mcg	**First injection**: Use 1 orange pen (294 mcg / 0.98 mL pen) + **Second injection**: Use 1 burgundy pen (420 mcg / 1.4 mL pen)
	Burgundy pen (420 mcg / 1.4 mL)		**Burgundy pen (420 mcg / 1.4 mL)**	Use **2 separate burgundy pens** one after the other in 2 separate injection sites
48 mcg/day	24 mcg	+	24 mcg	
51 mcg/day	24 mcg	+	27 mcg	
54 mcg/day	27 mcg	+	27 mcg	
57 mcg/day	27 mcg	+	30 mcg	
60 mcg/day	30 mcg	+	30 mcg	

Yorvipath 294 mcg / 0.98 mL pen delivers doses of 15, 18, or 21 mcg (with orange push button).
Yorvipath 420 mcg / 1.4 mL pen delivers doses of 24, 27, or 30 mcg (with burgundy push button).

Overdose:

If you use more Yorvipath than you should, immediately contact your healthcare professional and describe any symptoms you get. An overdose may lead to high levels of calcium in the blood. Symptoms may include but are not limited to being sick (vomiting), dizziness, feeling thirsty, confusion, muscle weakness, and irregular heartbeat.

If you think you, or a person you are caring for, have taken too much Yorvipath, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you forget to inject a dose of Yorvipath, and:

- **less than** 12 hours have passed: inject the missed dose as soon as you remember.
- **more than** 12 hours have passed: skip the missed dose. Inject your next dose as you normally would.

Do NOT take two doses at the same time to make up for a missed dose.

What are possible side effects from using Yorvipath?

These are not all the possible side effects you may have when taking Yorvipath. If you experience any side effects not listed here, tell your healthcare professional.

- Headache
- Thirst
- Rash
- Tingling in your fingertips, toes and lips
- Nausea or vomiting
- Feeling tired or weak
- Redness, bruising, pain, bleeding, rash or swelling where you injected the medicine
- Feeling like your heart Is fluttering or beating too fast
- Sore mouth or sore throat
- Diarrhea or constipation
- Abdominal pain or abdominal discomfort
- Skin reaction to sunlight
- The need to pass urine often or at night
- Chest pain or chest discomfort
- High blood pressure

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Hypercalcemia (high levels of calcium in the blood): being sick (vomiting), dizziness, feeling thirsty, confusion, muscle weakness, and irregular heartbeat			√
Hypocalcemia (low levels of calcium in the blood): muscle pain, bone pain, muscle twitching, chest discomfort, chest pain, tingling in your fingertips, toes and lips (paraesthesia), muscle spasms and cramps, oral numbness, and seizures			√
Orthostatic Hypotension: Dizziness, light-headedness or fainting when you sit up or stand up		√	

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Do not use this medicine after the expiry date which is stated on the carton.
- Do not use this medicine if you notice that the solution is cloudy, coloured, or has visible particles in it.
- Keep out of reach and sight of children.

Before first use:

- Store in a refrigerator (2 °C to 8 °C). Do not freeze.
- Store in the original package with the pen cap on in order to protect from light.

After first use:

- Store at room temperature below 30°C.
- Keep the pen cap on the pre-filled pen in order to protect from light.
- Discard each pen 14 days after first use.

If you want more information about Yorvipath:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pendopharm.com or by calling 1-888-550-6060.

This leaflet was prepared by Pendopharm, a division of Pharmascience Inc.

Date of revision: January 28, 2026

INSTRUCTIONS FOR USE

PrYorvipath™

palopegteriparatide injection

168 mcg / 0.56 mL

For **6, 9 or 12 mcg doses** only

Solution for injection in pre-filled pen

For subcutaneous use

These instructions for use contain information on how to inject Yorvipath

Additional information
If you do not understand or are unable to complete a step that is described in these instructions for use, contact your doctor or nurse.

Important information you need to know before using your Yorvipath pen

Read and follow the package leaflet and these instructions for use carefully so that you inject Yorvipath the right way.

Make sure you have received training from your doctor or nurse before injecting. This is important to make sure that you get the correct treatment.

For correct use

- By failing to follow these instructions, you may not get the right dose, and may therefore not get the full effect of your medicine.
- If you are blind or visually impaired or if you have lack of concentration, **do not** use your pen without help. Instead get help from a person who is trained to use the Yorvipath pen.
- Keep out of the sight and reach of children.
- The pen and needles are for single-patient use only.
- **Do not** share your pen or needles with other people. It might lead to infection (cross-contamination).
- Always throw away your pen **after 14 days of use**, even if it still has medicine left inside. This is important to make sure that you get the right effect of your medicine.
- Always use the needles that come with the Yorvipath pen for your injections.
- Remove the needle after every use. **Do not** store the pen with the needle on.
- Avoid bending or breaking off the pen needle.

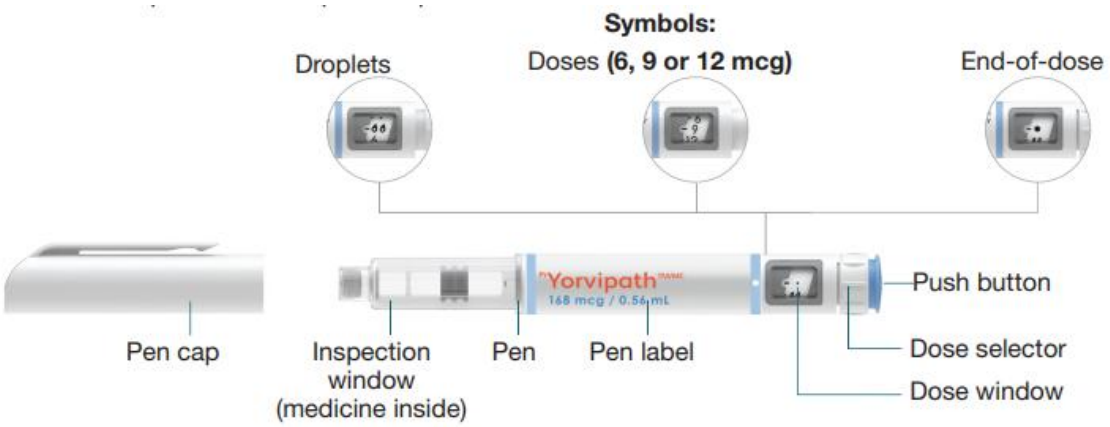
- **Do not** change the injection angle after the needle has been inserted into the skin. Changing the angle can cause the needle to bend or break off. A bent or broken needle can remain stuck in the body or remain completely under the skin. If a broken needle remains stuck in the body or remains under the skin, seek medical help right away.
- **Do not** use needles if the needle cover or needle foil are damaged.

