Part VI: Summary of the risk management plan

Summary of risk management plan for Curacné® (isotretinoin)

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

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

I. The medicine and what it is used for

Curacné® is authorised for severe forms of acne (such as nodular and 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 by oral route of administration.

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

Important risks of Curacné®, together with measures to minimise such risks and the proposed studies for learning more about Curacné®'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 (RMMs)*.

In the case of Curacné®, these measures are supplemented with *additional RMMs* 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 Curacné® 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 Curacné®. 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 of isotretinoin	
Important identified risks	- Teratogenicity and congenital malformations - 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 cutaneous adverse reactions (including erythema multiforme, SJS and TEN) - Severe lipid metabolism disorders with acute pancreatitis - Transaminases increased and hepatitis
Important potential risks	- Inflammatory bowel disease (ulcerative colitis and Crohn's disease)
Missing information	None

II.B Summary of important risks

Important identified risk 1: Teratogenicity and congenital malformations	
Description of the risk title	Side effects of isotretinoin on child exposed *in utero*
Evidence for linking the risk to the medicine	Isotretinoin is a stereoisomer of all-trans retinoic acid which is teratogen. Exposure to isotretinoin during pregnancy is associated with a high risk of major foetal malformations, congenital anomaly, birth defect/severe congenital malformations (sometimes fatal) and spontaneous abortion. Post-marketing data, scientific literature, clinical trial and pharmacoepidemiologic studies bring sufficient scientific evidence to support a causal association between isotretinoin and its teratogenicity.
Risk factors and risk groups	The risk group is women of child-bearing potential exposure during the first trimester without effective method of contraception (e.g. one user independent form such as an Intra Uterine Device (IUD)) or 2 complementary forms of contraception including a barrier method (e.g. condom and contraceptive pill) for at least 1 month before beginning Curacne® treatment, throughout the duration of treatment, and for 1 month after the end of treatment.
Risk minimisation measures	<u>Routine RMMs:</u> - Outer packaging (boxed warning); - SmPC Sections 4.3, 4.4 and 4.6;

Important identified risk 1: Teratogenicity and congenital malformations	
	- PL Sections 2 and 4; - SmPC section 4.4 and PL section 2 where recommendations are given to perform pregnancy test and use of contraception; - SmPC section 4.2 and PL section 1 (prescription restricted to specialist in retinoids); - SmPC section 4.4 and PL section 2 (prescription ideally limited to 1 month and, depending on the National Competent Authority (NCA), dispensing within 7 days after the prescription). Additional RMMs (in Europe): - Pregnancy Prevention Program (PPP) - Patient Reminder Card (PRC) - Physician checklist/ ack form - Pharmacist checklist (depending on the National Competent Authority (NCA) decision). Additional RMMs depending on the MS (only in France, Luxembourg, Czech Republic, Belgium): - Index card (CZ) - Patient brochure (CZ, FR, LUX) - Examination check-list (CZ) - Physician guide (CZ, FR, LUX) - Communication letters between dermatologist initiating the treatment and the physician in charge of the patient (FR, LUX) - Communication letters between dermatologist initiating the treatment and the physician in charge of contraception (FR, LUX) - Pharmacist guide (FR, LUX) - Videos (FR) - DHPC sent every 2 years to HCPs newcomers (BE) Additional RMM depending on Competent Authority agreement at a national level: planned DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Qualitative Study – Barriers and Facilitators Assessment of the use of Risk Minimisation Measures (RMMs) of the Pregnancy Prevention Program (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 2: Psychiatric disorders (including depression, suicidality and anxiety)	
Description of the risk title	Not applicable.
Evidence for linking the risk to the medicine	In a study using functional brain imaging examining the effects of isotretinoin use among adults on the persistence of brain function in the orbitofrontal cortex, isotretinoin was associated with a 21% decrease in functioning whereas the antibiotic group experienced an increase of 2% in brain function in the orbitofrontal cortex. However, this study did not find any difference in the severity of depression between the isotretinoin group and the antibiotic group (Bremner *et al.*, 2005). The available data in relation to oral retinoids and the occurrence of neuropsychiatric disorders have a number of important limitations that preclude the establishment of a clear causal association (Magin P et al., 2005). There have concerns and controversy regarding whether isotretinoin is associated with psychiatric morbidity, including suicidality (Bremner et al., 2021). Nevertheless, the data from patients presented in case series, spontaneous case reports and individual patients' experiences are considered to be very important. Although the underlying risk of psychiatric disorders within the patient populations can be significant, it is advisable that patients taking oral Isotretinoin are warned about the potential risk of psychiatric reactions and the signs and symptoms to look out for.
Risk factors and risk groups	The patients with personal history of depression or psychotic disorders are considered at risk. Furthermore, it is recognised that patients with severe skin disorders are themselves at an increased risk of psychiatric disorders (PRAC, 2018).
Risk minimisation measures	<u>Routine RMMs:</u> - SmPC Sections 4.4 and 4.8; - PL Sections 2 and 4; - PL section 4 where symptoms of a depression or other mental problems are provided, to encourage patients to consult their doctor; - SmPC section 4.2 and PL section 1 (prescription restricted to specialist in retinoids). <u>Additional RMMs depending on the MS</u> (only in France, Luxembourg, Czech Republic): - Index card (CZ) - Patient brochure (CZ, FR, LUX) - Examination check-list (CZ) - Physician guide (CZ, FR, LUX) - Additional support tool derived from the ADRS scale (FR, LUX) - Informed consent (CZ) - Communication letters between dermatologist initiating the treatment and the physician in charge of the patient (FR, LUX) - Pharmacist guide (FR, LUX) - Videos (FR)

