VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Atopic dermatitis/ eczema (a condition that makes skin red and itchy):

Atopic dermatitis (AD) is a common skin condition with significant associated social and financial burden. AD affects adults and children with worldwide presence rates of 1-20%. Study of epidemiology and geographic variability in presence of AD has been conducted in three phases with 1,000,000 patients in study. Presence continues to vary and has changed in different regions of the world. Nigeria, the United Kingdom and New Zealand had been areas of the highest presence; Latin America has emerged as a region of relatively high presence in follow up data. The presence of AD seems to have reached a plateau around 20% in countries with highest presence, suggesting that AD may not be on a continued rise but that a finite number of individuals may be susceptible to the condition. Risk factors associated with increased presence include higher socioeconomic status, higher level of family education, smaller family size and urban environment.

VI.2.2 Summary of treatment benefits

In a six-month study, 0.1% tacrolimus ointment was administered twice-a-day to adults with moderate to severe atopic dermatitis and compared to a topical corticosteroid based regimen. The primary endpoint was the response rate at month 3 defined as the proportion of patients with at least 60% improvement in the atopic dermatitis between baseline and month 3. The response rate in the 0.1% tacrolimus group was significantly higher than that in the topical corticosteroid based treatment group.

In the second study, children aged from 2 to 15 years with moderate to severe atopic dermatitis received twice daily treatment for three weeks of 0.03% tacrolimus ointment, 0.1% tacrolimus ointment or 1% hydrocortisone acetate ointment. The results of this study showed that tacrolimus ointment, 0.03% and 0.1%, is significantly more effective than 1% hydrocortisone acetate ointment.

Accord Healthcare Limited has performed Therapeutic Equivalence Study of Two Tacrolimus 0.1% Topical Ointment Formulations comparing with innovator formulation in 630 Adult Patients with Moderate to Severe Atopic Dermatitis.

From the study it was concluded that the test product is therapeutic equivalent to innovator product (Protopic®) and superior to Placebo.

VI.2.3 Unknowns relating to treatment benefits

Safety and efficacy of Tacrolimus ointment in children under 2 years of age have not been established.

Safety and efficacy of Tacrolimus ointment for maintenance treatment beyond 12 months have not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Severe itching of the skin where tacrolimus ointment apply (Application site pruritus/irritation/burning)	While using tacrolimus ointment, patient experienced burning sensation and itching very common (may affect more than 1 in 10 people)	Talk to your doctor if you have burning sensation and itching on the site where tacrolimus ointment is applied.
An abnormal sensation, typically tingling or pricking ('pins and needles'), caused chiefly by pressure on or damage to peripheral nerves (Paraesthesia)	While using tacrolimus ointment, patient experienced skin tingling commonly (may affect up to 1 in 10 people)	Talk to your doctor if you have skin tingling with tacrolimus ointment.

Risk	What is known	Preventability
Flushes or blotches associated with erythema on the face, neck, shoulders, and in some cases, the entire body after consuming alcoholic beverages (Alcohol flushing)	While using tacrolimus ointment, drinking alcohol may cause the skin or face to become flushed or red and feel hot and patient commonly (may affect up to 1 in 10 people) experienced facial flushing or skin irritation after drinking alcohol is also common	Do not drink alcohol while using tacrolimus ointment as it cause facial flushing or skin irritation.
Type of viral infection (Folliculitis /herpes simplex)	Like all medicines, Tacrolimus ointment can cause side effects, although not everybody gets them. Common (may affect up to 1 in 10 people): Local skin infection regardless of specific cause including but not limited to: inflamed or infected hair follicles, cold sores, generalised herpes simplex infections.	Talk to your doctor if you have any such side effects.
Increase in Systemic absorption of tacrolimus with defects of skin barrier (Systemic absorption in conjunction	The use of tacrolimus ointment is not recommended in patients with a skin barrier defect such as Netherton's syndrome, lamellar ichthyosis (extensive scaling of the	Talk to your doctor if you have any such side effects.

Risk	What is known	Preventability
with extensive, inherited or acquired, defects of skin barrier function)	skin due to a thickening of the outer layer of the skin), or if you suffer from generalised erythroderma (inflammatory reddening and scaling of the entire skin). These skin conditions may increase systemic absorption of tacrolimus. Oral use of tacrolimus is also not recommended to treat these skin conditions. Post-marketing cases of increased tacrolimus blood level have been reported in these conditions.	

