ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Opzelura 15 mg/g cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of cream contains 15 mg of ruxolitinib (as phosphate).

Excipients with known effect

Propylene glycol (E1520), 150 mg/g of cream
Cetyl alcohol, 30 mg/g of cream
Stearyl alcohol, 17.5 mg/g of cream
Methyl parahydroxybenzoate (E218), 1 mg/g of cream
Propyl parahydroxybenzoate, 0.5 mg/g of cream
Butylated hydroxytoluene (as an antioxidant in paraffin, white soft) (E321)
Polysorbate 20 (E432)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream

White to off-white cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Opzelura is indicated for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age.

4.2 Posology and method of administration

Opzelura should be initiated and supervised by physicians with experience in the diagnosis and treatment of non-segmental vitiligo.

Posology

Adults

The recommended dose is a thin layer of cream applied twice daily to the depigmented skin areas up to a maximum of 10% of body surface area (BSA), with a minimum of 8 hours between two applications of ruxolitinib cream. 10% BSA represents an area as large as 10 times the palm of one hand with the 5 fingers. Ruxolitinib cream should be used at the smallest skin area necessary.

No more than two tubes of 100 grams a month should be used.

Satisfactory repigmentation may require treatment beyond 24 weeks. If there is less than 25% repigmentation in treated areas at week 52, treatment discontinuation should be considered.

Once satisfactory repigmentation is achieved, treatment in those areas can be stopped. If depigmentation recurs after treatment discontinuation, therapy can be reinitiated on the affected areas.

There is no need to consider tapering therapy.

Special populations

Hepatic impairment

No studies with ruxolitinib cream have been performed in patients with hepatic impairment. However, due to limited systemic exposure, dose adjustment is not necessary in patients with hepatic impairment.

Renal impairment

No studies with ruxolitinib cream have been performed in patients with renal impairment. However, due to limited systemic exposure, dose adjustment is not necessary in patients with renal impairment. As a precautionary measure, ruxolitinib cream should not be used by patients with end stage renal disease, due to lack of data regarding the safety.

Elderly

A limited number of patients aged 65 years and above have been enrolled in the clinical studies with Opzelura in vitiligo to determine whether they respond differently from younger subjects (see section 5.1). No dose adjustment is required in patients aged 65 years and above.

Paediatric population

For adolescents (12-17 years) the posology is the same as for adults.

The safety and efficacy of ruxolitinib cream in children below 12 years of age have not been established. No data are available.

Method of administration

The cream is for cutaneous use only.

Avoid washing treated skin for at least 2 hours after application of ruxolitinib cream.

The cream should not be applied to the lips to avoid its ingestion.

Patients should be instructed to wash their hands after applying the cream, unless it is their hands that are being treated. If someone else applies the cream to the patient, they should wash their hands after application.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Pregnancy and breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

The cream is not for ophthalmic, oral, or intravaginal use (see section 4.2). In cases of accidental exposure in the eyes or mucous membranes, the cream should be thoroughly wiped off and/or rinsed with water.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs), 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. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Excipients with known effect

Propylene glycol
This medicinal product contains 150 mg propylene glycol (E1520) in each gram of cream which may cause skin irritation.

Cetyl alcohol and stearyl alcohol
This medicinal product contains cetyl alcohol and stearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).

Parahydroxybenzoates
This medicinal product contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

Butylated hydroxytoluene
This medicinal product contains butylated hydroxytoluene (E321) which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Polysorbate 20
This medicinal product contains polysorbate 20 (E432) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with topically administered ruxolitinib.

The potential for interactions with ruxolitinib is considered to be low because of the limited systemic exposure following topical administration.

Based on *in vitro* data, ruxolitinib is predominantly cleared by cytochrome P450 3A4 (CYP3A4) metabolism. Interaction potential was evaluated for oral ruxolitinib in dedicated clinical pharmacology studies that included co-administration of strong or moderate CYP3A4 inhibitors or a strong inducer. The plasma AUC is approximately doubled with co-administration of a potent inhibitor of CYP3A4 while only a modest increase was seen with co-administration of a moderate CYP3A4 inhibitor.

