Summary of the Swiss Risk Management Plan (RMP)

Name of the medicinal product:	Yorvipath
Active substance(s):	Palopegteriparatidum
Version number of the current RMP:	0.4
Name of the marketing authorisation holder:	Ascendis Pharma Switzerland GmbH
Data lock point for the RMP:	12 January 2022

Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Yorvipath is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Yorvipath in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Ascendis Pharma Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Yorvipath".

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Yorvipath (Palopegteriparatide)

This is a summary of the Risk Management Plan (RMP) for Yorvipath. The RMP details important risks of Yorvipath, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information).

The summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how Yorvipath should be used.

This summary of the RMP for Yorvipath should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current risks will be included in updates of Yorvipath RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Yorvipath is authorised as a parathyroid hormone replacement therapy indicated for the treatment of chronic hypoparathyroidism in adults (see SmPC for the full indication). It contains palopegteriparatide as the active substance and it is given by subcutaneous route of administration.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Yorvipath, together with measures to minimise such risks and the proposed studies for learning more about the risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Yorvipath is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Yorvipath are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Yorvipath. Potential risks are where an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Summary of Safety Concerns	
Important identified risks	Hypercalcaemia
Important potential risks	None identified
Missing information	Use in pregnant and breastfeeding women Use in patients with severe and chronic renal impairment Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)

II.B Summary of Important Risks

Important Identified Risk: Hypercalcaemia	
Evidence for linking the risk to the medicine	Clinical trials and literature
Risk factors and risk groups	Hypercalcaemia occurred almost exclusively during early treatment. This is consistent with the observation that serum calcium initially increased during study drug titration before returning to baseline levels. Patients at higher risk for hypercalcaemia include elderly patients with renal insufficiency, subjects with a disease predisposing to hypercalcaemia (e.g., active neoplasia, multiple myeloma, granulomatous disease, endocrinopathy), and persons taking concomitant medications that affect serum calcium levels such as thiazide diuretics (Powers 2013, Clarke 2011, Mitchell 2012, Underbjerg 2013). For any drug that affects serum calcium levels (lithium, thiazide diuretics), the patient's serum calcium levels should be monitored especially during treatment start or dose adjustment. Thiazide diuretics are sometimes used in patients with hypoparathyroidism to increase urinary calcium reabsorption at the distal tubule and induce osteoblast differentiation which will contribute to increasing serum calcium levels. In patients with a history of calcium stones (Li 2020), thiazide diuretics are prescribed to reduce recurrent calcium stones. Thus, the concomitant treatment of thiazide diuretics and palopegteriparatide is likely to reduce the adverse renal effects (including nephrolithiasis, nephrocalcinosis) but can augment the risk for transient hypercalcaemia. It is therefore recommended to monitor serum calcium when adding or changing the dose of thiazide diuretics in patients treated with palopegteriparatide.

Important Identified Risk: Hypercalcaemia	
Risk minimisation measures	Routine risk communication: *SmPC Sections 4.2 , 4.4 and 4.8* *Corresponding PL sections* Other routine risk minimisation measures beyond the Product Information: Legal status: *Restricted medical prescription.*
Additional pharmacovigilance activities	Open label extension studies TCP-201 and TCP-304

Important Potential Risk: None identified	
Evidence for linking the risk to the medicine	Not Applicable
Risk factors and risk groups	Not Applicable
Risk minimisation measures	Not Applicable
Additional pharmacovigilance activities	Not Applicable

Missing Information: Use in Pregnant and Breastfeeding Women	
Risk minimisation measures	Routine risk communication: *SmPC Section 4.6* Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Follow-up questionnaire* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Restricted medical prescription*
Additional pharmacovigilance activities	None

Missing Information: Use in Patients with Severe and Chronic Renal Impairment	
Risk minimisation measures	Routine risk communication: *SmPC sections 4.2, 4.4 and 5.2* *Corresponding PL sections* Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Follow-up questionnaire* Other routine risk minimisation measures beyond the Product Information: Legal status: *Restricted medical prescription*
Additional pharmacovigilance activities	None

Missing Information: Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)	
Risk minimisation measures	Routine risk communication: *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *None*

Missing Information: Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)	
	Legal status: *Restricted medical prescription*
Additional pharmacovigilance activities	Open label extension studies TCP-201 and TCP-304

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Yorvipath.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Yorvipath.