Caring for your pen

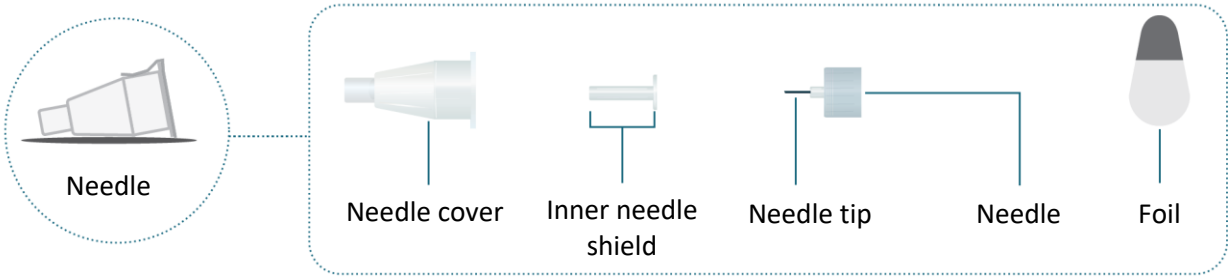
- Handle your pen with care.
- Keep your pen dry.
- Use a moist cloth to clean your pen.
- **Do not** drop or knock your pen against hard surfaces. If you do, test the pen flow again (section 2, steps A - C) before next use.
- **Do not** apply extra force to your pen. It might be empty, damaged and no longer work properly.
- **Do not** attempt to repair a damaged pen yourself.
- Never use a damaged pen.

Parts overview

Figure A
Parts of the Yorvipath multi-use prefilled pen



Pen needle parts (needles are included in the inner carton)

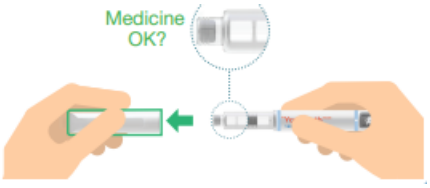


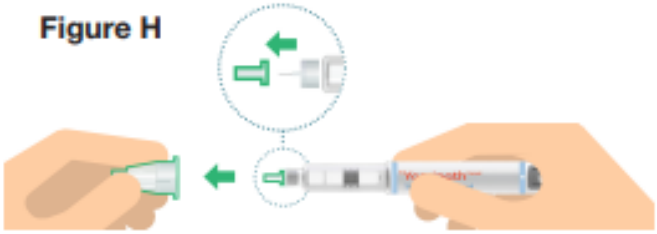
You will also need

Figure B

Sharps disposal container

Alcohol wipe

1 Prepare your supplies for the injection	
Before you start: **Step 1** • Find a well-lit, flat work surface, like a table. • When you open the Yorvipath outer carton, you will find two inner cartons inside. Take out one inner carton from the refrigerator prior to first use and unpack the pen-injector. Leave second inner carton in the refrigerator until first use. • You should take your pen out of the refrigerator **20 minutes** before first use. • Gather your supplies (see Figures A and B): - Yorvipath Pen - Needle (included in the inner carton) - Sharps disposal container - Alcohol wipe	
Step 2 Wash your hands well with soap and water (figure C).	**Figure C** 
2 Prepare pen with a new needle	
Step 1 Take your Yorvipath pen out from the inner carton. Make sure it is the correct strength and check the **expiry date**. Take a needle and check the **expiry date** on the needle (figure D). **Important:** If the medicine is expired, **do not** use the pen. Use a new pen.	**Figure D** 
Step 2 Pull off the pen cap and check the inspection window to make sure the medicine inside the pen is clear and colourless (figure E). **Important:** If the medicine has visible particles in it **do not** use the pen. Use a new pen.	**Figure E** 

Step 3 Pull the foil off the needle (figure F). This needle can only be used **1 time**. Always use a new needle for each injection. **Important:** Make sure to only use the needles that come with the Yorvipath pen for your injections.	**Figure F** 
Step 4 Attach the needle **straight** onto your pen, then screw the needle onto the pen until secure (clockwise) (figure G).	**Figure G** 
Step 5 Pull off the needle cover and the inner needle shield (figure H). Throw away the inner needle shield (in the regular garbage) and keep the needle cover for later.	**Figure H** 

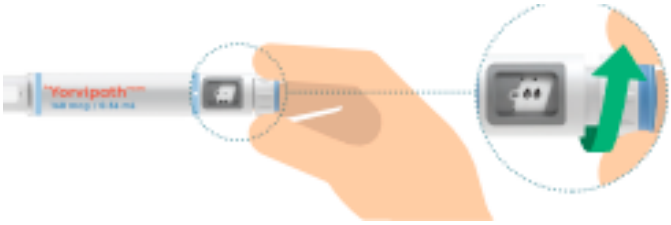
3 If new pen, test pen flow

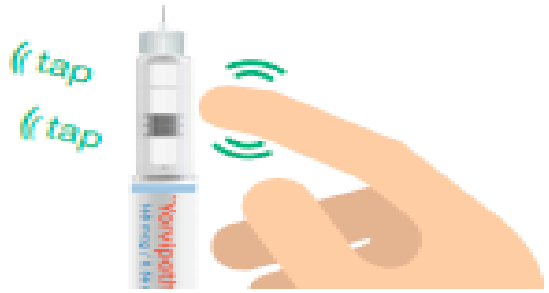
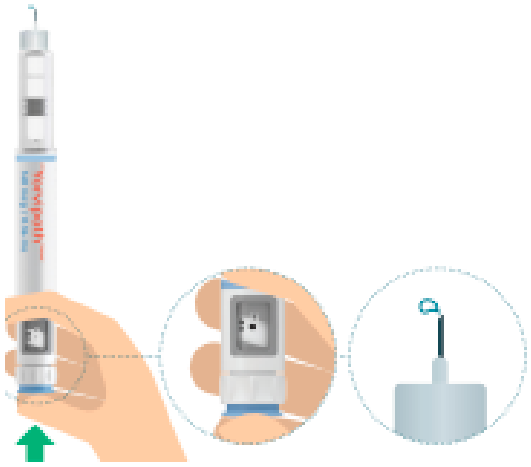
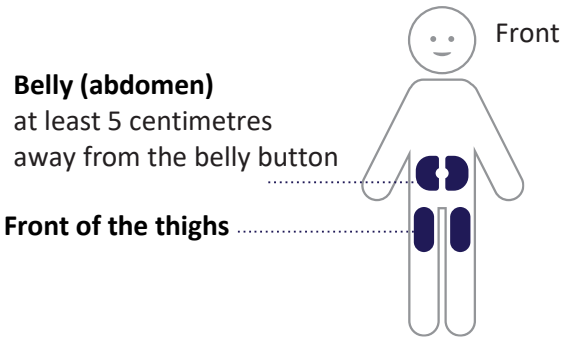
ATTENTION