The use of ruxolitinib cream in combination with other topical medicinal products used to treat vitiligo has not been evaluated and co-application on the same skin areas is not recommended. The efficacy and safety of the combination of ruxolitinib cream with narrow-band ultraviolet B (NB-UVB) phototherapy has not been established; no recommendation can be made.

Other topical medicinal products used to treat other conditions on the same skin areas should be applied with a minimum of 2 hours after the application of ruxolitinib cream. This is also applicable to the use of sunscreen or emollients.

4.6 Fertility, pregnancy and lactation

Contraception in women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and for 4 weeks after discontinuation of treatment.

Pregnancy

There are no or limited amount of data from the use of ruxolitinib in pregnant women. Data on systemic absorption of topical ruxolitinib during pregnancy are lacking. There could also be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure. Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic following oral administration. Teratogenicity was not observed in rats or rabbits (see section 5.3). Opzelura is contraindicated during pregnancy (see section 4.3).

Breast-feeding

No data are available regarding the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production after topical application of Opzelura. Following oral administration of ruxolitinib to lactating rats, ruxolitinib and/or its metabolites were present in the milk with a concentration 13-fold higher than the maternal plasma concentration. In juvenile rat studies, oral administration of ruxolitinib resulted in effects on growth and bone measures (see section 5.3). Opzelura is contraindicated during breast-feeding (see section 4.3) and treatment must be discontinued approximately 4 weeks before the beginning of breastfeeding.

Fertility

There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effect of oral ruxolitinib on fertility was observed.

4.7 Effects on ability to drive and use machines

Ruxolitinib cream has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction is application site acne (5.8%).

Tabulated list of adverse reactions

Adverse reactions are ranked under headings of frequency, with the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System Organ Class	Frequency	Adverse Reaction
General disorders and administration site conditions	Common	Application site acne

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose following cutaneous administration is unlikely. If too much of the cream has been applied, the excess can be wiped off.

In cases of accidental ophthalmic, oral mucosa, or intravaginal exposure, the cream should be thoroughly wiped off and/or rinsed with water (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH09

Mechanism of action

Ruxolitinib is a Janus Kinase (JAK) inhibitor with selectivity for the JAK1 and JAK2 isoforms. Intracellular JAK signalling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, and subsequent modulation of gene expression. Autoimmune IFNγ producing cytotoxic T lymphocytes are thought to be directly responsible for melanocyte destruction in human vitiligo. Recruitment of cytotoxic lymphocytes to lesional skin is mediated via IFNγ dependent chemokines, such as CXCL10. Downstream signalling of IFNγ is JAK1/2 dependent and treatment with ruxolitinib reduces CXCL10 levels in vitiligo patients.

Clinical efficacy and safety

Efficacy
Two double-blind, randomised, vehicle-controlled studies of identical design (TRuE-V1 and TRuE-V2) enrolled a total of 674 patients who have vitiligo on the face and total body vitiligo area (facial and nonfacial) not exceeding 10% BSA, with disease extent at initiation ranging from 3.2% to 10.1% of BSA, aged 12 years and older (10.7% of patients were 12 to 17 years of age and 6.7% were 65 years or older). Females constituted 53.1% of patients, 81.9% of patients were White, 4.7% were Black, and 4.2% were Asian. The majority of patients had Fitzpatrick skin types III, IV, V, or VI (67.5%).

In both studies, patients were randomised 2:1 to treatment with ruxolitinib cream or vehicle twice daily for 24 weeks with affected BSA not exceeding 10%, followed by an additional 28 weeks of treatment with ruxolitinib cream BID for all patients. The primary efficacy endpoint was the proportion of patients achieving a 75% repigmentation in the facial Vitiligo Area Scoring Index (F-VASI75) at week 24. Key secondary endpoints included the proportions of patients achieving a 90% repigmentation in F-VASI (F-VASI90), 50% improvement in total body Vitiligo Area Scoring Index (T-VASI50), and a Vitiligo Noticeability Scale (VNS) score of 4 or 5 (vitiligo "a lot less noticeable" or "no longer noticeable").

