swissmedic

Date: 12 February 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Yorvipath

International non-proprietary name:	palopegteriparatide
Pharmaceutical form:	solution for injection in pre-filled pen
Dosage strength(s):	168 µg/0.56 ml, 294 µg/0.98 ml, 420 µg/1.4 ml
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	Ascendis Pharma Switzerland GmbH
Marketing authorisation no.:	69889
Decision and decision date:	approved on 9 December 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PTH	Parathyroid hormone
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for palopegteriparatide in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 19 July 2024.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

Treatment of hypoparathyroidism in adults.
Palopegteriparatide has only been studied in patients who had hypoparathyroidism for at least 6 months, but not in acute (and potentially reversible) postoperative hypoparathyroidism.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended starting dose is 18 µg once daily with dose adjustments in 3 µg increments thereafter every 7 days. The dose range is 6 to 60 µg per day. The dose should be individualised based on serum calcium.

The applicant withdrew part of the dosage initially claimed for Yorvipath for the dose range of more than 30 up to 60 µg per day.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	5 September 2024
Preliminary decision to reject application of art. 13 TPA and formal objection	4 October 2024
Response to preliminary decision to reject application of art. 13 TPA and formal objection	11 November 2024
Formal control completed	22 November 2024
List of Questions (LoQ)	18 March 2025
Response to LoQ	15 May 2025
Preliminary decision	12 August 2025
Response to preliminary decision	16 September 2025
Labelling corrections and/or other aspects	6 November 2025
Response to labelling corrections and/or other aspects	12 November 2025
Final decision	9 December 2025
Decision	approval

Based on Art. 13 TPA Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the assessment report Yorvipath, Procedure No. EMEA/H/C/005934/0000 dated 14.09.2023 issued by the EMA (EMA/439682/2023).

3 Medical context

Hypoparathyroidism is a condition characterised by an underfunction of the parathyroid glands with reduced secretion of parathyroid hormone (PTH). The most common cause of hypoparathyroidism is iatrogenic, typically due to accidental removal of the parathyroid glands during a thyroidectomy. Less commonly, this occurs during partial thyroid resections performed to treat benign thyroid diseases. In cases of malignancy, however, the removal of the parathyroid glands may even be necessary.

Less common causes of hypoparathyroidism include autoimmune diseases (affecting various glands) or radiation therapy in the neck region. Hypoparathyroidism also occurs in cases of DiGeorge syndrome, a congenital immunodeficiency associated with aplasia or hypoplasia of the thymus. Infiltrative diseases such as haemochromatosis or thalassaemia can also lead to hypoparathyroidism.

Chronic hypoparathyroidism is diagnosed when the associated changes persist for more than six months following the causative surgical intervention.

The lack of PTH secretion results in hypocalcaemia, which leads to corresponding symptoms (e.g. paraesthesia, tetany, alopecia, dry and brittle skin, or cataract formation) and associated risks. The symptoms and complications of hypoparathyroidism affect various organ systems and also impair quality of life. A typical sign of tetany is carpopedal spasm (characteristic paw hand posture). Life-threatening manifestations such as laryngospasm, bronchospasm, seizures, or arrhythmias are also possible.

Long-term risks include increased susceptibility to infections, heart failure, kidney failure, skeletal changes, and ectopic calcifications, e.g. in the lenses of the eyes or the basal ganglia.

While hypocalcaemia would normally trigger a reactive increase in PTH levels, in the case of hypoparathyroidism, PTH concentrations are significantly reduced. In addition, hyperphosphataemia may be present.

PTH deficiency impairs the intestinal absorption of both calcium and phosphate. In the kidneys, calcium reabsorption is inhibited, while phosphate excretion is increased. Additionally, PTH deficiency reduces bone turnover. A long-term risk of hypoparathyroidism is osteopenia. Furthermore, chronic hypercalciuria is associated with an increased risk of nephrolithiasis.

The prevalence of hypoparathyroidism in the EU is estimated at 3.2 cases per 10,000 inhabitants (95% CI 2.7–4.2). Postoperative hypoparathyroidism is more common, with 2.1 cases per 10,000 inhabitants, compared to non-surgical hypoparathyroidism, which occurs in only 1.2 cases per 10,000.

Until now, the only treatment for hypoparathyroidism available in Switzerland has been vitamin D preparations in combination with calcium supplements. The preferred vitamin D analogue is calcitriol, as this therapy is easier to manage compared to cholecalciferol. Calcium is administered orally for chronic treatment, while intravenous administration is used in acute cases (e.g. during tetany). In some cases, magnesium is also supplemented. Treatment with calcium and vitamin D requires regular monitoring of calcium levels in the serum and urine, as well as serum phosphate levels. High doses of calcium carry the risk of hypercalciuria.

While conventional therapy can effectively manage acute symptoms, it remains a compromise overall, as hypercalciuria increases the risk of long-term complications such as nephrolithiasis, nephrocalcinosis, and kidney failure. Furthermore, conventional therapy increases calcium levels but does not lower phosphate levels. As a result, the calcium-phosphate product in the serum increases, promoting ectopic calcifications.

4 Quality aspects

Swissmedic has only assessed parts of the primary data relating to quality aspects submitted with this application and principally relies on the assessment of the foreign reference authority: EMA. The SwissPAR relating to quality aspects refers to the publicly available CHMP assessment report Yorvipath, Procedure No. EMEA/H/C/005934/0000 dated 14.09.2023 issued by the EMA (EMA/439682/2023).