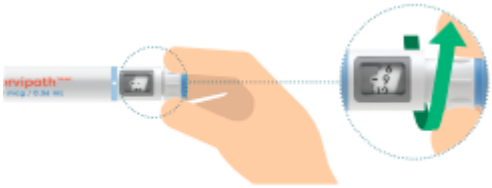
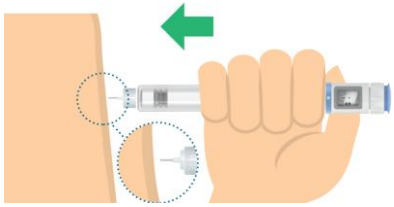
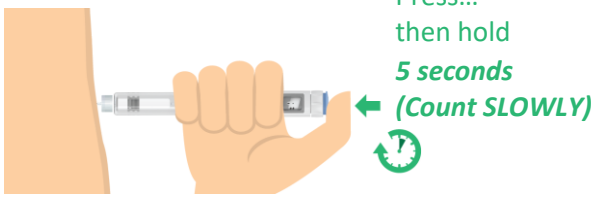
Only test pen flow (steps A - C) the first time you use a new pen. See below for instructions on troubleshooting.

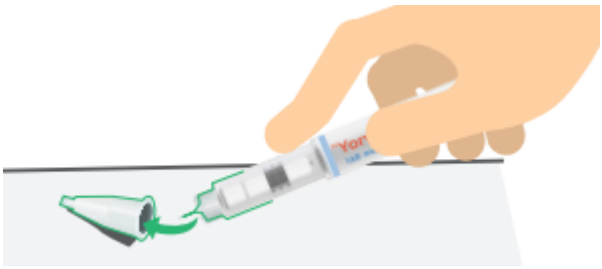
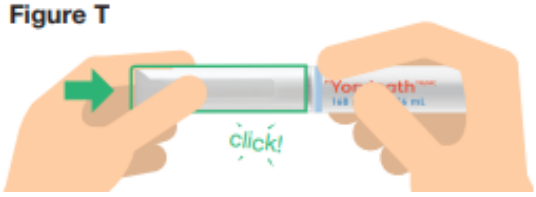
If your pen is already in use, go to section "3 Prepare injection and select dose".

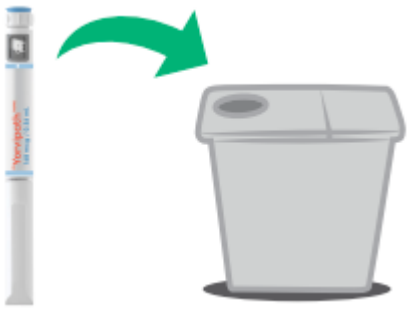
Day 1

Step A Turn the dose selector clockwise (to the right) **2 clicks** until you see the droplet symbol "💧💧" in the dose window (figure I). **Note:** You can always correct the selection by turning the dose selector.	**Figure I** 

Step B Make any air bubbles rise to the top of the pen by tapping the inspection window (figure J). Keep the pen with the needle tip pointed up. **Note:** Tiny air bubbles are ok.	**Figure J** 
Step C Press the push button and watch drops of medicine come out of the needle tip. When you press, make sure that the dose selector rotates back to the symbol "●" (figure K). **Important:** If you do not see drops of medicine, repeat this test (steps A - C) up to **5 times**. If drops are still not seen, change the needle and repeat the test.	**Figure K** 
4 Prepare injection and select dose	
Step 6 Choose injection site. There are **two** regions of your body you can inject into (figure L). Avoid injecting where skin is red, swollen or scarred. Choose a different injection site each time you inject.	**Figure L** 

Step 7 Clean the injection site with an alcohol wipe (figure M).	**Figure M** 
Step 8 Select your dose as prescribed by your doctor (**6, 9 or 12 mcg)** by turning the dose selector clockwise (to the right) (figure N). **Important:** Make sure not to press the push button while selecting your dose to not spill medicine. **Note:** Always throw away your pen and use another pen if you cannot dial a full dose.	**Figure N** 
5 Inject dose ATTENTION **Use the injection technique recommended by your doctor or nurse. Read this whole section (steps 9 - 11) before you start to inject.**	
Step 9 Make sure you can see the dose window. To insert the needle into the skin (figure O), press the pen against injection site in a straight movement.	**Figure O** 
Step 10 Press the push button all the way in and hold steady for **5 seconds (COUNT TO 5 S-L-O-W-L-Y)**. Make sure the dose selector rotates back to the symbol "●". This means that you have given the full dose (figure P).	**Figure P** 

Step 11 Slowly remove the pen from the injection site in a straight angle (figure Q).	**Figure Q** 
6 Throw away used needle	
Step 12 Reattach the needle cover to carefully remove the needle. Lead the needle tip into the needle cover and secure the needle cover onto the needle (figure R). **Important**: Always reattach the needle cover before removing the needle to reduce the risk of needle stick and cross-contamination.	
Step 13 Unscrew the needle. Safely throw away the needle according to local regulations. (figure S).	**Figure S** 
Step 14 Click the pen cap firmly onto the pen to protect it between injections and to protect the medicine from light (figure T).	**Figure T** 

7 **Throw away used pen**	Day **14**
Important: Always throw away your pen after **14 days of use**, even if it still has medicine inside (figure U). This is important to make sure that you get the full effect of your medicine. It is recommended to fill out the 'Open date:' field on the carton, in order to know when 14 days have passed. **Note:** Remember to throw away the extra needle when you throw away your pen.	**Figure U** 

Troubleshooting

1. How often must I test the pen flow?

You should only test the pen flow (section 2) the first time you use a new pen (or if you think it might be damaged) to not waste medicine. The test checks to make sure the medicine flows through the pen so that you get the right doses of medicine.

2. I do not see drops appear after I have tested the pen flow 5 times. What should I do?

If you see no drop on the needle tip after **5 attempts**, it might be because there is no flow through the pen and needle.

Change the needle (see section 5, step 12) and test the pen flow again (see section 2, steps A - C). You can be sure the flow works correctly when you see the drop of medicine.

If it still does not work discard the pen and contact your health care provider.

3. How do I know I have completed the injection?

Your injection is only completed after you have pressed the push button all the way in and the dose selector has rotated back to the "●" and you have kept the needle in the skin for **5 seconds (COUNT TO FIVE slowly)**.

4. Why do I have to keep holding the pen in the skin for 5 seconds?

Some medicine might flow back into the pen or flow backward from the injection site and be left on the skin. Holding the pen in the skin for **5 seconds** helps to make sure that all the medicine has been injected.

