PART VI: SUMMARY OF THE RMP

Summary of Risk Management Plan for Rayaldee (Calcifediol)

This is the summary of the risk management plan (RMP) for Rayaldee. The RMP details important risks of Rayaldee, how these risks can be minimised, and how more information will be obtained about Rayaldee's risks and uncertainties (missing information).

Rayaldee's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rayaldee should be used.

I. The Medicine and What It Is Used For

Rayaldee is authorised for treatment of secondary hyperparathyroidism (SHPT) in adult non-dialysis CKD Stage 3 or 4 and Vitamin D insufficiency or deficiency (see SmPC for the full indication).

It contains calcifediol (also known as calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D (abbreviated 25(OH)D)) as the active substance and is given orally.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Rayaldee, together with measures to minimise such risks and the proposed studies for learning more about Rayaldee's 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 so 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 Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine

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

II.A. List of Important Risks and Missing Information

Important risks of Rayaldee 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 Rayaldee. Hypercalcaemia is an important identified risk for Rayaldee. Potential risks are concerns for which 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. Important potential risks for Rayaldee are Blood phosphorus increased and Cardiac failure. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected. The list of important risks and missing information for Rayaldee is shown in below.

List of Important Risks and Missing Information	
Important identified risks	Hypercalcaemia
Important potential risks	Blood phosphorus increased Cardiac failure
Missing information	Use in pregnant women

II.B. Summary of Important Risks

Important Identified Risk: Hypercalcaemia	
Evidence for linking the risk to the medicine	The OPKO Pharmaceuticals Clinical Database, the Vifor Pharma Safety Database, data from interventional studies and literature.
Risk factors and risk groups	Risk factors for Vitamin D mediated hypercalcaemia include Vitamin D intoxication, excessive calcium intake, and low turnover bone disease (Annex 7 [21,23]).
Risk minimisation measures	Appropriate posology to reduce the risk of hypercalcaemia is listed in Section 4.2 of Rayaldee SmPC. Appropriate warnings are listed in Section 4.4 of Rayaldee SmPC. Overdose symptoms and treatment thereof are described in Section 4.9 of Rayaldee SmPC. Prescription only medicine.
Additional pharmacovigilance activities	N/A

Note: N/A=Not applicable; SmPC=Summary of Product Characteristics.

Important Potential Risk: Blood Phosphorus Increased	
Evidence for linking the risk to the medicine	The OPKO Pharmaceuticals Clinical Database, the Vifor Pharma Safety Database, data from interventional studies and literature.
Risk factors and risk groups	Blood phosphorus increased is principally observed in patients with reduced kidney function. Other potential causes include hypoparathyroidism, pseudohyperphosphataemia, excessive intake of phosphate, excessive cellular injury (for example rhabdomyolysis and tumour lysis syndrome), intracellular shifts (metabolic or respiratory acidosis) and Vitamin D toxicity.
Risk minimisation measures	Appropriate warnings listed in Section 4.4 of Rayaldee SmPC. Overdose symptoms are described in Section 4.9 of Rayaldee SmPC. Prescription only medicine.
Additional pharmacovigilance activities	N/A

Notes: CKD=Chronic kidney disease; N/A=Not applicable; SmPC=Summary of Product Characteristics.

Important Potential Risk: Cardiac Failure	
Evidence for linking the risk to the medicine	Data from interventional studies: A numerical difference in Cardiac failure congestive reported more frequently in the active treatment compared to the placebo group. The incidence at SMQ Cardiac failure level was comparable or less frequent on active treatment.
Risk factors and risk groups	All patients with underlying CKD and CV risk factors are at increased risk for cardiac failure. Patients with a pre-existing diagnosis of cardiac failure are at increased risk for all cause hospitalisation.
Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	N/A

Notes: CKD=Chronic kidney disease; N/A=Not applicable; SmPC=Summary of Product Characteristics.

Missing Information: Use in Pregnant Women	
Risk minimisation measures	Information relevant to pregnancy is presented in Section 4.6 of the SmPC. Prescription only medicine.
Additional pharmacovigilance activities	Not applicable.

Note: SmPC=Summary of Product Characteristics.

II.C. Post-authorisation Development Plan

There are currently no post-authorisation safety or efficacy studies for Rayaldee that are specific obligations and/or conditions of the marketing authorisation.

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

Not applicable. Until the DLP of this EU RMP Version 1.3, there are no studies which are conditions of the marketing authorisation or specific obligation for Rayaldee.

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

Not applicable. There are no other studies required for Rayaldee in the post-authorisation development plan.