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority: EMA. The nonclinical aspects in this SwissPAR refer to the publicly available CHMP assessment report Yorvipath, Procedure No. EMEA/H/C/005934/0000 dated 14.09.2023 issued by the EMA (EMA/439682/2023)

6 Clinical aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA.
The available assessment report and respective product information from the EMA were used as a basis for the clinical and clinical pharmacology evaluation.

The clinical evaluation focused on the following aspect:

Dose Recommendation:

Due to concerns related to potential overdosing, the recommended maximum daily dose has been set at 30µg.
This is in congruence with the respective recommendation issued by the FDA on this product.

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see the appendix of this report.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Yorvipath was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Yorvipath

Composition

Active substances

Palopegteriparatide (PTH (1-34) transiently conjugated to a methoxypolyethylene glycol(mPEG) carrier via a linker).

Excipients

Succinic acid, mannitol, metacresol, sodium hydroxide (equivalent to 7.475 mg/mL sodium), hydrochloric acid (to adjust the pH value), water for injections.

Pharmaceutical form and active substance quantity per unit

Solution for injection in a prefilled pen equivalent to palopegteriparatide 0.3 mg/mL PTH (1-34), subcutaneous (SC)

Yorvipath 168 micrograms/0.56 mL, solution for injection in a prefilled pen:

Each prefilled pen contains 1935 µg palopegteriparatide corresponding to 168 µg PTH (1-34) in 0.56 mL solvent*.

The prefilled pen can dispense doses of 6, 9 or 12 µg.

Yorvipath 294 micrograms/0.98 mL, solution for injection in a prefilled pen:

Each prefilled pen contains 3387 µg palopegteriparatide corresponding to 294 µg PTH (1-34) in 0.98 mL solvent*.

The prefilled pen can dispense doses of 15, 18 or 21 µg.

Yorvipath 420 micrograms/1.4 mL, solution for injection in a prefilled pen:

Each prefilled pen contains 4838 µg palopegteriparatide corresponding to 420 µg PTH (1-34) in 1.4 mL solvent*.

The prefilled pen can dispense doses of 24, 27 or 30 µg.

* The reported strength refers to the amount of PTH (1-34) without taking into account the mPEG carrier.

Indications/Uses

Treatment of hypoparathyroidism in adults.

Palopegteriparatide has only been studied in patients who had hypoparathyroidism for at least 6 months, but not in acute (and potentially reversible) postoperative hypoparathyroidism.

Dosage/Administration

Treatment should be initiated and monitored by physicians with qualifications and experience in the diagnosis and treatment of patients with hypoparathyroidism.

The dosage recommendations for Yorvipath refer to µg PTH (1-34). The dose must be determined individually for each patient on the basis of the serum calcium level. The optimal dose after titration is the minimum dose required for the prophylaxis of hypocalcemia. This is the dose at which serum calcium levels remain within the normal range without the need for active forms of vitamin D or calcium supplements in excess of the recommended supplementation for the general population (generally less than 600 mg of calcium per day). The doses of active forms of vitamin D and calcium supplements must be adjusted before and during treatment with Yorvipath based on serum calcium levels (see below).

In patients in whom hypocalcemia persists even at the maximum dose of 30 µg Yorvipath per day, concomitant administration of therapeutic doses of calcium and/or active forms of vitamin D may be necessary.

Before initiation of treatment

Serum 25(OH)-vitamin D should be within the normal range and serum calcium stable at or slightly below the normal range (1.95–2.64 mmol/L [7.8–10.6 mg/dL]) in at least 1 measurement within two weeks before the first dose of palopegteriparatide.

Initiation of treatment

The recommended starting dose is 18 µg once daily. The dose is then adjusted in steps of 3 µg every 7 days in a dose range of 6 to 30 µg per day (see Figure 1).

At the start of treatment with Yorvipath (i.e. from the day of the first dose), the previously used dosage of active vitamin D or calcium supplements must be adjusted as indicated in Table 1:

Table 1: Dose adjustment of active vitamin D and calcium

Albumin-corrected serum calcium concentration[a]	**Previous calcitriol dose**	**Adjusting the calcitriol dose**	**Adjustment of the calcium dose S**[b]
≥ 2.07 mmol/L (≥ 8.3 mg/dL)	> 1 µg/day	Reduction of the calcitriol dose by ≥ 50%	Maintaining the previous calcium dose

≥ 2.07 mmol/L (≥ 8.3 mg/dL)	≤ 1 µg/day	Discontinuation of calcitriol	Maintaining the previous calcium dose
≥ 1.95 to < 2.07 mmol/L (≥ 7.8 to < 8.3 mg/dL)	each dose	Reduction of the calcitriol dose by ≥ 50%	Maintaining the previous calcium dose
≥ 1.95 mmol/L (≥ 7.8 mg/dL)	no use of active vitamin D	not applicable	Reduction of the daily calcium dose by at least 1500 mg; if previous calcium dose ≤ 1500 mg: discontinue calcium supplements completely[c]

[a] Albumin-corrected serum calcium concentration

[b] All dosing information refers to elemental calcium.

[c] If supplementation is indicated to meet the recommendations for daily dietary calcium intake, continuing calcium supplementation at doses of ≤ 600 mg per day may be considered instead of discontinuing calcium altogether.

