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ASCENDIS SIGNATURE ACCESS PROGRAM®

Letter of Medical Necessity Guide

Conventional therapy

This sample letter shows what information and supplemental documentation you may include when submitting a Letter of Medical Necessity for YORVIPATH® (palopegteriparatide).

Important Safety Information

INDICATION AND LIMITATIONS OF USE

YORVIPATH (palopegteriparatide) is indicated for the treatment of hypoparathyroidism in adults.

- YORVIPATH was not studied for acute post-surgical hypoparathyroidism.
- YORVIPATH's titration scheme was only evaluated in adults who first achieved an albumin-corrected serum calcium of at least 7.8 mg/dL using calcium and active vitamin D treatment.

CONTRAINDICATIONS

YORVIPATH is contraindicated in patients with severe hypersensitivity to palopegteriparatide or to any of its excipients. Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been observed with parathyroid hormone (PTH) analogs.

WARNINGS AND PRECAUTIONS

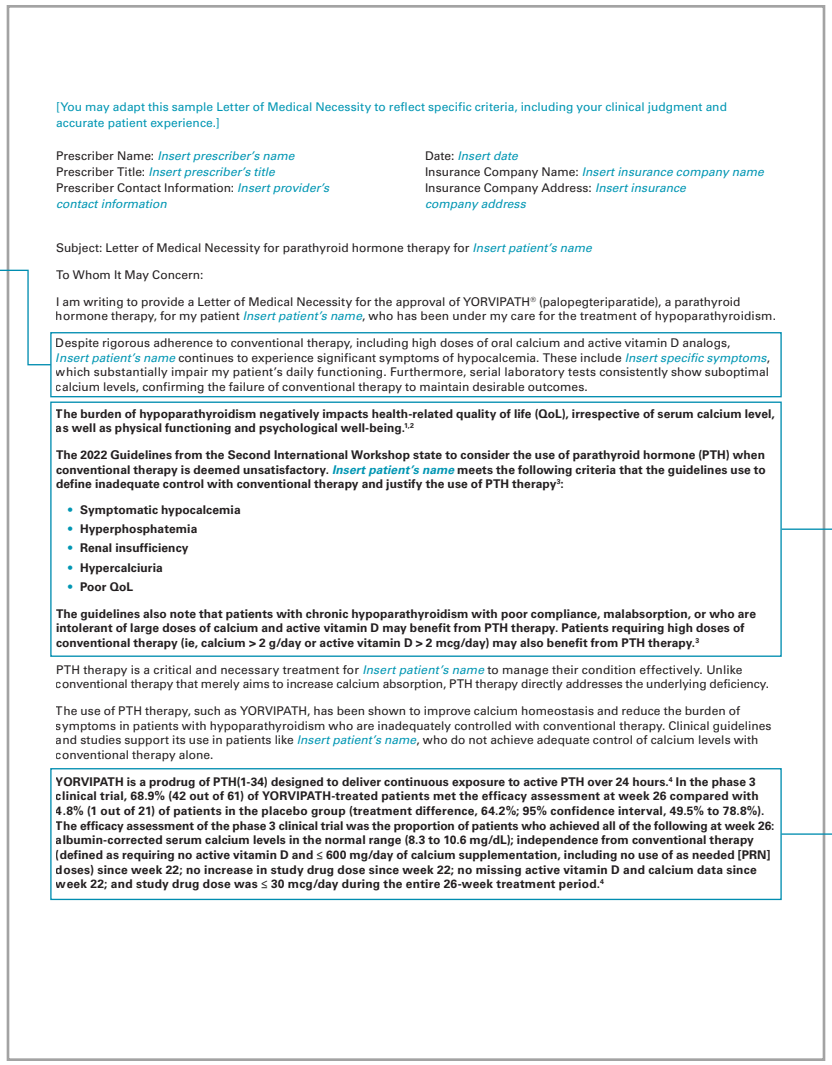
Risk of Unintended Changes in Serum Calcium Levels Related to Number of Daily Injections

Use only one YORVIPATH injection to achieve the recommended once daily dosage. Using two YORVIPATH injections to achieve the recommended once daily dosage increases the variability of the total delivered dose, which can cause unintended changes in serum calcium levels, including hypercalcemia and hypocalcemia.

