PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR RUXOLITINIB CREAM

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

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

This summary of the RMP for ruxolitinib cream should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I THE MEDICINE AND WHAT IT IS USED FOR

Ruxolitinib cream is authorised for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age (see SmPC for the full indication). It contains ruxolitinib phosphate as the active substance and it is applied topically.

Further information about the evaluation of ruxolitinib cream's benefits can be found in ruxolitinib cream's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of ruxolitinib cream, together with measures to minimise such risks and the proposed studies for learning more about ruxolitinib cream'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 (eg, 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, 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 ruxolitinib cream is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of ruxolitinib cream are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely applied. 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 ruxolitinib cream. 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 (eg, on the long-term use of the medicine).

Table II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Non-melanoma skin cancer at long-term use Embryo-foetal toxicity
Missing information	Impaired bone growth and development in paediatric patients < 18 years of age

II.B Summary of Important Risks

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

Important potential risk: Non-melanoma skin cancer at long-term use	
Evidence for linking the risk to the medicine	Non-melanoma skin cancer (NMSC) is considered a class effect of oral JAK inhibitors. A causal relationship between NMSC and oral ruxolitinib has not been established. Non-melanoma skin cancers, predominantly basal cell carcinomas have been reported in patients treated with topical ruxolitinib. Most of these patients had risk factors, such as prior phototherapy or prior NMSC. A causal relationship to topical ruxolitinib has not been established based on available safety data. A 52-week follow-up is not considered sufficient to determine if ruxolitinib cream could contribute to the induction of NMSC.

Important potential risk: Non-melanoma skin cancer at long-term use	
	Based on the limited long-term follow-up and because NMSC is considered a potential class effect of oral JAK inhibitors, NMSC at long-term use of topical ruxolitinib will continue to be monitored as an important potential risk.
Risk factors and risk groups	While the role of ultraviolet radiation in the pathogenesis of squamous cell carcinoma is undisputable, it has also been cited as the most important risk factor in the development of basal cell carcinoma (Bhari et al 2016, Situm et al 2008). Basal cell carcinoma, has been reported in patients with vitiligo treated with phototherapy. This may be explained by the mechanism of thymine dimer formation and cumulative DNA damage by ultraviolet light, which results in numerous mutations and local immune system depression leading to decreased immune surveillance for new tumor cells (Situm et al 2008). In the Phase 2/3 Vitiligo Population, 29.6% of participants had received phototherapy prior to enrolling in the studies. Other risk factors include patients with a personal or family history of NMSC or pre-malignant skin lesions, sun beds, skin type 1 or 2, immunosuppression, occupational exposure to chemicals (coal tar, creosote, arsenic, radium or pitch) and previous radiotherapy (Situm et al 2008, Perera 2014).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study INCB88888-037 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	There are limited data from the use of ruxolitinib in pregnant women. Data on systemic absorption of topical ruxolitinib during pregnancy are lacking. There could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure. Embryo-foetal toxicity was observed following oral administration of ruxolitinib to rats and rabbits during gestation; similar findings have been identified in nonclinical studies with other JAK inhibitors. The conclusions from the non-clinical data point to a potential relevant risk in humans. Additionally, human PK data

Important potential risk: Embryo-foetal toxicity	
	show that there is a non-negligible systemic exposure after ruxolitinib cream application, so negative effects from dermal use of ruxolitinib during pregnancy on developing foetus cannot be entirely excluded.
Risk factors and risk groups	Women of child bearing potential not using effective contraception.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.6 Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Missing information: Impaired bone growth and development in paediatric patients < 18 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 5.3 Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of ruxolitinib cream.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study INCB88888-037: Evaluation of the Incidence of Non-Melanoma Skin Cancer after Long-term exposure to Ruxolitinib Cream

Purpose of the Study: Recent data have been published that draw a relationship between JAK inhibitors and NMSC, including basal cell and squamous cell carcinomas (Lin et al 2022, Greif et al 2021). Such literature findings have suggested that in chronic inflammatory conditions, patients with such underlying disease may also be at risk for outcomes of NMSC. Upon review of the marketing application for ruxolitinib cream, and in alignment with previously published safety risks concerning oral JAK inhibitors, the European Medicines Agency requested consideration of a non-interventional clinical study to evaluate the relationship

between the long-term use of ruxolitinib cream for vitiligo, and the development of non-melanoma skin cancers.

Study INCB 18424-308: A Double-Blind, Vehicle-Controlled, Randomized Withdrawal, and Treatment Extension Study to Assess the Long-Term Efficacy and Safety of Ruxolitinib Cream in Participants with Vitiligo (TRuE-V LTE)

Purpose of the Study:

This study is designed to evaluate the duration of response following withdrawal of ruxolitinib cream (Cohort A vehicle group) and maintenance of response with continued use of ruxolitinib cream in individuals with vitiligo who have experienced repigmentation with ruxolitinib cream treatment. This study is also designed to characterize the long-term efficacy and safety profile of ruxolitinib cream in individuals with vitiligo treated for up to a total of 104 weeks.

Study INCB 18424-309: Double-blind, randomised, placebo-controlled trial to evaluate efficacy and safety of ruxolitinib cream in children from 6 years to less than 12 years of age with non-segmental vitiligo

Purpose of the Study:

To evaluate efficacy and safety of ruxolitinib cream in children from 6 years to less than 12 years of age with non-segmental vitiligo.