Dose titration and maintenance therapy for serum calcium concentrations < 12 mg/dL

The serum calcium concentration must be monitored during titration (see “Warnings and precautions”).

The Yorvipath dose can be titrated in 3 µg increments at intervals of at least 7 days (see Figure 1). The dose must not be increased more often than every 7 days. In case of hypercalcemia, the dose of Yorvipath must not be reduced more frequently than every 3 days in steps of 3 µg (see Figure 1).

Serum calcium must be determined 7 days after the first dose. The appropriate dosage of Yorvipath, active vitamin D and calcium supplements should then be determined according to Figure 1.

After any subsequent change in the dose of Yorvipath, active vitamin D or calcium supplements, the patient should be monitored for clinical symptoms of hypocalcemia or hypercalcemia. Serum calcium should also be determined within 7–14 days after the dose adjustment. If necessary, the dose of Yorvipath, active vitamin D and/or calcium supplements must be adjusted again according to Figure 1. Changes to the dose of Yorvipath, active vitamin D or calcium supplements must be made on the same day.

The maintenance dose should be defined as the dose below which the serum calcium remains within the normal range without the need for additional active forms of vitamin D or therapeutic doses of calcium. Calcium supplements in sufficient doses to meet nutritional requirements (≤ 600 mg per day) may be continued (optional).

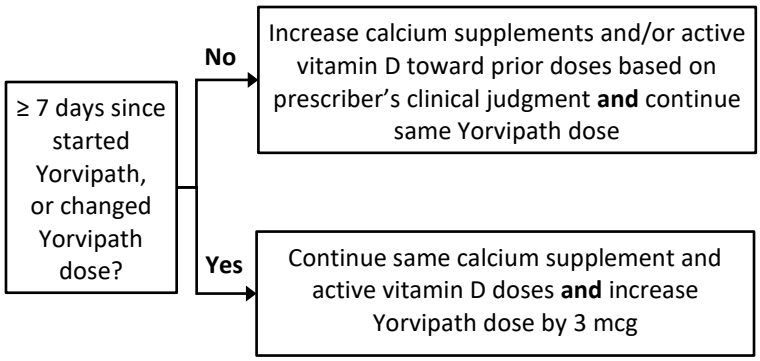
Once an appropriate maintenance dose has been achieved in this way, further serum calcium checks should be carried out at least every 4–6 weeks or when relevant clinical symptoms occur. Serum

25(OH)-vitamin D should be monitored according to the usual standard of care. The additional administration of a 25(OH)-vitamin D preparation (non-active vitamin D) may be necessary to achieve normal serum calcium levels.

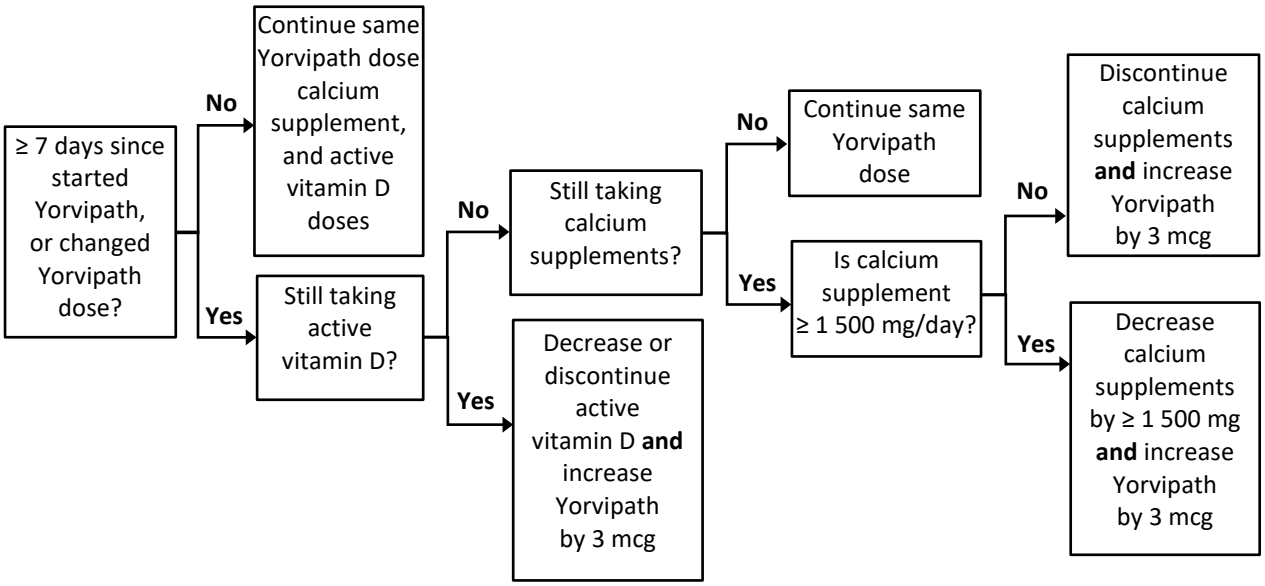
There is no experience to date for a therapy duration of more than three years.