Serious Hypercalcemia

Serious events of hypercalcemia requiring hospitalization have been reported with YORVIPATH. The risk is highest when starting or increasing the dose of YORVIPATH but may occur at any time. Measure serum calcium 7 to 10 days after any dose change or if there are signs or symptoms of hypercalcemia, and at a minimum of every 4 to 6 weeks once the maintenance dose is achieved. Treat hypercalcemia if needed. If albumin-corrected serum calcium is greater than 12 mg/dL, withhold YORVIPATH for at least 2-3 days. For less serious hypercalcemia, adjust the dose of YORVIPATH, active vitamin D, and/or calcium supplements.

Please see Important Safety Information throughout and accompanying full Prescribing Information for YORVIPATH.



[You may adapt this sample Letter of Medical Necessity to reflect specific criteria, including your clinical judgment and accurate patient experience.]

Prescriber Name: *Insert prescriber's name*
Prescriber Title: *Insert prescriber's title*
Prescriber Contact Information: *Insert provider's contact information*

Date: *Insert date*
Insurance Company Name: *Insert insurance company name*
Insurance Company Address: *Insert insurance company address*

Subject: Letter of Medical Necessity for parathyroid hormone therapy for *Insert patient's name*

To Whom It May Concern:

I am writing to provide a Letter of Medical Necessity for the approval of YORVIPATH® (palopegteriparatide), a parathyroid hormone therapy, for my patient *Insert patient's name*, who has been under my care for the treatment of hypoparathyroidism.

Despite rigorous adherence to conventional therapy, including high doses of oral calcium and active vitamin D analogs, *Insert patient's name* continues to experience significant symptoms of hypocalcemia. These include *Insert specific symptoms*, which substantially impair my patient's daily functioning. Furthermore, serial laboratory tests consistently show suboptimal calcium levels, confirming the failure of conventional therapy to maintain desirable outcomes.

The burden of hypoparathyroidism negatively impacts health-related quality of life (QoL), irrespective of serum calcium level, as well as physical functioning and psychological well-being.[1,2]

The 2022 Guidelines from the Second International Workshop state to consider the use of parathyroid hormone (PTH) when conventional therapy is deemed unsatisfactory. *Insert patient's name* meets the following criteria that the guidelines use to define inadequate control with conventional therapy and justify the use of PTH therapy[3]:

- **Symptomatic hypocalcemia**
- **Hyperphosphatemia**
- **Renal insufficiency**
- **Hypercalciuria**
- **Poor QoL**

The guidelines also note that patients with chronic hypoparathyroidism with poor compliance, malabsorption, or who are intolerant of large doses of calcium and active vitamin D may benefit from PTH therapy. Patients requiring high doses of conventional therapy (ie, calcium > 2 g/day or active vitamin D > 2 mcg/day) may also benefit from PTH therapy.[3]

PTH therapy is a critical and necessary treatment for *Insert patient's name* to manage their condition effectively. Unlike conventional therapy that merely aims to increase calcium absorption, PTH therapy directly addresses the underlying deficiency.

The use of PTH therapy, such as YORVIPATH, has been shown to improve calcium homeostasis and reduce the burden of symptoms in patients with hypoparathyroidism who are inadequately controlled with conventional therapy. Clinical guidelines and studies support its use in patients like *Insert patient's name*, who do not achieve adequate control of calcium levels with conventional therapy alone.

YORVIPATH is a prodrug of PTH(1-34) designed to deliver continuous exposure to active PTH over 24 hours.[4] In the phase 3 clinical trial, 68.9% (42 out of 61) of YORVIPATH-treated patients met the efficacy assessment at week 26 compared with 4.8% (1 out of 21) of patients in the placebo group (treatment difference, 64.2%; 95% confidence interval, 49.5% to 78.8%). The efficacy assessment of the phase 3 clinical trial was the proportion of patients who achieved all of the following at week 26: albumin-corrected serum calcium levels in the normal range (8.3 to 10.6 mg/dL); independence from conventional therapy (defined as requiring no active vitamin D and ≤ 600 mg/day of calcium supplementation, including no use of as needed [PRN] doses) since week 22; no increase in study drug dose since week 22; no missing active vitamin D and calcium data since week 22; and study drug dose was ≤ 30 mcg/day during the entire 26-week treatment period.[4]

A

Current conventional therapy

This is where you can include information regarding your patient's experience with their current conventional therapy. List specific symptoms that your patient is continuing to observe with conventional therapy, such as muscle cramps, tingling, fatigue, cognitive disturbances, and/or seizures.

