

## Part VI: Summary of the risk management plan

### Summary of risk management plan for Isotretinoin GAP (isotretinoin)

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

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

Important new concerns or changes to the current ones will be included in updates of Isotretinoin GAP's RMP

#### I. The medicine and what it is used for

Isotretinoin GAP 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 & 40mg soft capsules.

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

Important risks of Isotretinoin GAP, together with measures to minimise such risks and the proposed studies for learning more about Isotretinoin GAP 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 the case of Isotretinoin GAP, these measures are supplemented with additional risk minimisation 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 GAP 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 GAP. 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);

<b>List of important risks and missing information</b>	
Important identified risks	<ul style="list-style-type: none"> <li>• <b>Teratogenicity and Congenital malformations</b></li> <li>• <b>Eye disorders</b></li> <li>• <b>Musculoskeletal and Connective Tissue Disorders</b></li> <li>• <b>Severe Cutaneous Adverse Reactions</b></li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• <b>Psychiatric disorders</b></li> <li>• <b>Inflammatory Bowel Disease (Ulcerative colitis and Chron's disease)</b></li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• <b>None</b></li> </ul>

## **II.B Summary of important risks**

<b>Important identified risk: Teratogenicity and Congenital Malformations</b>	
Evidence for linking the risk to the medicine	Like other vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic.
Risk Factors and risk groups	Pregnant women and women of childbearing potential
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p><i>SmPC sections 4.3, 4.4, 4.6, 5.3</i></p> <p><i>PL section 2, section 4</i></p> <p>Prescription only medicine</p> <p>Prescription and distribution restrictions to be decided at national level</p> <p>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</p>

	<p><u>Additional risk minimisation measures:</u></p> <p>-Pregnancy Prevention Programme (PPP) materials / The PPP materials will be consisted of: 1) Patient reminder card, 2) Physician checklist/acknowledgement form, 3) Pharmacist checklist.</p> <p>Specific requirements to be agreed on national level</p> <p>-DHPC to be decided at national level</p>
Additional pharmacovigilance activities	<p>Drug Utilisation Study (Category 1) Patient and Prescriber Survey (Category 3)</p> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>

<b>Important potential risk: Psychiatric disorders</b>	
Evidence for linking the risk to the medicine	Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin
Risk Factors and risk groups	Patients with a history of depression
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p><i>SmPC section 4.4, 4.8.</i></p> <p><i>PL section 2, 4</i></p> <p>Prescription only medicine</p> <p><u>Additional risk minimisation measures:</u></p> <p>DHPC to be decided at national level</p>

## **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