13 Part VI: Summary of the risk management plan (RMP) Isotretinoin, 10 mg and 20 mg, Soft capsule

This is a summary of the RMP for isotretinoin, 10 mg and 20 mg, soft capsule. The RMP details important risks of isotretinoin soft capsule, how these risks can be minimized, and how more information will be obtained about isotretinoin's risks and uncertainties (missing information).

Isotretinoin soft capsule's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how isotretinoin soft capsule should be used.

Important new concerns or changes to the current ones will be included in updates of the isotretinoin soft capsule's RMP.

13.1 Part VI: I. The medicine and what it is used for

Isotretinoin is a substance related to vitamin A, and one of a group of medicines called retinoids (for treatment of acne (red pimples on the skin)). It reduces sebum production by preventing blackheads (small, dark spots on face or neck) forming and reducing skin inflammation (localized reaction causing redness, warmth, swelling, and pain due to infection, irritation, or injury).

Isotretinoin soft capsule is indicated in adults and adolescents from 12 years of age only after puberty (the period during which adolescents reach sexual maturity) for the treatment of severe forms of acne, which have not improved with intake of antibiotics (drugs used to kill bacteria and treat infections) and local acne treatments, such as acne with formation of lumps, acne with blackheads or acne at the risk of permanent scarring (a mark on the skin which is left after a wound has healed)

It contains isotretinoin as active substance and is given orally as 10 mg and 20 mg soft capsule.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of isotretinoin soft capsule, together with measures to minimize such 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 PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized 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 minimize its risks.

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

In the case of isotretinoin soft capsule, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important identified risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Reports (PSURs) assessment 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 soft capsule is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of isotretinoin soft capsule 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 isotretinoin soft capsule. 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).

Table 13-1 List of important risks and missing information

Important identified risks	Teratogenicity
	Psychiatric disorders-including depression, suicidality and anxiety
	Eye disorders including corneal opacities, reduced night vision and keratitis
	Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis
	Severe skin reactions (including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN))
	Benign intracranial hypertension
	Severe increase in triglyceride levels, sometimes associated with acute pancreatitis
	Severe allergic reactions
Important potential risks	Gastrointestinal disorders including inflammatory bowel disease
Missing information	None

13.2.2 Part VI – II.B: Summary of important risks

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

Table 13-2 Important identified risk: Teratogenicity

Risk minimization measures	Routine risk minimization measures SmPC section 4.3, 4.4, 4.6, and 5.3. Recommendations are given in SmPC section 4.4 not to prescribe isotretinoin unless all the conditions of the pregnancy prevention program (PPP) are met

	PL section 2 where strict recommendation is given to pregnant women or women with childbearing potential not to take isotretinoin and consult their doctor before taking isotretinoin as it can cause serious abnormalities in the unborn baby Legal status: Prescription only Additional risk minimization measures: Direct healthcare professional communication (DHPC), Physician checklist/ Acknowledgement form for prescribing to female patients, Pharmacist checklist, Patient reminder card and Visual reminder on the outer package
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Evaluation of the effectiveness of PPP for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilization study (DUS) using secondary data Patient and Prescriber Survey: Effectiveness measures to investigate awareness, knowledge and adherence to the risk minimization measures (RMMs) of the PPP for Oral Retinoids (Acitretin, Alitretinoin, and Isotretinoin)

Table 13-3 Important identified risk: Psychiatric Disorders- including depression, suicidality and anxiety

Risk minimization measures	Routine risk minimization measures SmPC section 4.4 and 4.8 Recommendations are given in SmPC section 4.4 for special care of patients with a history of depression and monitoring of signs of depression should be done in all patients with referral for appropriate treatment if necessary PL section 2 and 4 where recommendation is given to consult a doctor before taking isotretinoin in case of mental health problems including depression, aggressive tendencies, thoughts of hurting oneself or ending his/her life Legal status: Prescription only Additional risk minimization measures: DHPC

Table 13-4 Important identified risk: Eye disorders including corneal opacities, reduced night vision and keratitis

Risk minimization measures	Routine risk minimization measures SmPC section 4.4, 4.7 and 4.8 Instructions are given in SmPC section 4.4 to patients experiencing visual disturbances not to drive, operate machinery or take part in any other activities where the symptoms put either themselves or others at risk. PL section 2 and 4 where recommendation is given to consult a doctor if they experience visual disturbances during isotretinoin therapy

	Legal status: Prescription only Additional risk minimization measures: None

Table 13-5 Important identified risk: Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis

Risk minimization measures	Routine risk minimization measures SmPC section 4.4 and 4.8 PL section 2 and 4 where recommendation is given to patients to avoid vigorous physical activity during isotretinoin therapy Legal status: Prescription only Additional risk minimization measures: None