5. I cannot dial the dose selector to the required dose. What should I do?

The pen does not allow a larger dose to be set than what is left in the pen.
If your dose is larger than the amount of medicine left in the pen you will not be able to dial a full dose. You must throw away your pen and take the full dose of medicine with a new pen.

INSTRUCTIONS FOR USE

PrYorvipath™

palopegteriparatide injection

294 mcg / 0.98 mL

For **15**, **18 or 21 mcg doses** only

Solution for injection in pre-filled pen

For subcutaneous use

These instructions for use contain information on how to inject Yorvipath

Additional information
If you do not understand or are unable to complete a step that is described in these instructions for use, contact your doctor or nurse.

Important information you need to know before using your Yorvipath pen

Read and follow the package leaflet and these instructions for use carefully so that you inject Yorvipath the right way.

Make sure you have received training from your doctor or nurse before injecting. This is important to make sure that you get the correct treatment.

For correct use

- By failing to follow these instructions, you may not get the right dose, and may therefore not get the full effect of your medicine.
- If you are blind or visually impaired or if you have lack of concentration, **do not** use your pen without help. Instead get help from a person who is trained to use the Yorvipath pen.
- Keep out of the sight and reach of children.
- The pen and needles are for single-patient use only.
- **Do not** share your pen or needles with other people. It might lead to infection (cross-contamination).
- Always throw away your pen **after 14 days of use**, even if it still has medicine left inside. This is important to make sure that you get the right effect of your medicine.
- Always use the needles that come with the Yorvipath pen for your injections.
- Remove the needle after every use. **Do not** store the pen with the needle on.
- Avoid bending or breaking off the pen needle.
- **Do not** change the injection angle after the needle has been inserted into the skin. Changing the angle can cause the needle to bend or break off. A bent or broken needle can remain

stuck in the body or remain completely under the skin. If a broken needle remains stuck in the body or remains under the skin, seek medical help right away.

- **Do not** use needles if the needle cover or needle foil are damaged.

Special instructions for doses larger than 30 mcg/day

If your dose is above 30 mcg/day:

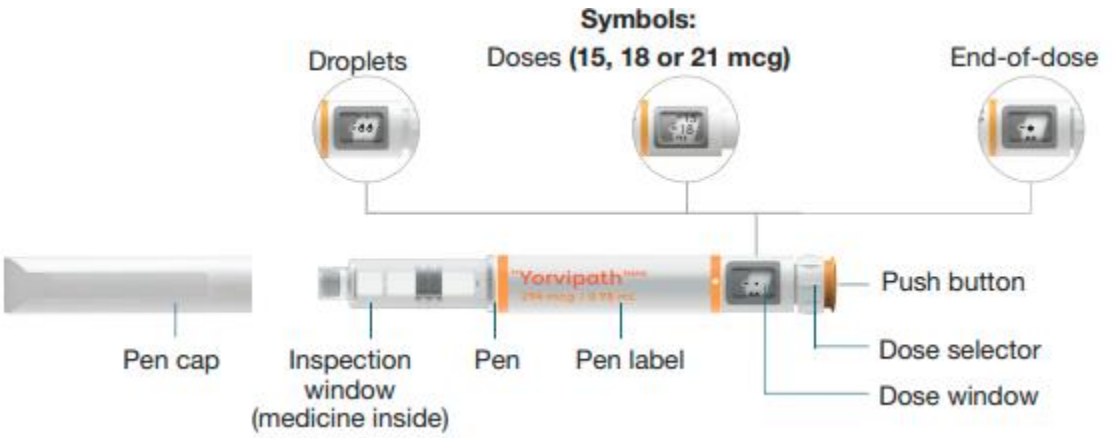
- Administer two injections, one after the other, in separate injection sites (see table with recommended scheme in section 3 of Package leaflet).
- It is recommended to use a different Yorvipath pen for the second daily injection, even if the two pens have the same-coloured push button (same strength).
- Follow the steps in the instructions for use for each injection.

Caring for your pen

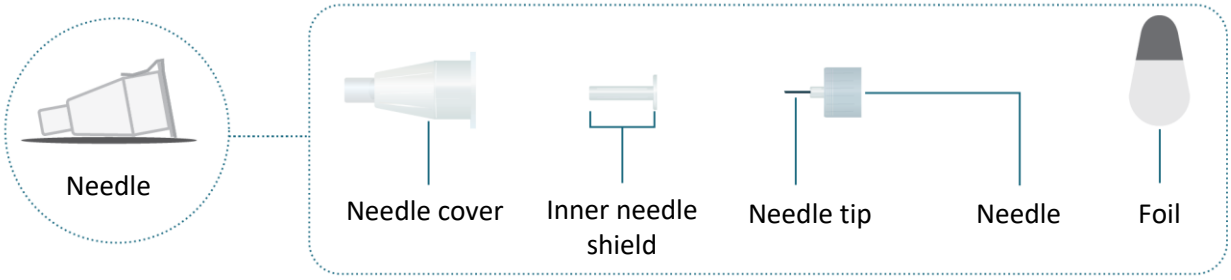
- Handle your pen with care.
- Keep your pen dry.
- Use a moist cloth to clean your pen.
- **Do not** drop or knock your pen against hard surfaces. If you do, test the pen flow again (section 2, steps A - C) before next use.
- **Do not** apply extra force to your pen. It might be empty, damaged and no longer work properly.
- **Do not** attempt to repair a damaged pen yourself.
- Never use a damaged pen.

Parts overview

Figure A
Parts of the Yorvipath multi-use prefilled pen



Pen needle parts (needles are included in the inner carton)



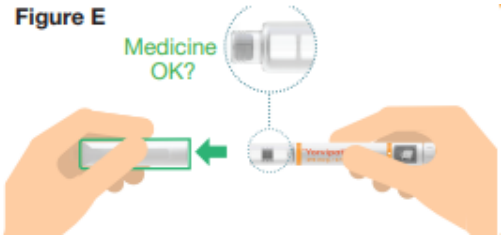
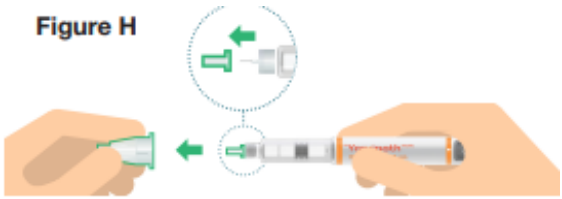
You will also need

Figure B

Sharps disposal container

Alcohol wipe

1 Prepare your supplies for the injection	
Before you start: **Step 1** • Find a well-lit, flat work surface, like a table. • When you open the Yorvipath outer carton, you will find two inner cartons inside. Take out one inner carton from the refrigerator prior to first use and unpack the pen-injector. Leave second inner carton in the refrigerator until first use. • You should take your pen out of the refrigerator **20 minutes** before first use. • Gather your supplies (see Figures A and B): - Yorvipath Pen - Needle (included in the carton) - Sharps disposal container - Alcohol wipe	
Step 2 Wash your hands well with soap and water (figure C).	**Figure C** 