Repigmentation of treated vitiligo lesions and superiority of ruxolitinib cream over vehicle cream were observed for both studies, as demonstrated by statistically significant differences in response rates for F-VASI75/90, T-VASI50, and VNS score of 4 or 5 at week 24 (Table 2).

The treatment effect difference from vehicle emerges numerically as early as week 12. Continued repigmentation as assessed by VASI and VNS scores was observed through week 52 for patients who had continuously applied ruxolitinib cream twice daily from baseline. The proportion of patients who achieved F-VASI75 over the 52-week treatment period in pooled data from study TRuE-V1 and TRuE-V2 are shown in Figure 1.

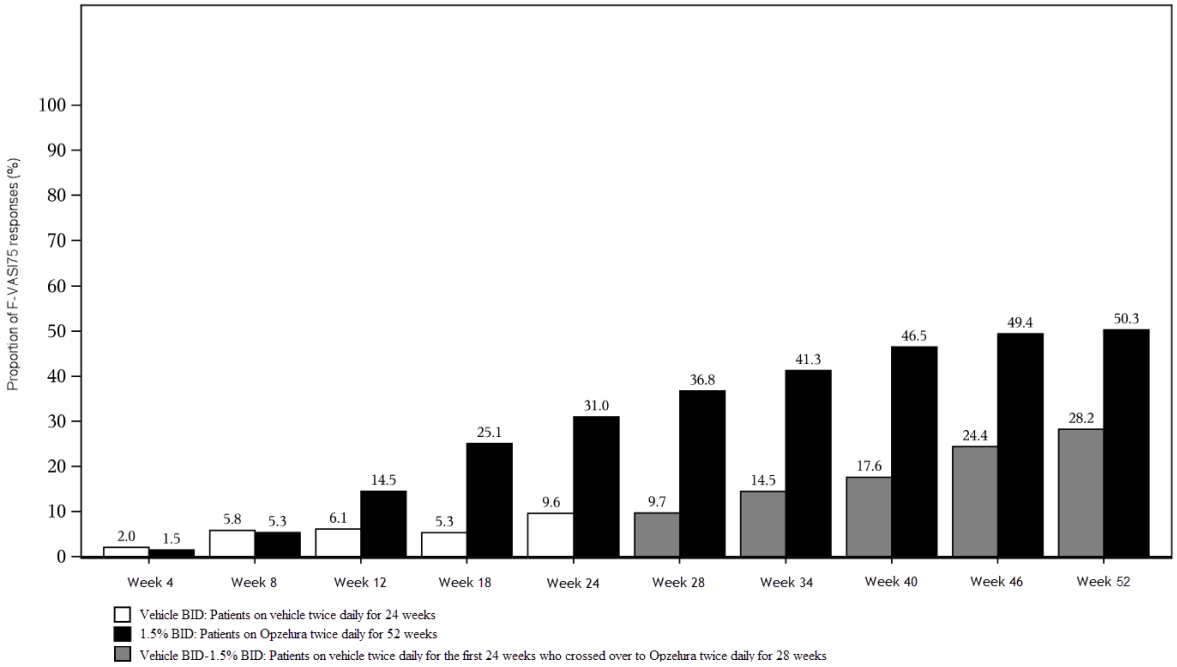
Similar treatment responses at week 52 are seen for those who crossed over from vehicle to ruxolitinib (Figure 1).

Table 2: Percent of patients with vitiligo achieving the primary and key secondary endpoints at week 24 (intent-to-treat)[a]

	TRuE-V1		TRuE-V2	
	Opzelura	**Vehicle**	**Opzelura**	**Vehicle**
	(N = 221)	(N = 109)	(N = 222)	(N = 109)
F-VASI75 (%)	29. 8	7. 4	30.9	11.4
Response rate difference (95% CI)	22.3[b] (14.214, 30.471)	-	19.5[c] (10.537, 28.420)	-
F-VASI90 (%)	15. 3	2.2	16.3	1.3
Response rate difference (95% CI)	13.2[d] (7.497, 18.839)	-	15.0[e] (9.250, 20.702)	-
T-VASI50 (%)	20.6	5.1	23.9	6.8
Response rate difference (95% CI)	15.5[d] (8.339, 22.592)	-	17.1[c] (9.538, 24.721)	-
VNS 4 or 5 (%)	24.5	3.3	20.5	4.9
Response rate difference (95% CI)	21.2[c] (14.271, 28.143)	-	15.5[d] (8.515, 22.561)	-