Table 13-6 Important identified risk: Severe skin reactions (including SJS and TEN)

Risk minimization measures	Routine risk minimization measures SmPC section 4.3, 4.4, 4.8 and 4.9 SmPC section 4.4, PL section 2 and 4 where recommendation is given to patients to stop treatment and consult their doctor immediately in case of severe skin reactions Legal status: Prescription only Additional risk minimization measures: None

Table 13-7 Important identified risk: Benign intracranial hypertension

Risk minimization measures	Routine risk minimization measures SmPC section 4.4, 4.5 and 4.8 Recommendations are given in SmPC section 4.4 to patients to discontinue isotretinoin treatment immediately if benign intracranial hypertension is developed PL section 2 and 4 where advice is given to patients not to take isotretinoin if already taking antibiotics with active substance names ending in “cycline” as these antibiotics may lead to benign increase in the skull pressure Legal status: Prescription only Additional risk minimization measures: None

Table 13-8 Important identified risk: Severe increase in triglyceride levels, sometimes associated with acute pancreatitis Overdose

Risk minimization measures	Routine risk minimization measures

	SmPC section 4.3, 4.4, 4.8 and 5.3 SmPC section 4.4, PL section 2 and 4 where recommendation is given to patients not to take isotretinoin if they have very high fat levels in blood Legal status: Prescription only Additional risk minimization measures: None

Table 13-9 Important identified risk: Severe allergic reactions

Risk minimization measures	Routine risk minimization measures SmPC section 4.3, 4.4, 4.8 and 4.9 SmPC section 4.4, PL section 2 and 4 where advice is given to patients to stop treatment and consult their doctor immediately in case of severe allergic reactions Legal status: Prescription only Additional risk minimization measures: None

Table 13-10 Important potential risk: Gastrointestinal disorders including inflammatory bowel disease

Risk minimization measures	Routine risk minimization measures SmPC section 4.4 and 4.8 Recommendations are given in SmPC section 4.4 to patients to discontinue isotretinoin immediately if experiencing severe (hemorrhagic) diarrhea PL section 2 and 4 where recommendation is given to patients to consult their doctor in case they experience gastrointestinal disorders including inflammatory bowel disease Legal status: Prescription only Additional risk minimization measures: None

Table 13-11 Missing information:

None

13.2.3 Part VI – II.C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of isotretinoin soft capsule.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-12 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Evaluation of the effectiveness of PPP for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after DUS using secondary data	In January 2016, a Pharmacovigilance Risk Assessment Committee (PRAC) review noted that there are concerns about how well the requirements of the PPP are followed in clinical practice. In July 2016, the PRAC initiated an article 31 referral (Procedure number: EMEA/H/A-31/1446) to assess the effectiveness of risk minimization in relation to the PPP. After completion of the review in March 2018, the European Medicines Agency (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 study) and a complementary survey (category 3 study) to assess the effectiveness of these updated RMMs. In June 2018, the decision to strengthen the recommendations for pregnancy prevention for oral retinoids was issued by the European Commission (EC) [(2018) 4024 of 21/06/2018]. The aim of this DUS is to describe the prescribing practices before and after the update of the PPP for the oral retinoids acitretin, alitretinoin and isotretinoin in order to assess the effectiveness of these updated RMMs in WCBP *Primary objective:* • To describe the prescribing practices in females of childbearing potential receiving prescriptions of the oral retinoids acitretin, alitretinoin, or isotretinoin during the pre- and the post-implementation period with respect to key elements of the PPP *Secondary objectives:* • To describe the patient profile, prescriber specialty and exposure characteristics during the pre-and post-implementation periods • To describe the incidence of pregnancies exposed to oral retinoids during the pre- and the post-implementation period • To describe trends in the prescribing practice of oral retinoids with respect to measures of the PPP over time covering the pre- and the post-implementation period
Patient and Prescriber Survey: Effectiveness measures to investigate awareness, knowledge and adherence to the RMMs of the PPP for Oral Retinoids (Acitretin, Alitretinoin, and Isotretinoin)	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 July 2016, the PRAC initiated an article 31 referral (Procedure number: EMEA/H/A-31/1446) 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 study) and a complementary survey (category 3 study) to assess the effectiveness of these updated RMMs. In June 2018, the decision to strengthen the recommendations for pregnancy prevention for oral retinoids was issued by the EC [(2018) 4024 of 21/06/2018]. This survey aims to provide information on the HCP and patient awareness of the PPP and RMMs during the standard clinical use of oral retinoids (acitretin, alitretinoin and isotretinoin). *Primary objective:*

Study short name	Rationale and study objectives
	• 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 HCP and patient awareness of the updated PPP • To assess HCP and patient 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