Important identified risk 2: Psychiatric disorders (including depression, suicidality and anxiety)	
	- DHPC sent every 2 years to HCPs newcomers (BE)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important identified risk 3: Eye disorders (including corneal opacities, reduced night vision and keratitis)	
Description of the risk title	Cornea is the clear dome on the front surface of the eye. Keratitis is a condition in which the eye's cornea becomes inflamed.
Evidence for linking the risk to the medicine	Eye disorders such as corneal opacities, reduced night vision and keratitis are class effects related to oral retinoids and are identified as ADRs for isotretinoin. There is sufficient scientific evidence in literature and on post-marketing experience data to support a causal association between isotretinoin and this risk.
Risk factors and risk groups	The risk group is patients wearing contact lenses.
Risk minimisation measures	Routine RMMs: - SmPC Sections 4.4 and 4.8; - PL Sections 2 and 4; - SmPC section 4.2 and PL section 1 (prescription restricted to specialist in retinoids). Additional RMMs: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important identified risk 4: Musculoskeletal and connective tissue disorders (including bone changes and rhabdomyolysis)	
Description of the risk title	Bone changes such as reduction in the density of the bone. Rhabdomyolysis is the breakdown of muscle fibres which leads to the release of a protein called myoglobin into the bloodstream.
Evidence for linking the risk to the medicine	The mechanism of the isotretinoin effect on muscle is unclear, but creatine phosphokinase values may return to normal when vigorous physical activity is stopped, even if isotretinoin is continued at the same or lower dosage (Landau *et al*., 2001).

Important identified risk 4: Musculoskeletal and connective tissue disorders (including bone changes and rhabdomyolysis)	
	Many of the patients had a recent history of strain physical exercise. The hypothesis that isotretinoin tends to potentiate the muscular disorders caused by the physical activity cannot be excluded. Bones changes and rhabdomyolysis are considered as identified ADRs of isotretinoin and were reported with another oral retinoid. Post marketing data and scientific literature bring sufficient scientific evidence to support a causal association between isotretinoin and this risk.
Risk factors and risk groups	The risk group is patients undergoing vigorous physical activity while on isotretinoin therapy. Risk factor is pre-existing bone demineralization would likely predispose to further retinoid-induced osteoporosis.
Risk minimisation measures	Routine RMMs: - SmPC Sections 4.4 and 4.8; - PL Sections 2 and 4; - SmPC section 4.2 and PL section 1 (prescription restricted to specialist in retinoids). Additional RMMs: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important identified risk 5: Severe cutaneous adverse reactions (including erythema multiforme, Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN))	
Description of the risk title	Erythema multiforme presents with a skin eruption characterised by a typical target lesion. There may be mucous membrane involvement. It is acute and self-limiting. Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are types of severe skin reaction. Early symptoms include fever and flu-like symptoms. A few days later the skin begins to blister and peel forming painful raw areas. Mucous membranes, such as the mouth, are also typically involved.
Evidence for linking the risk to the medicine	Type IV reactions are mediated by T cells causing 'delayed' hypersensitivity reactions. Drug-related delayed-type hypersensitivity reactions include SJS and TEN. However, the mechanism triggering by Curacne® is not known. Erythema multiforme, SJS, TEN have been reported after isotretinoin use during post-marketing experience. These severe skin reactions are considered as identified ADRs of isotretinoin. Post marketing data and