[a] Primary and key secondary outcomes were corrected using multiple imputation method.
[b] p-value < 0.0001
[c] p-value < 0.001
[d] p-value < 0.005
[e] p-value < 0.01

Figure 1: Proportion of patients achieving F-VASI75 during the 52 week treatment period (Intent-to-treat) – pooled data from study TRuE-V1 and TRuE-V2



At week 52, the observed response rate for F-VASI90, T-VASI50 and VNS was 30.3%, 51.1%, and 36.3% respectively for the ITT pooled population.

Durability of response

A Phase 3, double-blind, vehicle-controlled, randomised, withdrawal and treatment-extension study of ruxolitinib cream twice daily enrolled 458 eligible patients with vitiligo who had completed either of the parent studies using ruxolitinib (TRuE-V1 and TRuE-V2; week 52); patients were assigned to either cohort A or B with a follow-up up to 104 weeks.

Cohort A comprised 116 patients who reached ≥ F-VASI90 at week 52 of the parent study. These patients were re-randomised to either ruxolitinib or vehicle (i.e. withdrawal) to study relapse (< F-VASI75). A relapse occurred in 15% of patients in the ruxolitinib group, and in 29% of patients in the vehicle group. In the latter group, the majority of relapses (9/16) occurred during the first 4 months after stopping ruxolitinib cream. Among the 16 patients in the vehicle group who relapsed and were retreated, re-treatment resulted in a regained F-VASI75 in 12 (75%) patients in a median of 12 weeks and F-VASI90 was regained by 11 (69%) patients in a median of 15 weeks.
Cohort B comprised 342 patients who reached < F-VASI90 at week 52 of the parent study. These patients continued with open-label ruxolitinib treatment; at week 104, among patients originally randomised to ruxolitinib cream twice daily, 66% reached F-VASI75, and 34% reached F-VASI90.

Safety
Safety in the long-term extension study up to 104 weeks cumulatively was consistent with the profile reported in the parent studies up to 52 weeks.

Paediatric population

A total of 72 adolescents (12 to < 18 years; n = 55 ruxolitinib cream, n = 17 vehicle) were included in the pivotal studies. Adolescents showed equal response rates in primary and key secondary endpoints at 24 weeks when treated with ruxolitinib, as compared to adults from 18-65 years of age.

The European Medicines Agency has deferred the obligation to submit the results of studies with Opzelura in one or more subsets of the paediatric population for the treatment of vitiligo (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of ruxolitinib cream were investigated in 429 subjects with vitiligo aged 12 years and older (12.6% were 12-17 years of age) with a mean ± STD BSA involvement of 7.31 ± 2.02% (range 3.2% to 10.0%). Subjects applied approximately 1.58 mg/cm^2 of ruxolitinib cream (dose range was approximately 0.18 grams to 8.4 grams of ruxolitinib cream per application) to the same skin areas twice daily for 24 weeks.

The mean ± STD steady-state trough plasma concentrations was 56.9 ± 62.6 nM with a projected $AUC_{0\text{-}12h}$ at 683 ± 751 h*nM, which is approximately 25% of the observed mean $AUC_{0\text{-}12h}$ at steady state (2716 h*nM) following 15 mg twice daily oral administration in healthy participants. The mean (geometric mean) topical bioavailability for ruxolitinib cream in vitiligo participants in the pooled data of the two Phase 3 studies was 9.72% (5.78%).

Distribution

Based on an *in vitro* study, ruxolitinib is 97% bound to human plasma proteins, mostly to albumin.

Biotransformation

Ruxolitinib is metabolised by CYP3A4 and to a lesser extent by CYP2C9.

Elimination

The mean elimination half-life of orally administered ruxolitinib is approximately 3 hours. The mean apparent terminal half-life of ruxolitinib following topical application of Opzelura was estimated in 9 adult and adolescent patients with ≥ 25% BSA involvement with atopic dermatitis and is approximately 116 hours, reflecting the slow drug absorption rate rather than the drug elimination rate.