B

Literature evidence

You may include any evidence from published literature to support your clinical argument, including guideline recommendations for treating hypoparathyroidism.

C

Support for YORVIPATH®

This is a space where you may provide rationale and support for why you think YORVIPATH is the right treatment for your patient. It is important to highlight your patient's clinical needs and how YORVIPATH may help.

Important Safety Information

WARNINGS AND PRECAUTIONS (cont'd)

Serious Hypocalcemia

Serious events of hypocalcemia have been observed with PTH products, including YORVIPATH. The risk is highest when YORVIPATH is abruptly discontinued, but may occur at any time, even in patients who have been on stable doses of YORVIPATH. Measure serum calcium 7 to 10 days after any dose change or if there are signs or symptoms of hypocalcemia, and at a minimum of every 4 to 6 weeks once the maintenance dosage is achieved. Treat hypocalcemia if needed, and adjust the dose of YORVIPATH, active vitamin D, and/or calcium supplements if hypocalcemia occurs.

Potential Risk of Osteosarcoma

YORVIPATH is a PTH analog. An increased incidence of osteosarcoma (a malignant bone tumor) has been reported in male and female rats treated with 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.

Considering the above, it is medically necessary for *Insert patient's name* to receive YORVIPATH® to manage their hypoparathyroidism effectively. This treatment may prevent potential complications associated with chronic hypocalcemia.

Thank you for your attention to this matter and your consideration of this request for the approval of PTH therapy for *Insert patient's name*.

Sincerely,

Insert your name
Insert your title
Insert your medical institution or practice name
Insert your contact information

Attachments:
1. Patient medical records
2. Recent laboratory results
3. Relevant clinical guidelines and supporting literature

Please see the diagnosis criteria and attached clinicals:

ICD-10 code: ***YORVIPATH is indicated for [E20.9, E89.2]***
PTH level: ***Result; Date***
24-hour urine calcium: ***Result; Date***
Serum calcium level: ***Result; Date***
Serum 25(OH) vitamin D: ***Result; Date***
Daily calcium supplement dose: ***mg elemental calcium/day***
Daily active vitamin D (calcitriol) dose: ***mcg/day; Date***
Date of surgery: ***Date***

Clinical risks persisting under current conventional therapy:

- **Renal complications**
  - Patients with chronic hypoparathyroidism who receive long-term treatment with conventional therapy (oral calcium and active vitamin D) have an increased risk of renal complications compared to the general population[5-7]
  - Up to 41% (44 out of 107) of patients with chronic hypoparathyroidism treated with conventional therapy have reported chronic kidney disease (CKD), and 36% (92 out of 259) have reported nephrolithiasis[5-7]
- **Skeletal**
  - Hypoparathyroidism is associated with reduced bone turnover and high bone mineral density[8,9]
- **Cardiovascular**
  - Longer duration of hypoparathyroidism, lower time-weighted serum ionized calcium, and the occurrence of 4 or more hypercalcemic episodes all significantly increased the risk of developing cardiovascular disease in a case-control study of 431 patients with hypoparathyroidism treated with conventional therapy[10]
- **Neuropsychiatric**
  - In interviews conducted during the development of the Hypoparathyroidism Patient Experience Scale (HPES), a majority of patients reported reduced functioning and well-being despite treatment with conventional therapy, including having anxiety (81% or 34 out of 42), feeling sad or depressed (62% or 26 out of 42), and feeling irritable or short-tempered (43% or 18 out of 42).[2] The HPES was developed through interviews of 5 clinical experts and 42 adult participants with hypoparathyroidism to evaluate the symptoms (physical and cognitive) and impact (characterized as physical functioning, psychological well-being, daily life, and social life and relationships) associated with hypoparathyroidism[2,11]

