PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Toctino/Cehado (alitretinoin)

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

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

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

I. The medicine and what it is used for

Toctino is authorised for use in adults with severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids (see SmPC for the full indication). It contains alitretinoin as the active substance and it is given by the oral route of administration.

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

Important risks of Toctino, together with measures to minimise such risks and the proposed studies for learning more about Toctino's 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 Toctino, 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*.

If important information that may affect the safe use of Toctino is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Toctino 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 Toctino. 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	Foetal malformations (birth defects) Hyperlipidaemia Inflammatory Bowel Disease
Important potential risks	Neuropsychiatric disorders
	Bone demineralisation
Missing information	None

II.B Summary of important risks

Risk 1 - Important identified risk: Foetal malformations/birth defects	
Evidence for linking the risk to the medicine	Evidence originates from pregnancies exposed to other medicines in the same drug class, including isotretinoin (Browne *et al,* 2014)
Risk factors and risk groups	Females of child bearing potential
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3, Contraindications • SmPC section 4.4, Special Warnings and Precautions for Use: Pregnancy Prevention Programme • Patient leaflet, Black box • Patient leaflet, Section 2: Pregnancy Prevention Program

	• Packaging: Black box or pictogram • Pack size: Limited to 30-day supply Additional risk minimisation measures: • Educational materials for physicians, pharmacists, and patients • Patient reminder card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **Drug utilisation study to evaluate the** effectiveness of Pregnancy Prevention Programme **Patient and Prescriber survey** to evaluate effectiveness of Pregnancy Prevention Programme

Risk 2 - Important identified risk: Hyperlipidaemia	
Evidence for linking the risk to the medicine	Pooled data analysis from randomised clinical trials
Risk factors and risk groups	As known from epidemiological research, risk for hypertriglyceridaemia and hypercholesterolemia consist of pre-existing disorders of the lipid and cholesterol metabolism and increased nutritional intake of lipids and/or cholesterol. In addition, patients with high underlying CV risk, e.g. diabetes, are at increased risk from dyslipidemia.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Patient leaflet sections 2 and 4 Additional risk minimisation measures: None

Risk 3- Important identified risk: Inflammatory Bowel Disease	
Evidence for linking the risk to the medicine	Post-marketing surveillance

Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Patient leaflet sections 2 and 4 Additional risk minimisation measures: None

Risk 4 - Important potential risk: Neuropsychiatric disorders	
Evidence for linking the risk to the medicine	Safety signal observed for medicines in the same drug class (retinoids)
Risk factors and risk groups	No particular risk groups have been identified
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Patient leaflet sections 2 and 4 Additional risk minimisation measures: None

Risk 5- Important Potential risk: Bone demineralisation	
Evidence for linking the risk to the medicine	Reports from currently marketed retinoids, special safety assessment in studies BAP00089 and BAP00091
Risk factors and risk groups	Patients with pre-existing osteoporosis

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Patient leaflet section 4 Additional risk minimisation measures: None

II.C Post-authorisation development plan

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

The following study is a condition of the marketing authorisation:

Drug Utilisation Study.

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

Purpose of the Study: Therapy with systemic retinoids is associated with birth defects; therefore, women who are pregnant or are planning a pregnancy must not be prescribed retinoids. Prescription guidelines and a PPP comprising education material for patients, physicians, and pharmacists had been put in place but exposure during pregnancy still occurred. In July 2016, the EU Pharmacovigilance Risk Assessment Committee (PRAC) initiated an Article 31 referral to assess the effectiveness of risk minimisation in relation to the PPP. After completion of the review in March 2018, the European Medicines Agency (EMA) confirmed that an update of the PPP for the oral retinoids acitretin, alitretinoin and isotretinoin was needed and mandated the conduct of a DUS (category 1) The aim of this DUS is to describe prescribing practices before and after the update of the PPP in order to assess the effectiveness of the updated risk minimisation measures (RMMs).

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

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: Therapy with systemic retinoids is associated with teratogenicity; therefore, women who are pregnant or are planning a pregnancy must not be prescribed retinoids. Prescription guidelines and a PPP comprising education material for patients, physicians, and pharmacists had been put in place but exposure during pregnancy still occurred. A January 2016 PRAC review noted that there are concerns about how well the

requirements of the PPP are followed in clinical practice. Data from this review also suggested 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. This survey aims to provide information on healthcare professional (HCP) and patient awareness of the PPP and its RMMs during the standard clinical use of oral retinoids (acitretin, alitretinoin and isotretinoin).