Special populations

Renal impairment
The estimated AUC which is adjusted for the pharmacological activity of ruxolitinib plus the metabolites increases approximately two-fold in case of end stage renal disease (ESRD). As a precautionary measure, Opzelura should not be used by patients with ESRD, due to lack of data regarding the safety.

Hepatic impairment
Although the AUC was increased following oral administration of ruxolitinib to patients with hepatic impairment, there was no clear relationship between the severity of hepatic impairment and the increase in AUC. A dosing advice for patients with hepatic impairment is not necessary.

5.3 Preclinical safety data

Ruxolitinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity, and carcinogenicity studies following oral administration. Additional studies were conducted following dermal administration in minipigs and mice. Target organs associated with the pharmacological action of ruxolitinib in repeated dose oral studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Margins (based on unbound AUC) at non-adverse levels in chronic toxicity studies were approximately 6- and 200-fold in male and female rats, and 10-fold in dogs, relative to systemic exposure observed in patients with vitiligo that applied 1.5% ruxolitinib cream twice daily. Adverse decreases in blood pressure along with increases in heart rate were noted in a dog telemetry study, and an adverse decrease in minute volume was noted in a respiratory study in rats. The margins (based on unbound C_{max}) at the non-adverse level in the dog and rat studies were approximately 300-fold and 100-fold greater, respectively, than systemic exposure observed in patients with vitiligo that applied 1.5% ruxolitinib cream twice daily. No adverse effects were noted in an evaluation of the neuropharmacological effects of ruxolitinib in rats.

A 3-month dermal repeat dose study revealed decreased lymphocyte counts in mice. Margins (based on unbound AUC) at non-adverse levels were approximately 10-fold in male and 24-fold in female mice relative to systemic exposure observed in patients with vitiligo that applied 1.5% ruxolitinib cream twice daily. Non-adverse decreased peripheral lymphocyte counts were also noted in minipigs in a 9-month dermal toxicity study. Margins (based on unbound AUC) at non-adverse levels in minipigs were approximately 3-fold relative to systemic exposure observed in patients with vitiligo that applied 1.5% ruxolitinib cream twice daily. This effect was not observed in a 3-month dermal toxicity study in minipigs. No evidence of systemic toxicity was observed in Gottingen minipigs following topical administration of 1.5% ruxolitinib cream formulation twice daily for up to 9 months.

In juvenile rat studies, oral administration of ruxolitinib resulted in effects on growth and bone measures. Reduced bone growth was observed at doses ≥ 5 mg/kg/day when treatment started on postnatal day 7 (comparable to human newborn) and at ≥ 15 mg/kg/day when treatment started on postnatal days 14 or 21 (comparable to human infant, 1–3 years). Fractures and early termination of rats were observed at doses ≥ 30 mg/kg/day when treatment was started on postnatal day 7. Based on unbound AUC, the exposure at the NOAEL (no observed adverse effect level) in juvenile rats treated as early as postnatal day 7 was approximately 20-fold that of adult patients with vitiligo, while reduced bone growth and fractures occurred at exposures that were 22- and 150-fold that of adult patients with vitiligo, respectively. The effects were generally more severe in males and when administration was initiated earlier in the postnatal period. Other than bone development, the effects of ruxolitinib in juvenile rats were similar to those in adult rats. Juvenile rats are more sensitive than adult rats to ruxolitinib toxicity.

In embryofetal development studies, oral administration of ruxolitinib to rats and rabbits during gestation resulted in decreased foetal weight and increased post-implantation loss at doses associated with maternal toxicity. There was no evidence of a teratogenic effect in rats and rabbits. Margins (based on unbound AUC) at non-adverse levels for developmental toxicity in rats were approximately 25-fold the systemic exposure observed in patients with vitiligo that applied 1.5% ruxolitinib cream twice daily. No effects of oral ruxolitinib were noted on fertility in male or female rats. In a pre- and postnatal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. Ruxolitinib was not mutagenic or clastogenic. Ruxolinitib showed no carcinogenic potential following topical administration in mice or following oral administration in Sprague-Dawley rats and Tg.rasH2 mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxytoluene (as an antioxidant in paraffin, white soft) (E321)
Cetyl alcohol
Dimeticone (E900)
Disodium edetate (E385)
Self -emulsifying Glyceryl stearate
Macrogol
Medium chain triglycerides
Methyl parahydroxybenzoate (E218)
Paraffin (E905), Liquid light
Paraffin (E905), White soft
Phenoxyethanol
Polysorbate 20 (E432)
Propylene glycol (E1520)
Propyl parahydroxybenzoate
Purified water
Stearyl alcohol
Xanthan gum (E415)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