2 Prepare pen and needle	
Step 1 Take your Yorvipath pen out from the inner carton. Make sure it is the correct strength and check the **expiry date**. Take a needle and check the **expiry date** on the needle (figure D). **Important:** If the medicine is expired, **do not** use the pen. Use a new pen.	**Figure D** 
Step 2 Pull off the pen cap and check the inspection window to make sure the medicine inside the pen is clear and colourless (figure E). **Important:** If the medicine has visible particles in it **do not** use the pen. Use a new pen.	**Figure E** 
Step 3 Pull the foil off the needle (figure F). This needle can only be used **1 time**. Always use a new needle for each injection. **Important:** Make sure to only use the needles that come with the Yorvipath pen for your injections.	**Figure F** 
Step 4 Attach the needle **straight** onto your pen, then screw the needle onto the pen until secure (clockwise) (figure G).	**Figure G** 
Step 5 Pull off the needle cover and the inner needle shield (figure H). Throw away the inner needle shield in the regular garbage and keep the needle cover for later.	**Figure H** 

3 If new pen, test pen flow

Day 1

ATTENTION

Only test pen flow (steps A - C) the first time you use a new pen. See below for instructions on troubleshooting.

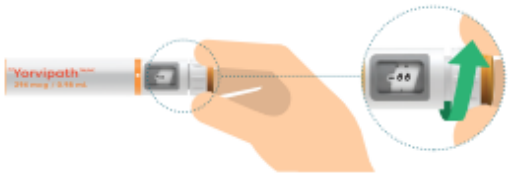
If your pen is already in use, go to section "3 Prepare injection and select dose"

Step A

Turn the dose selector clockwise (to the right) **2 clicks** until you see the droplet symbol "💧" in the dose window (figure I).

Note: You can always correct the selection by turning the dose selector.

Figure I



Step B

Make any air bubbles rise to the top of the pen by tapping the inspection window (figure J). Keep the pen with the needle tip pointed up.

Note: Tiny air bubbles are ok.

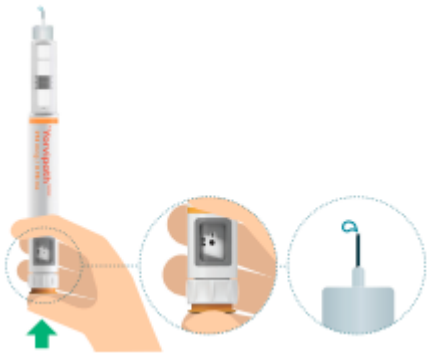
Figure J

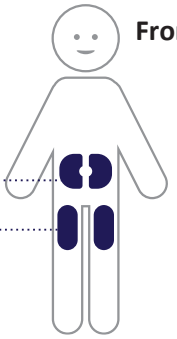
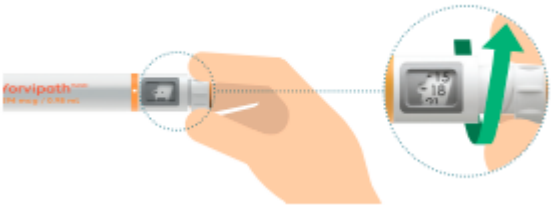
Step C

Press the push button and watch drops of medicine come out of the needle tip. When you press, make sure that the dose selector rotates back to the symbol "●" (figure K).

Important: If you do not see drops of medicine, repeat this test (steps A - C) up to **5 times**. If drops are still not seen, change the needle and repeat the test.

Figure K



4 Prepare injection and select dose	
Step 6 Choose injection site. There are **two** regions of your body you can inject into (figure L). Avoid injecting where skin is red, swollen or scarred. Choose a different injection site each time you inject.	**Figure L** **Belly (abdomen)** at least 5 centimetres away from the belly button **Front of the thighs** 
Step 7 Clean the injection site with an alcohol wipe (figure M).	**Figure M** 
Step 8 Select your dose as prescribed by your doctor (**15, 18 or 21 mcg**) by turning the dose selector clockwise (to the right) (figure N). **Important:** Make sure not to press the push button while selecting your dose to not spill medicine. **Note:** Always throw away your pen and use another pen if you cannot dial a full dose.	**Figure N** 

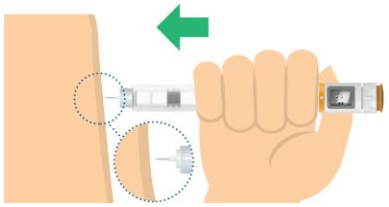
5 Inject dose

ATTENTION **Use the injection technique recommended by your doctor or nurse. Read this whole section (steps 9 - 11) before you start to inject.**

Step 9

Make sure you can see the dose window. To insert the needle into the skin (figure O), press the pen against injection site in a straight movement.

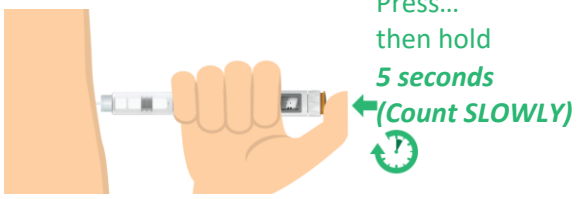
Figure O



Step 10

Press the push button all the way in and hold steady for **5 seconds (COUNT TO 5 S-L-O-W-L-Y)**.
Make sure the dose selector rotates back to the symbol "●". This means that you have given the full dose (figure P).

Figure P



Step 11

Slowly remove the pen from the injection site in a straight angle (figure Q).

Figure Q

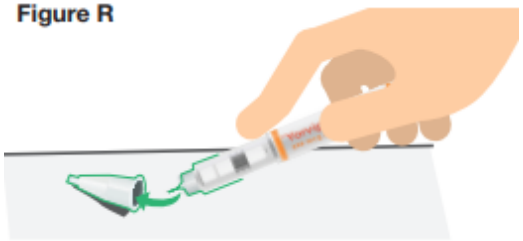
6 Throw away used needle

Step 12

Reattach the needle cover to carefully remove the needle. Lead the needle tip into the needle cover and secure the needle cover onto the needle (figure R).

Important: Always reattach the needle cover before removing the needle to reduce the risk of needle stick and cross-contamination.

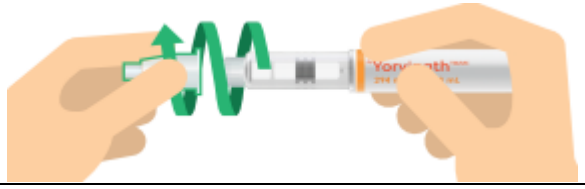
Figure R



Step 13

Unscrew the needle. Safely throw away the needle according to local regulations (figure S).