References: 1. Kontogeorgos G, Mamasoula Z, Krantz E, Trimpou P, Landin-Wilhelmsen K, Laine CM. Low health-related quality of life in hypoparathyroidism and need for PTH analog. *Endocr Connect.* 2022;11(1):e210379. doi:10.1530/EC-21-0379 **2.** Brod M, Waldman LT, Smith A, Karpf D. Living with hypoparathyroidism: development of the Hypoparathyroidism Patient Experience Scale-Impact (HPES-Impact). *Qual Life Res.* 2021;30(1):277-291. doi:10.1007/s11136-020-02607-1 **3.** Khan AA, Bilezikian JP, Brandi ML, et al. Evaluation and management of hypoparathyroidism summary statement and guidelines from the Second International Workshop. *J Bone Miner Res.* 2022;37(12):2568-2585. doi:10.1002/jbmr.4691 **4.** Yorvipath. Prescribing information. Ascendis Pharma, Inc.; 2024. **5.** Gosmanova EO, Houillier P, Rejnmark L, Marelli C, Bilezikian JP. Renal complications in patients with chronic hypoparathyroidism on conventional therapy: a systematic literature review: renal disease in chronic hypoparathyroidism. *Rev Endocr Metab Disord.* 2021;22(2):297-316. doi:10.1007/s11154-020-09613-1 **6.** Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab.* 2012;97(12):4507-4514. doi:10.1210/jc.2012-1808 **7.** Hadker N, Egan J, Sanders J, Lagast H, Clarke B. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract.* 2014;20(7):671-679. doi:10.4158/EP13328.OR **8.** Shoback DM, Bilezikian JP, Costa AG, et al. Presentation of hypoparathyroidism: etiologies and clinical features. *J Clin Endocrinol Metab.* 2016;101(6):2300-2312. doi:10.1210/jc.2015-3909 **9.** Rubin MR, Dempster DW, Zhou H, et al. Dynamic and structural properties of the skeleton in hypoparathyroidism. *J Bone Miner Res.* 2008;23(12):2018-2024. doi:10.1359/JBMR.080803 **10.** Underbjerg L, Sikjaer T, Rejnmark L. Long-term complications in patients with hypoparathyroidism evaluated by biochemical findings: a case-control study. *J Bone Miner Res.* 2018;33(5):822-831. doi:10.1002/jbmr.3368 **11.** Brod M, Waldman LT, Smith A, Karpf D. Assessing the patient experience of hypoparathyroidism symptoms: development of the Hypoparathyroidism Patient Experience Scale-Symptom (HPES-Symptom). *Patient.* 2020;13(2):151-162. doi:10.1007/s40271-019-00388-5

D

Clinical findings

Ensure that you give a comprehensive profile for your patient. Any documentation should be attached to your submission. Submitting this letter without the attached clinical documentation may result in a delay or denial of your patient's insurance authorization.

E

Risks associated with conventional therapy

You may also include additional context regarding clinical risks for your patient that may persist.

Important Safety Information

WARNINGS AND PRECAUTIONS (cont'd)

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

- Open epiphyses. YORVIPATH is not approved in pediatric patients.
- Metabolic bone diseases other than hypoparathyroidism, including Paget's disease of bone.
- Unexplained elevations of alkaline phosphatase.
- Bone metastases or a history of skeletal malignancies.
- History of external beam or implant radiation therapy involving the skeleton.
- Hereditary disorders predisposing to osteosarcoma.

Instruct patients to promptly report clinical symptoms (e.g., persistent localized pain) and signs (e.g., soft tissue mass tender to palpation) that could be consistent with osteosarcoma.

Orthostatic 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.

Please see Important Safety Information throughout and accompanying full Prescribing Information for YORVIPATH.

Important Safety Information

WARNINGS AND PRECAUTIONS (cont'd)

Risk of Digoxin Toxicity with Concomitant Use of Digitalis Compounds

YORVIPATH increases serum calcium, and therefore, 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.