21 months

After first opening: 6 months.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Laminate tube with an inner lining of low-density and high-density polyethylene with a polypropylene cap, or aluminium tube with internal lacquer coating with a polypropylene puncture cap.

Tube of 100 g. One tube per carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1726/001
EU/1/23/1726/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 April 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton (aluminium tube)

1. NAME OF THE MEDICINAL PRODUCT

Opzelura 15 mg/g cream
ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g of cream contains 15 mg of ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Butylated hydroxytoluene (E321), cetyl alcohol, dimeticone (E900), disodium edetate (E385), glyceryl stearate, paraffin (E905), macrogol, medium chain triglycerides, methyl parahydroxybenzoate (E218), phenoxyethanol, polysorbate 20 (E432), propylene glycol (E1520), propyl parahydroxybenzoate, purified water, stearyl alcohol and xanthan gum (E415).

4. PHARMACEUTICAL FORM AND CONTENTS

Cream

1 tube (100 g)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1726/001 1 tube (100 g)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Opzelura

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton (laminate tube)

1. NAME OF THE MEDICINAL PRODUCT

Opzelura 15 mg/g cream
ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g of cream contains 15 mg of ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Butylated hydroxytoluene (E321), cetyl alcohol, dimeticone (E900), disodium edetate (E385), glyceryl stearate, paraffin (E905), macrogol, medium chain triglycerides, methyl parahydroxybenzoate (E218), phenoxyethanol, polysorbate 20 (E432), propylene glycol (E1520), propyl parahydroxybenzoate, purified water, stearyl alcohol and xanthan gum (E415).

4. PHARMACEUTICAL FORM AND CONTENTS

Cream

1 tube (100 g)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1726/002 1 tube (100 g)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Opzelura

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

TUBE (printed tube or label, aluminium tube) (100 g)

1. NAME OF THE MEDICINAL PRODUCT

Opzelura 15 mg/g cream
ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g of cream contains 15 mg of ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

E321, cetyl alcohol, E900, E385, glyceryl stearate, E905, macrogol, medium chain triglycerides, E218, phenoxyethanol, E432, E1520, propyl parahydroxybenzoate, purified water, stearyl alcohol and E415.

4. PHARMACEUTICAL FORM AND CONTENTS

Cream

100 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Incyte Biosciences Distribution B.V. (as Incyte logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1726/001 1 tube (100 g)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

TUBE (printed tube, laminate tube) (100 g)

1. NAME OF THE MEDICINAL PRODUCT

Opzelura 15 mg/g cream
ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g of cream contains 15 mg of ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

E321, cetyl alcohol, E900, E385, glyceryl stearate, E905, macrogol, medium chain triglycerides, E218, phenoxyethanol, E432, E1520, propyl parahydroxybenzoate, purified water, stearyl alcohol and E415.

4. PHARMACEUTICAL FORM AND CONTENTS

Cream

100 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

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EU/1/23/1726/002 1 tube (100 g)

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B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Opzelura 15 mg/g cream
ruxolitinib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Opzelura is and what it is used for

Opzelura contains the active substance ruxolitinib. It belongs to a group of medicines called Janus kinase inhibitors.

Opzelura is used on the skin to treat vitiligo with facial involvement in adults and adolescents from 12 years. Vitiligo is an autoimmune disease, where the body's immune system attacks the cells that produce the skin pigment melanin. This causes a loss of melanin, leading to patches of pale pink or white skin. In vitiligo, ruxolitinib reduces the immune system's activity against the melanin-producing cells, allowing the skin to produce pigment and regain its normal colour.