Important identified risk 5: Severe cutaneous adverse reactions (including erythema multiforme, Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN))	
	scientific literature bring sufficient scientific evidence to support a causal association between isotretinoin and this risk.
Risk factors and risk groups	No identified data.
Risk minimisation measures	Routine RMMs: - SmPC Sections 4.3, 4.4 and 4.8; - PL Sections 2 and 4; - SmPC section 4.2 and PL section 1 (prescription restricted to specialist in retinoids). Additional RMMs: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important identified risk 6: Severe lipid metabolism disorders with acute pancreatitis	
Description of the risk title	The increase of blood level of triglycerides or cholesterol can lead to pancreatitis, *i.e.* the inflammation of the pancreas.
Evidence for linking the risk to the medicine	Isotretinoin treatment alters the plasma lipids level but the mechanisms and the effects on the metabolism of triglyceride-rich lipoproteins such as chylomicrons and very-low-density lipoproteins remains unclear. Increased blood lipids, especially triglycerides that could lead to pancreatitis, have been reported with isotretinoin and other active substances that belong to oral retinoids (e.g. alitretinoin or acitretin). Lipid metabolism disorders are considered as identified ADRs of isotretinoin and there is sufficient scientific evidence in literature and on post-marketing experience data to support a causal association between isotretinoin and this risk.
Risk factors and risk groups	The risk factors are obesity, diabetes, alcoholism or lipid metabolism disorder.
Risk minimisation measures	Routine RMMs: - SmPC Sections 4.3, 4.4 and 4.8; - PL Sections 2 and 4; - SmPC section 4.4 where a check-up of the serum lipids is indicated; - PL section 4 where symptoms of a pancreatitis are provided, to encourage patients to consult their doctor; - SmPC section 4.2 and PL section 1 (prescription restricted to specialist in retinoids).

Important identified risk 6: Severe lipid metabolism disorders with acute pancreatitis	
	Additional RMMs depending on the MS (only in France, Luxembourg, Czech Republic): - Index card (CZ) - Patient brochure (CZ, FR, LUX) - Examination check-list (CZ) - Physician guide (CZ, FR, LUX) - Informed consent (CZ) - Communication letters between dermatologist initiating the treatment and the physician in charge of the patient (FR, LUX) - Pharmacist guide (FR, LUX).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important identified risk 7: Transaminases increased and hepatitis	
Description of the risk title	Transaminases are liver enzymes. Hepatitis is the inflammation of the liver.
Evidence for linking the risk to the medicine	The mechanism of hepatotoxicity is not known. Transaminases increased and hepatitis are considered as identified ADRs of isotretinoin and were reported with another oral retinoid (e.g. acitretin). Post marketing data and scientific literature bring sufficient scientific evidence to support a causal association between isotretinoin and this risk.
Risk factors and risk groups	The risk group is patients with already elevated blood transaminases before the beginning of the treatment.
Risk minimisation measures	Routine RMMs: - SmPC Sections 4.4 and 4.8; - PL Sections 2 and 4; - SmPC section 4.4 where a check-up of the liver enzymes is indicated; - PL section 4 where symptoms of a hepatitis are provided, to encourage patients to consult their doctor; - SmPC section 4.2 and PL section 1 (prescription restricted to specialist in retinoids). Additional RMMs depending on the MS (only in France, Luxembourg, Czech Republic) - Index card (CZ) - Patient brochure (CZ, FR, LUX) - Examination check-list (CZ) - Physician guide (CZ, FR, LUX) - Informed consent (CZ)

Important identified risk 7: Transaminases increased and hepatitis	
	- Communication letters between dermatologist initiating the treatment and the physician in charge of the patient (FR, LUX) - Pharmacist guide (FR, LUX).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important potential risk 1: Inflammatory Bowel Disease (IBD) (ulcerative colitis and Crohn's disease)	
Description of the risk title	Inflammatory bowel disease (IBD) is an umbrella term used to describe disorders that involve chronic inflammation of the digestive tract.
Evidence for linking the risk to the medicine	Although a definite mechanism of action between the use of isotretinoin and IBD have been found, isotretinoin has been associated with IBD (including regional ileitis) in patients without a prior history of intestinal disorders. Same ADR has been reported with another oral retinoid (e.g. acitretin). Post marketing data and scientific literature bring sufficient scientific evidence to suspect a causal association between isotretinoin and this risk.
Risk factors and risk groups	No proven data available.
Risk minimisation measures	Routine RMMs: - SmPC Sections 4.4 and 4.8; - PL Sections 2 and 4; - PL section 4 where symptoms of an IBD are provided, to encourage patients to consult their doctor; - SmPC section 4.2 and PL section 1 (prescription restricted to specialist in retinoids). Additional RMMs: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Curacné®.

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

The following study is a study not considered as a condition of the marketing authorisation:

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Qualitative study Planned	To investigate the barriers and reasons why certain conditions stated in the PPP are not always followed in practice	Teratogenicity and congenital malformations	Protocol submission	11-Apr-2024
			Final report *(to be confirmed)*	December 2025