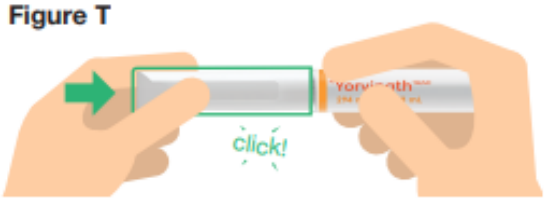
Figure S



Step 14

Click the pen cap firmly onto the pen to protect it between injections and to protect the medicine from light (figure T).

Figure T



7 Throw away used pen

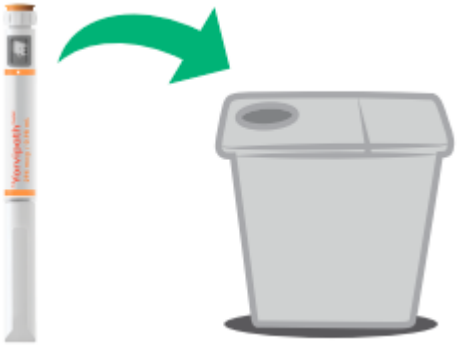
Day **14**

Important: Always throw away your pen after **14 days of use**, even if it still has medicine inside (figure U). This is important to make sure that you get the full effect of your medicine

It is recommended to fill out the 'Open date:' field on the carton, in order to know when 14 days has passed.

Note: Remember to throw away the extra needle when you throw away your pen.

Figure U



Troubleshooting

1. How often must I test the pen flow?

You should only test the pen flow (section 2) the first time you use a new pen (or if you think it might be damaged) to not waste medicine. The test checks to make sure the medicine flows through the pen so that you get the right doses of medicine.

2. I do not see drops appear after I have tested the pen flow 5 times. What should I do?

If you see no drop on the needle tip after **5 attempts**, it might be because there is no flow through the pen and needle.
Change the needle (see section 5, step 12) and test the pen flow again (see section 2, steps A - C).
You can be sure the flow works correctly when you see the drop of medicine.
If it still does not work discard the pen and contact your health care provider.

3. How do I know I have completed the injection?

Your injection is only completed after you have pressed the push button all the way in and the dose selector has rotated back to the "●" and you have kept the needle in the skin for **5 seconds (COUNT TO FIVE slowly)**.

4. Why do I have to keep holding the pen in the skin for 5 seconds?

Some medicine might flow back into the pen or flow backward from the injection site and be left on the skin. Holding the pen in the skin for **5 seconds** helps to make sure that all the medicine has been injected.

5. I cannot dial the dose selector to the required dose. What should I do?

The pen does not allow a larger dose to be set than what is left in the pen.
If your dose is larger than the amount of medicine left in the pen you will not be able to dial a full dose. You must throw away your pen and take the full dose of medicine with a new pen.

INSTRUCTIONS FOR USE

PrYorvipath™

palopegteriparatide injection

420 mcg / 1.4 mL

For **24, 27 or 30 mcg doses** only

Solution for injection in pre-filled pen

For subcutaneous use

These instructions for use contain information on how to inject Yorvipath

Additional information
If you do not understand or are unable to complete a step that is described in these instructions for use, contact your doctor or nurse.

Important information you need to know before using your Yorvipath pen

Read and follow the package leaflet and these instructions for use carefully so that you inject Yorvipath the right way.

Make sure you have received training from your doctor or nurse before injecting. This is important to make sure that you get the correct treatment.

For correct use

- By failing to follow these instructions, you may not get the right dose, and may therefore not get the full effect of your medicine.
- If you are blind or visually impaired or if you have lack of concentration, **do not** use your pen without help. Instead get help from a person who is trained to use the Yorvipath pen.
- Keep out of the sight and reach of children.
- The pen and needles are for single-patient use only.
- **Do not** share your pen or needles with other people. It might lead to infection (cross-contamination).
- Always throw away your pen **after 14 days of use**, even if it still has medicine left inside. This is important to make sure that you get the right effect of your medicine.
- Always use the needles that come with the Yorvipath pen for your injections.
- Remove the needle after every use. **Do not** store the pen with the needle on.
- Avoid bending or breaking off the pen needle.
- **Do not** change the injection angle after the needle has been inserted into the skin. Changing the angle can cause the needle to bend or break off. A bent or broken needle can remain

stuck in the body or remain completely under the skin. If a broken needle remains stuck in the body or remains under the skin, seek medical help right away.

- **Do not** use needles if the needle cover or needle foil are damaged.

Special instructions for doses larger than 30 mcg/day

If your dose is above 30 mcg/day:

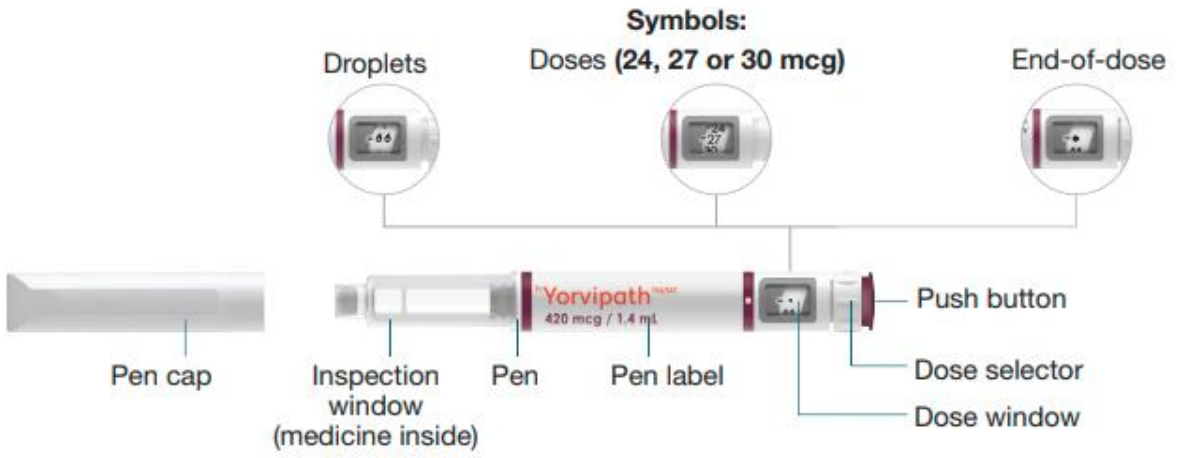
- Administer two injections, one after the other, in separate injection sites (see table with recommended scheme in section 3 of Package leaflet).
- It is recommended to use a different Yorvipath pen for the second daily injection, even if the two pens have the same-coloured push button (same strength).
- Follow the steps in the instructions for use for each injection.