2. What you need to know before you use Opzelura

Do not use Opzelura
- if you are allergic to ruxolitinib or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or breastfeeding.

Warnings and precautions
Talk to your doctor or pharmacist before using Opzelura.

Opzelura is not for use on the lips, in the eyes, mouth or vagina. If cream accidentally gets into these areas, thoroughly wipe off and/or rinse off the cream with water.

Children under 12 years
Do not give Opzelura to children younger than 12 years because it has not been studied in this age group.

Other medicines and Opzelura
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Using Opzelura at the same time as other medicines on the affected skin is not recommended, as it has not been studied.

After applying Opzelura, wait at least 2 hours before applying other medicines, sunscreen or body creams/oils to the same skin area.

Pregnancy and breast-feeding
Opzelura should not be used by pregnant or breast-feeding women as this has not been investigated. If you are a woman of childbearing age, you should use an effective contraception during treatment and during 4 weeks after applying Opzelura for the last time.

It is not known if ruxolitinib passes into breast milk after applying it to the skin. The effects of this medicine in breastfed infants are unknown; therefore, Opzelura should not be used if you are breast-feeding or planning to breastfeed. You may start breast-feeding approximately four weeks after applying Opzelura for the last time.

Driving and using machines
Opzelura is unlikely to have an effect on your ability to drive and use machines.

Opzelura contains propylene glycol, cetyl alcohol, stearyl alcohol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, butylated hydroxytoluene and polysorbate 20
- This medicine contains 150 mg propylene glycol (E1520) in each gram of cream, which may cause skin irritation.
- Cetyl alcohol and stearyl alcohol may cause local skin reactions (e.g. contact dermatitis).
- Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed).
- Butylated hydroxytoluene (E321) may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.
- Polysorbates can cause allergic reactions.

3. How to use Opzelura

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose
- Apply a thin layer of cream twice daily to affected areas of your skin. Wait at least 8 hours between applications.
- The cream should not be used on more than 10% (one tenth) of your body. This surface area represents the equivalent to ten times the palm of one hand with the five fingers.

Method of administration
- This medicine is for use on the skin only.
- Do not apply to skin surfaces other than the ones instructed by your doctor. The medicine should be used at the smallest skin area necessary.
- Wash your hands after applying this medicine, unless you are treating your hands. If someone applies this medicine to you, they should wash their hands after application.
- Avoid washing treated skin for at least 2 hours after application of Opzelura.

Duration of use
Your doctor will decide how long you should use the cream for.
A minimum duration of 6 months is recommended but satisfactory treatment may require over 12 months. If you achieve satisfactory repigmentation of treated areas, consult your doctor to discuss if treatment of those areas could be stopped. Consult your doctor if you experience loss of repigmentation after stopping treatment.

Do not use more than two 100 gram tubes a month.

If you use more Opzelura than you should
Wipe off the excess cream if this occurs.

If you forget to use Opzelura
If you forget to apply the cream at the scheduled time, do it as soon as you remember, then continue your normal dosing schedule. However, if the next scheduled dose is due within 8 hours, skip the missed dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported with Opzelura:
Common (may affect up to 1 in 10 people)
- acne at application site

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Opzelura

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the tube and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30 ºC.

Once the tube has been opened, use the cream within 6 months but not after the expiry date.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Opzelura contains
- The active substance is ruxolitinib.
  One gram of cream contains 15 mg of ruxolitinib.
- The other ingredients are butylated hydroxytoluene (E321), cetyl alcohol, dimeticone (E900), disodium edetate (E385), glyceryl stearate, paraffin (E905), macrogol, medium chain triglycerides, methyl parahydroxybenzoate (E218), phenoxyethanol, polysorbate 20 (E432),

propylene glycol (E1520), propyl parahydroxybenzoate, purified water, stearyl alcohol, xanthan gum (E415).

See section 2 “Opzelura contains propylene glycol, cetyl alcohol, stearyl alcohol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, butylated hydroxytoluene and polysorbate 20”.

What Opzelura looks like and contents of the pack
Opzelura cream is coloured white to off-white, supplied in a tube containing 100 g cream. There is one tube per carton.

Marketing Authorisation Holder and Manufacturer
Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu