PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ROACCUTANE (ISOTRETINOIN)

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

Roaccutane's Summary of product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *Roaccutane* should be used.

Important new concerns or changes to the current ones will be included in updates of *Roaccutane*'s RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Roaccutane is authorized for *severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy* (see SmPC for further information). It contains *isotretinoin* as the active substance, and it is given *orally*.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of *Roaccutane*, together with measures to minimize such risks and the proposed studies for learning more about *Roaccutane*'s risks, are outlined below.

Measures to minimize 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 authorized pack size—The amount of medicine in a pack is chosen so as 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 minimize its risks.

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

In the case of *Roaccutane*, these measures are supplemented with *additional risk-minimization* measures mentioned under relevant risks below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of *Roaccutane* are risks that need special risk-management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 *Roaccutane*. 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. Missing information refers to information about 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).

List of Important Risks and Missing Information	
Important identified risks	• Teratogenicity and Congenital Malformations • Psychiatric Disorders
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

Teratogenicity and Congenital Malformations	
Evidence for linking the risk to the medicine	Evidence of teratogenic risk associated with isotretinoin, that may cause birth defects via a toxic effect on an embryo or fetus, was identified in preclinical studies before the first use in humans, and has been confirmed subsequently by various observational studies and on the basis of adverse events reports.
Risk factors and risk groups	Women of childbearing potential. Maternal exposure from the semen and seminal fluid of patients receiving isotretinoin is not of a sufficient magnitude to be associated with teratogenic effects of isotretinoin. However, male patients should be reminded they must not share their medication with anyone, particularly not females.
Risk-minimization measures	**Routine risk-minimization measures:** Information regarding teratogenicity and congenital malformations with isotretinoin treatment is included in the SmPC under the following sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data - Teratogenicity

	Routine risk-minimization activities recommending specific clinical measures to address the risk: Specific measures to address the risk are captured in all the SmPC sections described. **Additional risk-minimization measures:** Educational material for patient, physician and pharmacist is available. A one-off Dear Healthcare Professional letter has been distributed, informing Healthcare Professionals of changes to the education material.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The marketing authorization holder (MAH) is undertaking PASS Qualitative study (Category 3) to identify, qualify and describe the barriers and reasons for lower adherence with the oral retinoid therapy PPP by HCPs who prescribe or dispense oral retinoid therapy and WCBP treated with oral retinoid therapy in Europe and the preferred ways of HCPs and patients to receive information on the PPP. The study is expected to be completed in December 2025. See Section II.C of this summary for an overview of the post-authorization development plan.

Psychiatric Disorders	
Evidence for linking the risk to the medicine	Research shows that vitamin A helps regulate gene expression in the brain and can cause negative neurologic outcomes. However, many trials and studies have been conducted to investigate the exact relationship between depression and isotretinoin, and none have found it to be causal. Study results are mixed for the causal role of isotretinoin in depression or suicide risk. The fact that severe acne vulgaris itself creates potentially severe psychosocial complications cannot be disputed. Multiple controlled studies actually suggest a very favorable effect of isotretinoin on depression and anxiety common in the population requiring isotretinoin.
Risk factors and risk groups	Patients with a history of depression.
Risk-minimization measures	**Routine risk-minimization measures:** Information regarding psychiatric disorders with isotretinoin treatment is included in the SmPC under the following sections: 4.4 Special warnings and precautions for use 4.8 Undesirable effects

	Additional risk-minimization measures: A one-off Dear Healthcare Professional letter has been distributed, informing Healthcare Professionals of changes to the education material.

II.C Post-Authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation of isotretinoin.

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

Study short name: PASS Qualitative Study

Purpose of the study: To identify, qualify and describe the barriers and reasons for lower adherence with the oral retinoid therapy PPP by HCPs who prescribe or dispense oral retinoid therapy and WCBP treated with oral retinoid therapy in Europe and the preferred ways of HCPs and patients to receive information on the PPP.