Caring for your pen

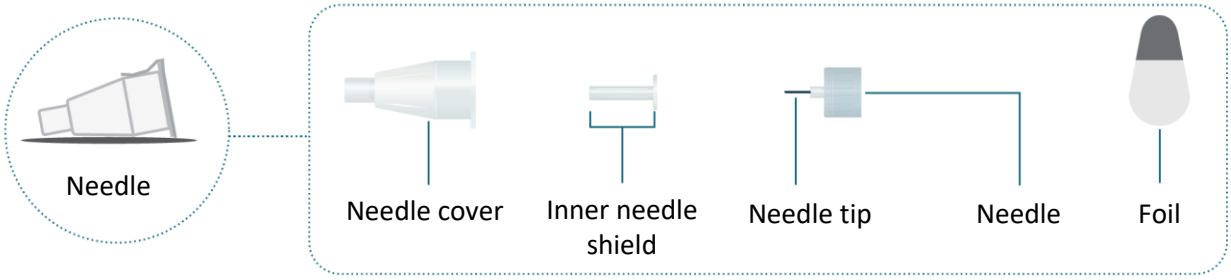
- Handle your pen with care.
- Keep your pen dry.
- Use a moist cloth to clean your pen.
- **Do not** drop or knock your pen against hard surfaces. If you do, test the pen flow again (section 2, steps A - C) before next use.
- **Do not** apply extra force to your pen. It might be empty, damaged and no longer work properly.
- **Do not** attempt to repair a damaged pen yourself.
- Never use a damaged pen.

Parts overview

Figure A
Parts of the Yorvipath multi-use prefilled pen



Pen needle parts (needles are included in the inner carton)



You will also need

Figure B

Sharps disposal container

Alcohol wipe

1 Prepare your supplies for the injection

Before you start:

Step 1

- Find a well-lit, flat work surface, like a table.
- When you open the Yorvipath outer carton, you will find two inner cartons inside. Take out one inner carton from the refrigerator prior to first use and unpack the pen-injector. Leave second inner carton in the refrigerator until first use.
- You should take your pen out of the refrigerator **20 minutes** before first use.
- Gather your supplies (see Figures A and B):
  - Yorvipath Pen
  - Needle (included in the carton)
  - Sharps disposal container
  - Alcohol wipe

Step 2
Wash your hands well with soap and water (figure C).

Figure C

2 Prepare pen and needle

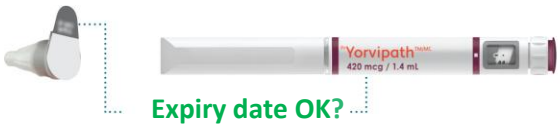
Step 1

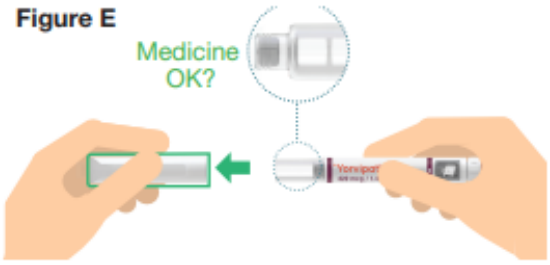
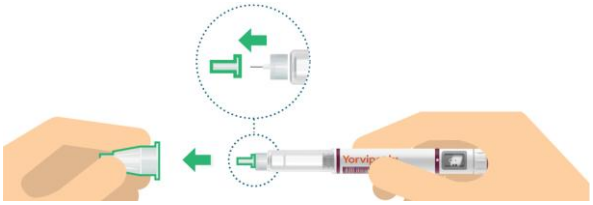
Take your Yorvipath pen out from the inner carton. Make sure it is the correct strength and check the **expiry date**.

Take a needle and check the **expiry date** on the needle (figure D).

Important: If the medicine is expired, **do not** use the pen. Use a new pen.

Figure D



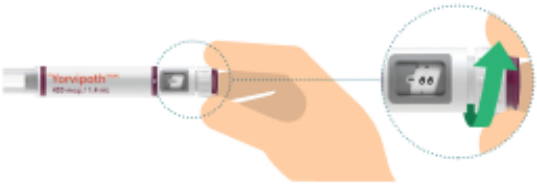
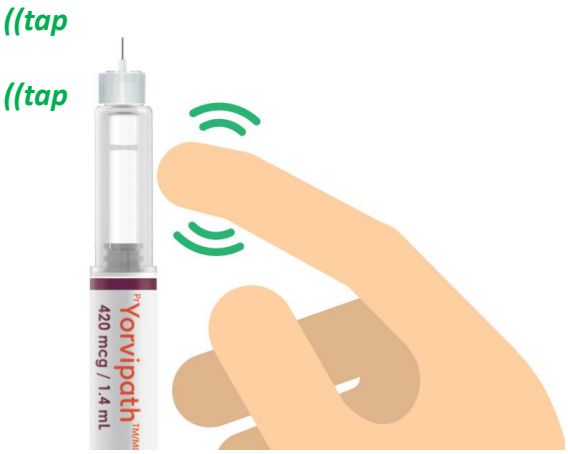
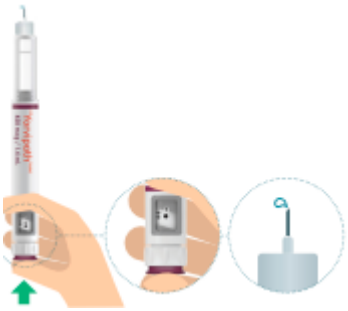
Step 2 Pull off the pen cap and check the inspection window to make sure the medicine inside the pen is clear and colourless (figure E). **Important:** If the medicine has visible particles in it **do not** use the pen. Use a new pen.	**Figure E** 
Step 3 Pull the foil off the needle (figure F). This needle can only be used **1 time**. Always use a new needle for each injection. **Important:** Make sure to only use the needles that come with the Yorvipath pen for your injections.	**Figure F** 
Step 4 Attach the needle **straight** onto your pen, then screw the needle onto the pen until secure (clockwise) (figure G).	**Figure G** 
Step 5 Pull off the needle cover and the inner needle shield (figure H). Throw away the inner needle shield (in the regular garbage) and keep the needle cover for later.	**Figure H** 