Important potential risks

Risk	What is known
Risk of cutaneous malignancy including Cutaneous T-cell lymphoma	A very small number of people who have used Tacrolimus ointment have had malignancies (for example: lymphoma). However, there is no established causal relationship with the product Talk to your doctor if you have a weakened immune system (immuno-compromised) whatever the cause.
Risk of other lymphoma	A very small number of people who have used Tacrolimus ointment have had malignancies (for example: lymphoma).

Risk	What is known
Off-label use of tacrolimus ointment 0.1% in children between 2-16 years of age	Only tacrolimus 0.03 % ointment should be used in children from the age of 2 to 16 years. Care should be exercised if applying tacrolimus ointment to patients with extensive skin involvement over an extended period of time, especially in children Tacrolimus 0.1 % ointment is not approved for children younger than 16 years of age. Therefore it should not be used in this age group. Please consult your doctor.

Missing information

Risk	What is known
Children below 2 years of age	Tacrolimus ointment is not approved for children younger than 2 years of age. Therefore it should not be used in this age group. Please consult your doctor.
Safety of maintenance treatment beyond 12 months (children above 2 years of age)	In children, maintenance treatment should be suspended after 12 months, to assess whether the need for continued treatment still exists.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

None

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concern	Comment
5.0	25 October 2017	Important potential risks has been revised from "Theoretical risk of cutaneous malignancy including Cutaneous T-cell lymphoma" and "Theoretical risk of other lymphoma" to "Risk of cutaneous malignancy including Cutaneous T-cell lymphoma" and "Risk of other lymphoma" respectively.	RMP has been updated as per Day-208 Germany (DE) comments.
4.0	17 October 2017	Following safety concerns have been added • Important identified risk - Systemic absorption in conjunction with extensive, inherited or acquired,	RMP has been updated as per suggestions provided by MHRA (RMS, UK) on Ireland

<table>
<tr><th>Version</th><th>Date</th><th>Safety Concern</th><th>Comment</th></tr>
<tr><td>5.0</td><td>25 October 2017</td><td>Important potential risks has been revised from “Theoretical risk of cutaneous malignancy including Cutaneous T-cell lymphoma” and “Theoretical risk of other lymphoma” to “Risk of cutaneous malignancy including Cutaneous T-cell lymphoma” and “Risk of other lymphoma” respectively.</td><td>RMP has been updated as per Day-208 Germany (DE) comments.</td></tr>
<tr><td></td><td></td><td>defects of skin barrier function
• Important potential risk - Off-label use of tacrolimus ointment 0.1% in children between 2-16 years of age</td><td>(CMS, IE) assessment for Day-195 comment.</td></tr>
<tr><td>3.0</td><td>05 September 2017</td><td>Below safety concerns has been in lined with the Protopic®
<table><tr><th colspan="2">Summary of safety concerns</th></tr><tr><td>Important identified risks</td><td>• Application site pruritus/irritation/burning
• Paraesthesia
• Alcohol flushing
• Folliculitis/herpes simplex</td></tr><tr><td>Important</td><td>• Theoretical risk of</td></tr></table></td><td>RMP has been updated as per Day-145 comments received from Ireland (RMS) and France (CMS) health authority.</td></tr>
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• Theoretical risk of other lymphoma</td></tr><tr><td>Missing information</td><td>• children below 2 years of age
• Safety of maintenance treatment beyond 12 months (children above 2 years of age)</td></tr></table></td><td></td></tr>
<tr><td>2.0</td><td>24-Apr-2015</td><td>Below safety concerns have been removed from this RMP:
<u>Important identified risks</u></td><td>SI.2 Concomitant medications in the target population have been modified in the RMP.</td></tr>
</table>

Version	Date	Safety Concern	Comment
5.0	25 October 2017	Important potential risks has been revised from "Theoretical risk of cutaneous malignancy including Cutaneous T-cell lymphoma" and "Theoretical risk of other lymphoma" to "Risk of cutaneous malignancy including Cutaneous T-cell lymphoma" and "Risk of other lymphoma" respectively.	RMP has been updated as per Day-208 Germany (DE) comments.
		• Alcohol flushing • Application site pruritus/irritation/burning • Paraesthesia **<u>Missing information</u>** • Use in Clinically infected atopic dermatitis • Use in Occlusive dressings • Impact on fertility	RMP accurately reflects the company's details. In this RMP change has been done as per RMS and CMS comments.