ADVERSE REACTIONS

The most common adverse reactions (≥ 5%) in patients treated with YORVIPATH were injection site reactions (39%), vasodilatory signs and symptoms (28%), headache (21%), diarrhea (10%), back pain (8%), hypercalcemia (8%) and oropharyngeal pain (7%).

DRUG INTERACTIONS

Drugs Affected by Serum Calcium

Digoxin: YORVIPATH increases serum calcium, therefore, 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, and monitor for signs and symptoms of digoxin toxicity. Adjustment of the digoxin and/or YORVIPATH dose may be needed.

Drugs Known to Affect Serum Calcium

Drugs that affect serum calcium may alter the therapeutic response to YORVIPATH. Measure serum calcium more frequently when YORVIPATH is used concomitantly with these drugs, particularly after these drugs are initiated, discontinued, or dose adjusted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Available data from reports of pregnancies in the clinical trials from drug development are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. If YORVIPATH is administered during pregnancy, or if a patient becomes pregnant while receiving YORVIPATH, healthcare providers should report YORVIPATH exposure by calling 1-844-442-7236.

Lactation

Monitor infants breastfed by females treated with YORVIPATH for symptoms of hypercalcemia or hypocalcemia. Consider monitoring serum calcium in the breastfed infant.

You are encouraged to report side effects to FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Ascendis Pharma at 1-844-442-7236.

Please see Important Safety Information throughout and accompanying full Prescribing Information for YORVIPATH.

References: 1. Kontogeorgos G, Mamasoula Z, Krantz E, Trimpou P, Landin-Wilhelmsen K, Laine CM. Low health-related quality of life in hypoparathyroidism and need for PTH analog. *Endocr Connect*. 2022;11(1):e210379. doi:10.1530/EC-21-0379 **2.** Brod M, Waldman LT, Smith A, Karpf D. Living with hypoparathyroidism: development of the Hypoparathyroidism Patient Experience Scale-Impact (HPES-Impact). *Qual Life Res*. 2021;30:277-291. doi:10.1007/s11136-020-02607-1 **3.** Khan AA, Bilezikian JP, Brandi ML, et al. Evaluation and management of hypoparathyroidism summary statement and guidelines from the Second International Workshop. *J Bone Miner Res*. 2022;37(12):2568-2585. doi:10.1002/jbmr.4691 **4.** Yorvipath. Prescribing information. Ascendis Pharma, Inc.; 2024. **5.** Gosmanova EO, Houillier P, Rejnmark L, Marelli C, Bilezikian JP. Renal complications in patients with chronic hypoparathyroidism on conventional therapy: a systematic literature review: renal disease in chronic hypoparathyroidism. *Rev Endocr Metab Disord*. 2021;22(2):297-316. doi:10.1007/s11154-020-09613-1 **6.** Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab*. 2012;97(12):4507-4514. doi:10.1210/jc.2012-1808 **7.** Hadker N, Egan J, Sanders J, Lagast H, Clarke B. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract*. 2014;20(7):671-679. doi:10.4158/EP13328.OR **8.** Shoback DM, Bilezikian JP, Costa AG, et al. Presentation of hypoparathyroidism: etiologies and clinical features. *J Clin Endocrinol Metab*. 2016;101(6):2300-2312. doi:10.1210/jc.2015-3909 **9.** Rubin MR, Dempster DW, Zhou H, et al. Dynamic and structural properties of the skeleton in hypoparathyroidism. *J Bone Miner Res*. 2008;23(12):2018-2024. doi:10.1359/JBMR.080803 **10.** Underbjerg L, Sikjaer T, Rejnmark L. Long-term complications in patients with hypoparathyroidism evaluated by biochemical findings: a case-control study. *J Bone Miner Res*. 2018;33(5):822-831. doi:10.1002/jbmr.3368 **11.** Brod M, Waldman LT, Smith A, Karpf D. Assessing the patient experience of hypoparathyroidism symptoms: development of the Hypoparathyroidism Patient Experience Scale-Symptom (HPES-Symptom). *Patient*. 2020;13(2):151-162. doi:10.1007/s40271-019-00388-5

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