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

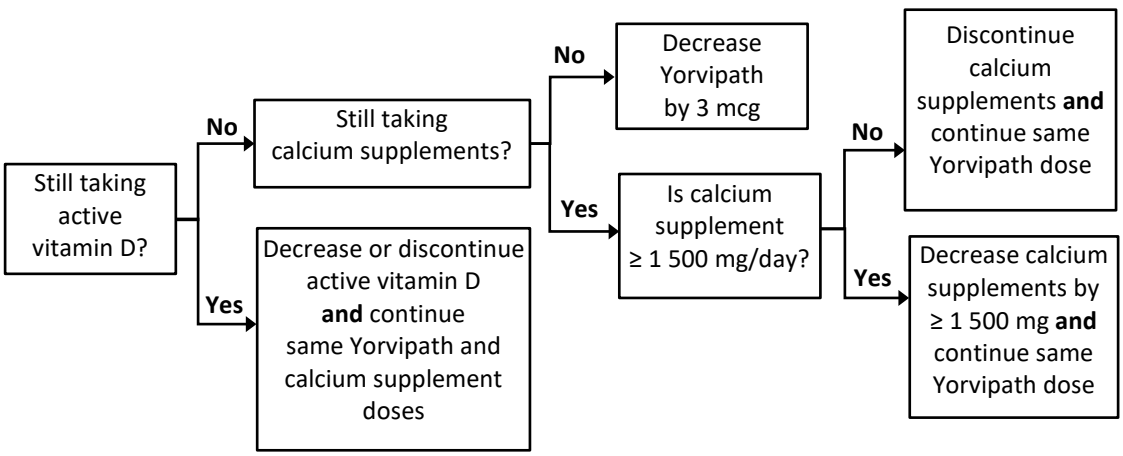
Serum calcium low (< 2.07 mmol/L [< 8.3 mg/dL]):



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



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



Dose titration and maintenance therapy for serum calcium concentrations ≥ 12 mg/dL
Treatment must be paused for 2 to 3 days. The serum calcium must then be checked again. Once the serum calcium returns to < 3.00 mmol/L [< 12 mg/dL], titration of Yorvipath, active vitamin D and calcium supplements should be resumed based on the last determined calcium level according to Figure 1. If the serum calcium is still ≥ 3.00 mmol/L [≥ 12 mg/dL], Yorvipath should be paused for a further 2 to 3 days. The serum calcium must then be checked again and the procedure described above must be followed. (for hypercalcemia, see also “Warnings and precautions”).

Missed dose
If it is noticed within 12 hours that a dose has been missed, the injection should be administered as soon as possible. If more than 12 hours have passed since the scheduled injection, the missed dose should be skipped and the next dose administered at the next scheduled time.

Pausing or discontinuing therapy
Pausing daily administration should be avoided in order to minimize fluctuations in serum PTH levels. Pausing or discontinuing treatment can lead to hypocalcemia. If treatment is paused for 3 or more consecutive days, patients must be monitored for signs of hypocalcemia and a determination of serum calcium should be considered. If indicated, treatment with calcium supplements and active vitamin D should be resumed.
After a pause, treatment should be resumed as soon as possible with the previously prescribed dose. If treatment is continued after a pause, serum calcium must be determined and the doses of Yorvipath, active vitamin D and calcium supplements must be adjusted according to Figure 1.

Special dosage instructions
Elderly patients
A dose adjustment based on age is not necessary (see “Pharmacokinetics”).

Children and adolescents
The safety and efficacy of palopegteriparatide has so far only been studied in adults. Yorvipath should therefore not be used in children and adolescents under the age of 18.

Patients with renal impairment
No dose adjustment is required in patients with an estimated glomerular filtration rate (eGFR) of ≥ 30 mL/min. However, in patients with an eGFR of < 45 mL/min, the serum calcium level should be determined more frequently. Yorvipath has not been studied in patients with hypoparathyroidism and severe renal impairment (eGFR < 30 mL/min) (see “Pharmacokinetics”).

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 “Warnings and precautions”).

Method of administration

Yorvipath must be administered as a subcutaneous injection into the abdominal wall (left or right) or into the anterior thigh (left or right). The injection site should be changed every day.

Due to the risk of orthostatic hypotension (see “Warnings and precautions”), the patient should be given the option to sit or lie down during the first injection of Yorvipath. If a patient experiences vasodilatory symptoms, it is recommended that the injection be given while the patient is lying down (e.g. before going to bed).

Contraindications

Pseudohypoparathyroidism.

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Only one Yorvipath injection should be given to reach the required daily dose. If two injections per day are administered, the variability of the total dose applied is greater, which can lead to unintended changes in serum calcium and even manifest hyper- or hypocalcemia.

Hypercalcemia

Serious hypercalcemic events (including those requiring hospitalization) have been reported with palopegteriparatide (see “Undesirable effects”). The risk is highest at the start of use and after increasing the dose. In principle, however, hypercalcemia can occur at any time during treatment. During treatment, serum calcium must be monitored (see “Dosage/Administration”) and patients should be monitored for signs of hypercalcemia. The calcium concentration should be determined within 7–14 days after each dose adjustment (or when clinical symptoms indicating hypercalcemia occur) and at least every 4–6 weeks during maintenance therapy. If necessary, hypercalcemia should be treated in accordance with the guidelines. The dose of palopegteriparatide, active vitamin D and/or calcium supplements must be adjusted (see “Dosage/Administration”). If calcium concentrations are > 12 mg/dL, treatment with palopegteriparatide must be paused for at least 2–3 days.

Hypocalcemia

Serious hypocalcemic events have been reported with palopegteriparatide (see “Undesirable effects”). The risk is highest if treatment is discontinued abruptly; however, hypocalcemia can occur at any time, even in patients who are stable on one dose. During treatment, serum calcium must be monitored, and patients should be monitored for signs of hypocalcemia. The calcium concentration

should be determined within 7–14 days after each dose adjustment (or when clinical symptoms indicating hypocalcemia occur) and at least every 4–6 weeks during maintenance therapy. The dose of palopegteriparatide, active vitamin D and/or calcium supplements must be adjusted (see "Dosage/Administration"). If necessary, hypocalcemia should be treated in accordance with the guidelines.

Orthostatic hypotension

Vasodilatory symptoms such as orthostatic hypotension have been reported with the use of PTH analogs including palopegteriparatide. Other possible vasodilatory symptoms include dizziness, palpitations, tachycardia, presyncope or syncope. The risk of such reactions can be reduced by using Yorvipath before going to bed.

Potential risk of osteosarcoma

An increased incidence of osteosarcoma was observed in rats treated with short-acting PTH preparations. The relevance of these findings for humans is not known, and no experience is available to date for PTH preparations with a long half-life such as palopegteriparatide. In non-interventional studies, no increased risk was found with short-acting PTH preparations. The use of palopegteriparatide is not recommended in patients who have an increased risk of osteosarcoma. These risk factors include but are not limited to:

- open growth plates (Yorvipath is not approved for the treatment of pediatric patients)
- metabolic bone diseases other than hypoparathyroidism (e.g. Paget's disease of the bones)
- unexplained increase in bone-specific alkaline phosphatase
- bone metastases or malignant skeletal disorders (including in the medical history)
- radiotherapy in which the skeleton was exposed
- hereditary predisposition to osteosarcoma

Concomitant administration with cardiac glycosides

Hypercalcemia of any cause increases the risk of digitalis toxicity. Conversely, hypocalcemia can reduce the efficacy of cardiac glycosides. In patients using palopegteriparatide concomitantly with cardiac glycosides, serum calcium and digitalis levels must be monitored and patients monitored for symptoms of digitalis toxicity (see "Interactions").

Severe renal or hepatic impairment

No studies have been conducted in patients with severe renal impairment or severe hepatic impairment. Caution should be exercised during use in such patients. Patients with an eGFR of < 45 mL/min may have an increased risk of hypercalcemia and a transient reduction in eGFR,

especially at the start of treatment. If treatment is initiated in such patients, serum calcium should be closely monitored.

Sodium

This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, i.e. it is essentially "sodium-free."

Interactions

No interaction studies have been conducted.

Effect of other medicinal products on the efficacy and safety of palopegteriparatide

Medicinal products that can affect serum calcium concentrations may alter the response to palopegteriparatide. This applies, for example, to bisphosphonates, denosumab, romosozumab, thiazide and loop diuretics, systemic corticosteroids or lithium. Patients receiving concomitant treatment with one of these medicinal products require particularly careful monitoring of serum calcium.

Effect of palopegteriparatide on the pharmacodynamics of other medicinal products

Cardiac glycosides have a narrow therapeutic range, and their efficacy and safety are influenced by serum calcium concentrations (see "Warnings and precautions"). If Yorvipath is taken concomitantly with cardiac glycosides, the patient must be monitored for symptoms of digitalis toxicity.

Pregnancy, lactation

Pregnancy

To date, there is no or only very limited experience with the use of palopegteriparatide in pregnant women. Animal studies have not shown any evidence of direct or indirect adverse health effects related to reproductive toxicity (see "Preclinical data"). However, a risk to the pregnant woman or the developing fetus cannot be ruled out. When deciding to start or continue treatment with Yorvipath during pregnancy, the possible risks must be weighed against the benefits for the pregnant woman. In pregnant women treated with palopegteriparatide, serum calcium should be monitored particularly carefully.

Lactation

It is not known whether palopegteriparatide or its metabolites pass into human milk, and no data are available on possible effects on milk production or on the breastfed infant. Breastfed infants of mothers treated with palopegteriparatide should be carefully monitored for possible symptoms of hyper- or hypocalcemia, and monitoring of serum calcium in the infant should be considered. The

benefits of breastfeeding and possible risks for the child as a result of hypoparathyroidism that is not optimally treated must be weighed against the benefits of the therapy for the mother and possible undesirable effects of palopegteriparatide on the breastfed infant. In breastfeeding women who are treated with palopegteriparatide, serum calcium should be monitored particularly carefully.
However, as palopegteriparatide is not absorbed from the gastrointestinal tract, undesirable effects on the breastfed infant are unlikely.

Fertility
No studies have been conducted on the possible effects of palopegteriparatide on fertility in humans. Animal studies have not shown any evidence of adverse effects on fertility (see “Preclinical data”).

Effects on ability to drive and operate machinery
Corresponding studies have not been conducted. However, adverse reactions such as dizziness, (pre)syncope and/or orthostasis syndrome have been reported with the use of palopegteriparatide, which may impair the ability to drive and operate machinery. Affected patients should not drive a vehicle or operate machinery until the symptoms have subsided.

Undesirable effects
The safety of palopegteriparatide was investigated in a phase II study and a phase III study in a total of n=141 patients, 139 of whom were exposed to palopegteriparatide during the double-blind phase. The most frequently reported adverse reactions in the clinical studies with palopegteriparatide were reactions at the injection site (39%), vasodilatory symptoms (28%), headache (21%) and paresthesia (19%). The most serious adverse reaction was hypercalcemia (8%).
“Vasodilatory symptoms” include the following adverse reactions: Headache, orthostatic vertigo, syncope, palpitations, orthostatic hypotension, orthostasis syndrome, postural orthostatic tachycardia syndrome. These adverse reactions occurred more frequently in the first three months of treatment than in the further course of treatment.
Some adverse reactions observed in the clinical studies should be interpreted as potential symptoms of hyper- or hypocalcemia.

The adverse reactions are listed below by MedDRA system organ classes and frequency according to the following convention:
“very common” (≥ 1/10)
“common” (≥ 1/100, < 1/10),
“uncommon” (≥ 1/1,000, < 1/100)
“rare” (≥ 1/10,000, < 1/1,000)
“very rare” (< 1/10,000)

"not known" (based mainly on spontaneous reports from market surveillance, exact frequency cannot be estimated)

Diseases of the immune system

Not known: Hypersensitivity reactions (including anaphylactic reactions)

Metabolism and nutrition disorders

Common: Hypercalcemia

Nervous system disorders

Very common: Headaches (21%), paresthesia (19%)

Cardiac disorders

Common: Palpitations, orthostatic tachycardia

Vascular disorders

Very common: vasodilatory symptoms (such as orthostatic hypotension, orthostasis syndrome, dizziness, orthostatic vertigo, presyncope, syncope; 28% in total)

Respiratory, thoracic and mediastinal disorders

Common: Pain in the oropharynx

Gastrointestinal disorders

Very common: Nausea (12%)

Common: Diarrhea, constipation, vomiting, abdominal pain, other abdominal complaints

Skin and subcutaneous tissue disorders

Common: Rash, photosensitivity reaction

Musculoskeletal and connective tissue disorders

Common: Arthralgias, myalgias, muscle twitching, musculoskeletal pain

Renal and urinary disorders

Uncommon: Polyuria

General disorders and administration site conditions

Very common: Reactions at the application site (such as erythema, rash, swelling, hematoma, pain or bleeding; 39% in total), fatigue (14%)

Common: Asthenia, thirst

Uncommon: Chest discomfort, chest pain

Description of specific adverse reactions and additional information

Hypercalcemia

Serious hypercalcemic events have been reported with palopegteriparatide. The incidence of hypercalcemia was greater in patients treated with Yorvipath than with placebo. While symptomatic hypercalcemia was reported in 8.6% of patients treated with palopegteriparatide during the blinded phase, there were no such cases observed with placebo. All of these events occurred within the first 3 months of starting treatment with Yorvipath.

Injection site reactions

Injection site reactions were the most common adverse reactions reported in clinical studies. They manifested a median of 2.5 days after the start of therapy. The most common reactions were local erythema (all < 5 cm, mostly 0 to < 2 cm) and were mild to moderate (grade 1 or 2) with a median duration of 72 hours. All injection site reactions were spontaneously reversible without treatment; none were serious or led to discontinuation of treatment.

Vasodilatory symptoms

The vasodilatory symptoms observed with palopegteriparatide were generally transient and resolved without treatment; they were never severe and did not lead to premature discontinuation of treatment.

Immunogenicity

The incidence of antibodies is highly dependent on the sensitivity and specificity of the assay used. The following findings are therefore not transferable to other studies due to possible differences in the assays used. In particular, the data do not allow a comparison with the antibody findings in studies with other PTH preparations.

Non-neutralizing anti-PTH antibodies were detected in 0.7% of patients at least once over the course of the study, and newly developed anti-PEG antibodies were detected in 6% compared to the initial findings (with a low titer). An effect of anti-PEG antibodies on pharmacokinetics (increased clearance of total PTH and mPEG) and pharmacodynamics (decrease in serum calcium concentration) was only

observed in patients who already had such antibodies at baseline and in whom there was an increase in the titer of these antibodies ("Boost") during treatment with Yorvipath. This affected 2.2% of all patients treated with Yorvipath. However, by adjusting the palopegteriparatide dose to the calcium level according to the titration algorithm of the study, the therapeutic effect was maintained.

Reporting suspected adverse reactions after authorization of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

During the clinical studies, there was one accidental overdose of approximately 3 times the prescribed dose for more than 7 consecutive days. This patient was found to have a serum calcium of up to 16.1 mg/dL. The patient was symptomatic (nausea), and the overdose required hospitalization. After temporary discontinuation of palopegteriparatide, calcium and active vitamin D, the patient recovered, and therapy could be continued at the correct dose.

Signs and symptoms

An overdose can cause hypercalcemia, which can manifest as dehydration, palpitations, ECG changes, hypotension, nausea, vomiting, dizziness, muscle weakness and confusion.

Treatment

Severe hypercalcemia may require medical intervention and careful monitoring (see "Warnings and precautions").

Properties/effects

ATC code

H05AA05

Mechanism of action

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

Palopegteriparatide is a prodrug and consists of PTH (1-34) conjugated to a methoxypolyethylene glycol (mPEG) carrier via a proprietary TransCon linker. PTH (1-34) and its main metabolite PTH (1-

33) are comparable to endogenous PTH in terms of its affinity to PTH1R and with regard to its activation. Under physiological conditions, PTH is cleaved from palopegteriparatide in a controlled manner to ensure continuous systemic exposure to active PTH.

Pharmacodynamics

Pharmacokinetic-pharmacodynamic relationships

A pharmacokinetic-pharmacodynamic sub-study in patients with hypoparathyroidism showed a dose-dependent increase in serum calcium levels with daily subcutaneous administration of palopegteriparatide.

Clinical efficacy

The efficacy of palopegteriparatide for the treatment of chronic hypoparathyroidism was investigated in a pivotal phase III study (PaTHway) in adults. For the 26-week, double-blind, placebo-controlled main phase of the study, a total of n=84 patients were randomized 3:1 to palopegteriparatide or placebo together with conventional therapy (calcium and active vitamin D). The starting dose was 18 µg/day. An individual dose titration was then performed according to a predefined dosing algorithm based on the albumin-corrected calcium concentrations in serum.
During an approximately 4-week screening phase, the calcium and active vitamin D dose was adjusted so that an albumin-corrected serum calcium concentration between 1.95 and 2.64 mmol/L (7.8–10.6 mg/dL), a 25(OH)-D concentration between 50 and 200 nmol/L (20–80 ng/mL) and a magnesium concentration ≥ 0.53 mmol/L (≥ 1.3 mg/dL) and below the upper normal limit were achieved.

The mean age of the patients was 49 years (19 to 78 years); 12% were ≥ 65 years old. Most patients were female (78%) and of Caucasian descent (93%). 85% of the patients had postoperative hypoparathyroidism. The remaining 12 patients had idiopathic disease in 7 cases, autoimmune polyglandular syndrome type 1 (APS 1) in 2 cases and autosomal dominant hypocalcemia type 1 (ADH1, CaSR mutation), DiGeorge syndrome and HDR syndrome (hypoparathyroidism, sensorineural deafness and renal dysplasia) (GATA3 mutation) in 1 case each.
At baseline, patients received elemental calcium as conventional therapy at a mean dose of 1,839 mg/day and active vitamin D at a mean dose of 0.75 µg/day in patients treated with calcitriol (n = 70) and 2.3 µg/day in patients treated with alfacalcidol (n = 12). The mean albumin-corrected serum calcium level and the mean 24-hour urinary calcium concentration were comparable in both treatment groups.
The primary efficacy endpoint was defined as the proportion of patients at week 26 who met the following criteria: Serum calcium within normal range (2.07–2.64 mmol/L [8.3–10.6 mg/dL]); no need

for conventional therapy (defined as a requirement for ≤ 600 mg/day of a calcium supplement and lack of requirement for active vitamin D); no increase in dose of study medication within the last 4 weeks before week 26.
The main secondary endpoints were a subset of domain scores on a Hypoparathyroidism Patient Experience Scale (HPES) and subscale scores on the 36-item Short Form Survey (SF-36) questionnaire.

The primary endpoint was achieved by 79% of patients on palopegteriparatide compared to 5% of patients on placebo. The difference between the two treatment groups was statistically significant ($p < 0.0001$).
The findings for the main secondary endpoints, which were also tested for confirmation, were consistent with this.

In patients treated with palopegteriparatide, the mean serum calcium level increased at the start of treatment and then remained within the normal range. Under placebo, the serum calcium level decreased slightly and was below the normal range at week 2 and week 26. Treatment with palopegteriparatide also led to a normalization of the mean 24-hour elimination of calcium in urine. In addition, the mean serum calcium-phosphate product decreased under palopegteriparatide and remained stable within the normal range until week 26.

Following the pivotal study, patients were able to participate in an open-label extension study. A total of n=61 patients were enrolled in this extension. So far, data for an observation period of up to 24 months is available from this study. The findings suggest that the efficacy of palopegteriparatide is maintained even with a treatment period of two years, although an increase in dose was sometimes necessary during the course of treatment.
Further long-term data are available from the open-label extension of a phase II study. A total of n=59 patients were enrolled in this extension. So far, data for an observation period of up to 36 months is available from this study. Here, too, the available data indicate that the efficacy of palopegteriparatide is maintained even with a treatment period of up to three years.
Both open-label extensions have not yet been completed.

Pharmacokinetics

Absorption

Yorvipath is a prodrug. When applied subcutaneously on a daily basis, this releases PTH with first-order kinetics via autocleavage of the TransCon linker. This leads to a continuous exposure over 24 hours in the normal range calculated on the basis of the molecular mass (approx. 4–26 pg/mL).

In patients with hypoparathyroidism receiving palopegteriparatide at a dose of 18 µg/day, the predicted maximum plasma concentration (C_{max}) (CV%) of palopegteriparatide was 5.18 ng/mL (36%) and of released PTH was 6.9 pg/mL (22%), with a median time to reach maximum concentrations (Tmax) of 4 hours. The predicted exposure over the 24-hour dosing interval (area under the curve, AUC) (CV%) for released PTH was 150 pg*h/mL (22%). After repeated administration, the AUC of palopegteriparatide increased up to 18-fold.

After several subcutaneous doses of palopegteriparatide in the range of 12 to 24 µg/day, the concentrations of palopegteriparatide and released PTH increased proportional to the dose and reached steady state within about 10 and 7 days, respectively. The peak-to-trough ratio at steady state was low, at around 1.1 for palopegteriparatide and 1.5 for released PTH over 24 hours.

Distribution

The apparent volume of distribution (CV%) of palopegteriparatide is estimated at 4.8 L (50%), that of the released PTH at 8.7 L (18%).

Metabolism

The released PTH consists of PTH (1-34) and the active metabolite PTH (1-33).

Studies on the metabolism or elimination of palopegteriparatide have not been conducted. The metabolism of parathyroid hormone presumably takes place mainly in the liver and kidneys.

Elimination

The clearance (CV%) of palopegteriparatide at steady state is estimated to be 0.58 L/day (52%), with a predicted half-life of 70 hours. The apparent half-life of PTH released from palopegteriparatide is around 60 hours.

Kinetics in specific patient groups

The pharmacokinetics of the released PTH was not influenced by gender or body weight. The available data on ethnicity did not show any trends suggesting differences but are too limited to allow definitive conclusions.

Elderly patients

The pharmacokinetics of released PTH was not affected by age (19–76 years).

Renal impairment

In a single-dose study, palopegteriparatide exposure in subjects with mild, moderate or severe renal impairment was comparable to that in subjects with healthy kidneys.

Preclinical data

Conventional safety pharmacology, genotoxicity and local tolerance studies conducted with palopegteriparatide do not indicate any particular harm to humans.

Repeated dose toxicity

In all species studied, repeated administration of palopegteriparatide resulted in undesirable persistent hypercalcemia, which in some studies resulted in premature death/euthanasia, clinical symptoms, weight loss and/or soft tissue mineralization, mainly in the kidneys. These findings are to be classified as a consequence of persistent exaggerated PTH pharmacology and are therefore not relevant in everyday clinical practice, where dose adjustments are made to normalize serum calcium levels.

Consistent with the expected pharmacologic effects, repeated daily administration of palopegteriparatide in rats increased bone turnover. At low doses (5 times the maximum recommended human dose, MRHD, based on the AUC of released PTH), there were overall catabolic effects on bone due to increased bone turnover. At high doses (9 times the MRHD, based on the AUC of released PTH), the increased bone turnover resulted in an overall anabolic bone effect. In rats, physical dysplasia was observed at the highest dose level (19 times the MRHD, based on the AUC of released PTH). These findings are not relevant in everyday clinical practice, where the Yorvipath dose is adjusted individually.

In single dose studies in monkeys (equivalent to five times the MRHD based on the C_{max} of released PTH) or repeated dose studies (equivalent to twice the MRHD based on the C_{max} of released PTH), there were no cardiovascular abnormalities up to and including the highest dose tested.

Carcinogenicity

No carcinogenicity study has been conducted with palopegteriparatide. In carcinogenicity studies with short-acting PTH analogs in rats, an increased incidence of osteosarcomas was observed (see also “Warnings and precautions”).

Reproductive toxicity

In animal reproduction studies, administration of palopegteriparatide to pregnant rats and rabbits during organogenesis up to and including the highest doses tested (equivalent to 16 and 13 times the MRHD, respectively, based on the AUC of released PTH) showed no evidence of embryonic lethality, fetotoxicity or dysmorphogenesis. At the highest doses tested in pregnant rats and rabbits, exaggerated pharmacological effects of PTH (increased serum calcium, reduced body weight, reduced feed intake and/or appearance of clinical signs) were observed. In pregnant rats and rabbits, the exposure at the NOAEL (No Observed Adverse Effect Level) for maternal toxicity was 3 and 5 times the MRHD, respectively, based on the AUC of released PTH.

Palopegteriparatide had no adverse effect on the pre- and postnatal development of offspring of pregnant and lactating rats up to and including the highest dose tested (7 times the MRHD, based on the C_{max} of released PTH).

Other information

Incompatibilities

Since no other compatibility studies have been conducted, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Shelf life after opening

Do not store above 30°C.

Leave the pen cap on the prefilled pen to protect the contents from light. Dispose of each pen 14 days after opening.

Special precautions for storage

Store in the refrigerator (2–8°C). Do not freeze.

Store in the original packaging with the pen cap in place to protect the contents from light.

Keep out of the reach of children.

Instructions for handling

A new Yorvipath pen should be taken out of the refrigerator 20 minutes before first use. The solution must be clear, colorless and free of visible particles. The medicinal product must not be injected if it is cloudy or contains suspended solids.

Each prefilled pen is intended for use by a single patient. Under no circumstances should a prefilled pen be used by more than one patient, even if the cannula is changed.

If a finished pen has been frozen or exposed to heat, it must be disposed of.

A new cannula must be attached each time a prefilled pen is prepared for administration. Cannulas must not be reused. The cannula must be removed after each injection, and the pen must be stored without the cannula attached. The cannulas must be disposed of after each injection.

For instructions on the preparation and use of Yorvipath, please refer to the package leaflet and the instructions for use.

<u>Waste disposal</u>

Unused medicinal products or waste material must be disposed of in accordance with national requirements.

Authorization number

69889 (Swissmedic)

Packs

Yorvipath 168 micrograms/0.56 mL, solution for injection in a prefilled pen (blue label and push button):

2 prefilled pens and 30 disposable needles or without needles [B]

Yorvipath 294 micrograms/0.98 mL, solution for injection in a prefilled pen (orange label and push button):

2 prefilled pens and 30 disposable needles or without needles [B]

Yorvipath 420 micrograms/1.4 mL, solution for injection in a prefilled pen (dark red label and push button):

2 prefilled pens and 30 disposable needles or without needles [B]

Marketing authorization holder

Ascendis Pharma Switzerland GmbH, Zurich

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August 2025