Part VI: Summary of the risk management plan

Summary of risk management plan for Isotretinoin [Nationally completed name] 5mg 10mg and 20mg soft capsules (isotretinoin)

This is a summary of the risk management plan (RMP) for Isotretinoin [Nationally completed name]. The RMP details important risks of Isotretinoin [Nationally completed name], how these risks can be minimised, and how more information will be obtained about Isotretinoin [Nationally completed name] risks and uncertainties (missing information).

Isotretinoin [Nationally completed name] summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Isotretinoin [Nationally completed name] should be used.

I. The medicine and what it is used for

Isotretinoin [Nationally completed name] is authorised 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 antibacterials and topical therapy (See SmPC for the full indication). It contains isotretinoin as the active substance and it is given orally.

Strength / pharmaceutical forms: 5mg, 10mg & 20mg soft capsules.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Isotretinoin [Nationally completed name], together with measures to minimise such risks and the proposed studies for learning more about Isotretinoin [Nationally completed name] 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 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 minimization* measures.

In the case of Isotretinoin [Nationally completed name], these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

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.

II.A List of important risks and missing information

Important risks of Isotretinoin [Nationally completed name] are risks that need special risk management activities to further investigate or minimise 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 Isotretinoin [Nationally completed name]. 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 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);

List of important risks and missing information	
Important identified risks	• **Teratogenicity and Congenital Malformations** • **Eye disorders** • **Musculoskeletal and Connective Tissue Disorders** • **Severe Cutaneous Adverse Reactions**
Important potential risks	• **Psychiatric disorders** • **Inflammatory Bowel Disease (Ulcerative colitis and Chron's disease)**
Missing information	• **None**

II.B Summary of important risks

Important identified risk: Teratogenicity and Congenital Malformations	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.4, 4.6, 4.8, 5.3* *PL section 2, section 4* Prescription only medicine Prescription and distribution restrictions to be decided at national level A boxed warning and optional a symbol/pictogram as a visual reminder on the outer package to warn patients about the harm to unborn baby and the need for effective contraception to be agreed at national level Additional risk minimisation measures: -Pregnancy Prevention Program (PPP) materials / The PPP materials will be consisted of: 1) Patient reminder card, 2) Physician checklist/acknowledgement form, 3) Pharmacist checklist -DHPC
Additional pharmacovigilance activities	Drug Utilisation Study (Category 1) Patient and Prescriber Survey (Category 3) See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Psychiatric disorders	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4, 4.8.* *PL section 2, 4* Prescription only medicine Additional risk minimisation measures: DHPC

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

A PASS, Drug Utilisation Study (DUS), is condition of the marketing authorisation:

PASS *Evaluation of the effectiveness of pregnancy prevention program (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilization study (DUS) using secondary data* summary

Purpose of the study:

The aim of the DUS is to address the following research question: Is there a difference in physicians' prescribing and monitoring practice in the periods before and after the update of the pregnancy prevention program (PPP) for the oral retinoids acitretin, alitretinoin, and isotretinoin when treating women of childbearing potential?

Primary objective

To evaluate the changes in the prescribing and monitoring practices following the update of the PPP in females of childbearing potential receiving prescriptions of the oral retinoids acitretin, alitretinoin, or isotretinoin by comparing the following key elements of the PPP between the pre- and the post-implementation period:

- Contraceptives* before, during, and after treatment with oral retinoids
- Time interval between prescription dates for oral retinoids during treatment episode
- Laboratory pregnancy tests – where available - before, during, and after treatment with oral retinoids

* contraceptive methods that require prescription and which are, therefore, captured in the administrative databases

Secondary objectives

- To describe the patient profile during the pre-and the post-implementation period, with respect to:
  - Patient age
  - Indication for oral retinoids
- To describe the prescriber specialty during the pre-and the post-implementation period
- To describe the exposure characteristics during the pre-and the post-implementation period, with respect to:
  - Active substance

    - Dose
    - Treatment duration
- To describe the incidence of pregnancies exposed to oral retinoids during the pre- and the post-implementation period
- To stratify the key elements of the PPP described in the primary objective by oral retinoid substance
- To describe trends in the physician's prescribing and monitoring practice of oral retinoids with respect to measures of the PPP (contraceptive use and performance of pregnancy tests) over the entire duration the study

II.C.2 Other studies in post-authorisation development plan

PASS Patient and Prescriber Survey: Effectiveness measures to investigate awareness, knowledge and adherence to the Risk Minimisation Measures (RMMs) of the Pregnancy Prevention Program (PPP) for Oral Retinoids (Acitretin, Alitretinoin, and Isotretinoin***)***

Purpose of the study:

This survey aims to assess the effectiveness of the updated risk minimisation measures among female oral retinoid patients who are of childbearing potential and their prescribers and to assess patients' and prescribers' (HCPs') awareness and knowledge of and adherence to the pregnancy prevention program.

Primary objective:

- To assess the effectiveness of the PPP based on the pre-defined success thresholds for PPP awareness, knowledge, and adherence in HCPs and patients

Secondary objectives:

- To assess HCPs' and patients' awareness of the updated PPP
- To assess HCPs' and patients' knowledge of the risks and RMMs associated with the use of oral retinoids
- To assess whether HCPs and patients adhere to the RMMs of the updated PPP