Part VI: Summary of the risk management plan

Summary of risk management plan for [ISOTRETINOIN] 10mg, 20mg soft capsules.

This is a summary of the risk management plan (RMP) for [ISOTRETINOIN] 10mg, 20mg soft capsules. The RMP details important risks of [ISOTRETINOIN] 10mg, 20mg soft capsules, how these risks can be minimised, and how more information will be obtained about [ISOTRETINOIN] 10mg, 20mg soft capsules risks and uncertainties (missing information).
[ISOTRETINOIN] 10mg, 20mg soft capsules summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how [ISOTRETINOIN] 10mg, 20mg soft capsules should be used.

I. The medicine and what it is used for

[ISOTRETINOIN] contains the active ingredient isotretinoin-a substance related to vitamin A, and one of a group of medicines called retinoids (for treatment of acne).
[ISOTRETINOIN] is used to treat severe forms of acne (such as nodular or conglobate acne or acne at risk of causing permanent scarring) in adults and adolescents from 12 years of age only after puberty. You will use [ISOTRETINOIN] when your acne has not got better with anti-acne treatments, including antibiotics and skin treatments.
The [ISOTRETINOIN] treatment must be supervised by a dermatologist (a doctor specialised in the treatment of skin problems).

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

Important risks of [ISOTRETINOIN] 10mg, 20mg soft capsules, together with measures to minimise such risks and the proposed studies for learning more about [ISOTRETINOIN] 10mg, 20mg soft capsules 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 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 [ISOTRETINOIN] 10mg, 20mg soft capsules is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of [ISOTRETINOIN] 10mg, 20mg soft capsules, 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 [ISOTRETINOIN] 10mg, 20mg soft capsules. 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);

Summary of safety concerns	
Important identified risks	• Teratogenicity and congenital malformations
Important potential risks	• Neuropsychiatric disorders
Missing information	• None

The summary of safety concerns is in accordance to the Innovator's (Roche-Roaccutane) provided in the PRAC AR; EMA/PRAC/817245/2018.

II.B Summary of important risks

The safety information in the Product Information is aligned to the reference medicinal product.

Important identified Risks: Teratogenicity and congenital malformations	
Risk minimization measures	*Routine risk minimisation measures:* SmPC section 4.4, PIL section 4 Prescription only medicine Prescription should be limited to 30 days treatment. *Additional risk minimisation measures:* • educational PPP • Patient reminder card • Pharmacist material (optional) • Physician checklist/acknowledgement form • DHPC
Additional risk minimization activities	*Additional pharmacovigilance activities:* *Drug Utilisation Study (DUS) for oral retinoids (acitretin, alitretinoin, and isotretinoin) in European Countries using established databases*: Evaluation of the effectiveness of PPP for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilization study (DUS) using secondary data *Survey study for Oral Retinoids (Acitretin, Alitretinoin, and Isotretinoin):* 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).
Important potential risks: Neuropsychiatric disorders	

Risk minimization measures	*Routine risk minimisation measures:* SmPC sections 4.4 and 4.8 PIL sections 2 and 4. Prescription only medicine Prescription should be limited to 30 days treatment. *Additional risk minimisation measures: DHPC*

II.C Post-authorisation development plan

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

DUS Study

Study short name: DUS for oral retinoids (acitretin, alitretinoin, and isotretinoin) in European Countries using established databases.

Purpose of the study: Retinoic acid analogues comprise of a group of compounds known as the retinoids and are available as topical and oral preparations. Therapeutic indications include the treatment of severe acne (such as nodular or conglobate acne), hand eczema resistant to empirical treatment measures, and severe forms of psoriasis and other skin conditions. Therapy with systemic retinoids is associated with both acute and chronic toxicities as well as teratogenicity. Therefore, women who are pregnant or are planning a pregnancy must not be prescribed retinoids. Strict prescription guidelines and a pregnancy prevention program (PPP) have been put in place but exposure during pregnancy still occurs.

In January 2016, a PRAC review noted that there are concerns about how well the requirements of the PPP are followed in clinical practice. In September 2016, PRAC initiated an article 31 referral to assess the effectiveness of risk minimization in relation to the PPP. After completion of the review in March 2018, the EMA confirmed that an update of measures of the PPP for the oral retinoids acitretin, alitretinoin and isotretinoin is needed. They, therefore, mandated the conduct of a DUS, category 1 to assess the effectiveness of these aRMMs. In June 2018, the decision to strengthen the recommendations for pregnancy prevention for oral retinoids was issued by the EC.

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 programme (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

Survey Study

Study short name: Survey to Evaluate Prescriber and Patient Awareness, Knowledge and Behaviour with respect to the Correct Implementation of the RMMs of the PPP for Oral Retinoids (Acitretin, Alitretinoin, and Isotretinoin).

Purpose of the study: In January 2016, the PRAC had reviewed the effectiveness of the PPP for oral isotretinoin. This review noted post-marketing data and published studies raising concerns about how well the requirements of the PPP are followed in clinical practice. This data suggested that there were a number of areas that may impact on the effectiveness of the PPP including inconsistencies in information provided with regard to contraceptive measures and a lack of up-to-date information about the most effective contraceptive methods; inadequate documentation of the required patient monitoring, and potential differences in the PPPs implemented across the generics. Consequently, the PRAC identified a need for a detailed assessment of compliance with the requirements of the PPP for oral retinoids.

A response to the article 31 request was submitted detailing the teratogenic risk, elements of the PPP, distribution of the PPP and an assessment of the effectiveness of the various elements. A list of outstanding issues has been received and PRAC has requested that the MAHs for the oral retinoids acitretin, alitretinoin and isotretinoin should provide proposals for studies to monitor the effectiveness of the RMMs particularly with regards to patient and prescriber awareness and adherence to the PPP and its RMMs.'

In a subsequent PRAC communication there is a requirement for a drug utilization study (category 1 study) and a complementary survey (category 3 study) to assess the effectiveness of the proposed RMMs. The study design should aim to evaluate and quantify the effectiveness of the RMM. This protocol describes the survey. The drug utilization study is described in a separate protocol.

This survey aims to provide information on the patient and prescriber awareness of the PPP and its RMMs during the standard clinical use of oral retinoids (including acitretin, alitretinoin and isotretinoin).

The objectives of this survey are as follows:

Primary objective:

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

Secondary objectives:

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