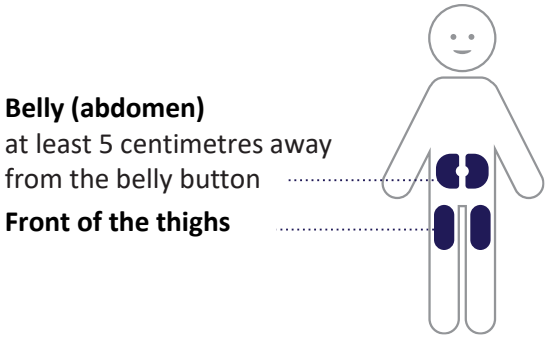
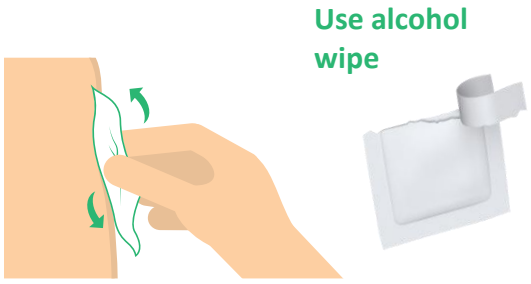
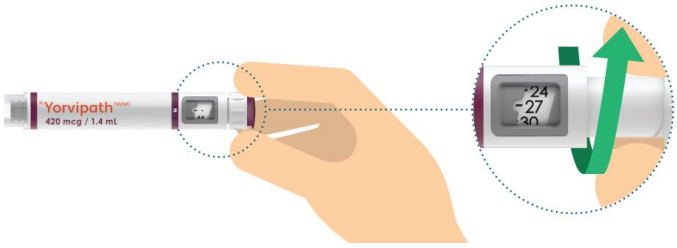
3 If new pen, test pen flow

Day 1

ATTENTION

Only test pen flow (steps A - C) the first time you use a new pen. See below for instructions on troubleshooting.
If your pen is already in use, go to section "3 Prepare injection and select dose".

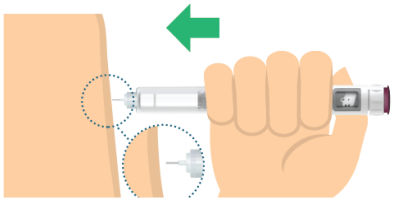
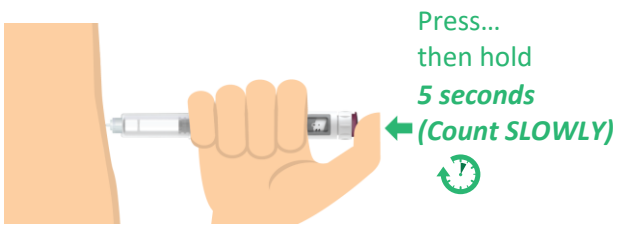
Step A Turn the dose selector clockwise (to the right) **2 clicks** until you see the droplet symbol "💧💧" in the dose window (figure I). **Note:** You can always correct the selection by turning the dose selector.	**Figure I** 
Step B Make any air bubbles rise to the top of the pen by tapping the inspection window (figure J). Keep the pen with the needle tip pointed up. **Note:** Tiny air bubbles are ok.	**Figure J** 
Step C Press the push button and watch drops of medicine come out of the needle tip. When you press, make sure that the dose selector rotates back to the symbol "●" (figure K). **Important:** If you do not see drops of medicine, repeat this test (steps A - C) up to **5 times**. If drops are still not seen, change the needle and repeat the test.	**Figure K** 

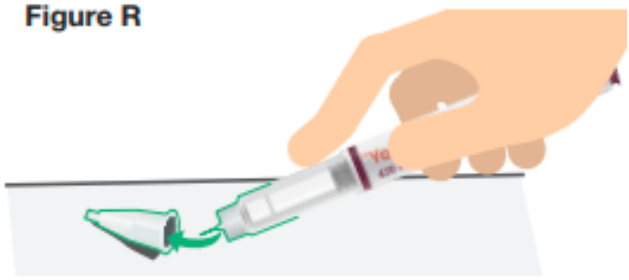
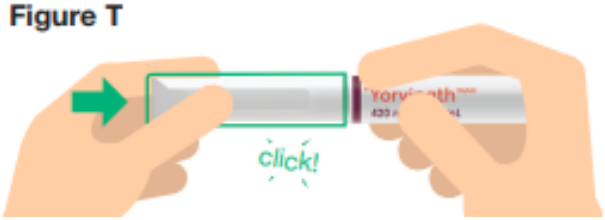
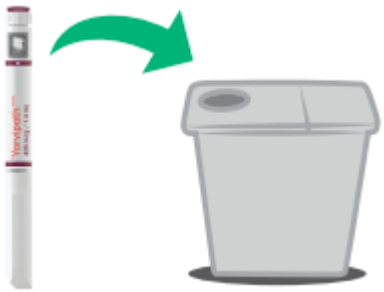
4 Prepare injection and select dose	
Step 6 Choose injection site. There are **two** regions of your body you can inject into (figure L). Avoid injecting where skin is red, swollen or scarred. Choose a different injection site each time you inject.	**Figure L** 
Step 7 Clean the injection site with an alcohol wipe (figure M).	**Figure M** 
Step 8 Select your dose as prescribed by your doctor **(24, 27 or 30 mcg)** by turning the dose selector clockwise (to the right) (figure N). **Important:** Make sure not to press the push button while selecting your dose to not spill medicine. **Note:** Always throw away your pen and use another pen if you cannot dial a full dose.	**Figure N** 

5 Inject dose

ATTENTION

Use the injection technique recommended by your doctor or nurse. Read this whole section (steps 9 - 11) before you start to inject.

Step 9 Make sure you can see the dose window. To insert the needle into the skin (figure O), press the pen against injection site in a straight movement.	**Figure O** 
Step 10 Press the push button all the way in and hold steady for **5 seconds (COUNT TO 5 S-L-O-W-L-Y)**. Make sure the dose selector rotates back to the symbol "●". This means that you have given the full dose (figure P).	**Figure P** 
Step 11 Slowly remove the pen from the injection site in a straight angle (figure Q).	**Figure Q** 

6 Throw away used needle	
Step 12 Reattach the needle cover to carefully remove the needle. Lead the needle tip into the needle cover and secure the needle cover onto the needle (figure R). **Important**: Always reattach the needle cover before removing the needle to reduce the risk of needle stick and cross-contamination.	**Figure R** 
Step 13 Unscrew the needle. Safely throw away the needle according to local regulations (figure S).	**Figure S** 
Step 14 Click the pen cap firmly onto the pen to protect it between injections and to protect the medicine from light (figure T).	**Figure T** 
7 Throw away used pen	
Important: Always throw away your pen after **14 days of use**, even if it still has medicine inside (figure U). This is important to make sure that you get the full effect of your medicine. It is recommended to fill out the 'Open date:' field on the carton, in order to know when 14 days has passed. **Note:** Remember to throw away the extra needle when you throw away your pen.	**Figure U** 

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Date of revision: January 28, 2026