Enstilar
21.1.2016, Version 3
PUBLIC SUMMARY OF RISK MANAGEMENT PLAN

VI.2.1 Overview of disease epidemiology

Psoriasis is a common skin disease where parts of the skin develop into thick, red and scaly patches and they may sometimes itch. These patches are called plaques and are often located on the knees, elbows and back, but they may be found on all parts of the body.

Psoriasis can start at any age and is more common in men than in women as well as in people with white skin compared with others. Psoriasis sometimes runs in the family from one generation to another and many environmental factors, particularly infections and drugs as well as stress have been shown to be a risk factor for psoriasis.

There is currently no cure for psoriasis, but there are several treatments available which alleviate the signs and symptoms of the disease. Topical treatment, applied directly to the skin, is one type of treatment for psoriasis.

VI.2.2 Summary of treatment benefits

LEO Pharma has marketed two kinds of products in EU for topical treatment of psoriasis in adults, Daivonex® and Daivobet®. The ingredients in the products that have an effect on psoriasis are referred to as the “active ingredients”.

Daivonex® contains one active ingredient, calcipotriol. Calcipotriol is a form of vitamin D, which reduce scaling and thickening of psoriasis plaques. Three kinds of Daivonex® products are on the market: Daivonex® cream (marketed since 1990), Daivonex® ointment (marketed since 1993), and Daivonex® scalp solution (marketed since 1994).

Daivobet® contains two active ingredients, calcipotriol and betamethasone dipropionate (hereafter referred to as “BDP”). BDP is a steroid, that reduces inflammation making the plaques and itching gradually disappear. Two kinds of Daivobet® products are on the market: Daivobet® ointment (marketed since 2001) and Daivobet® gel (marketed since 2008).

LEO Pharma has recently developed a new product for topical treatment for psoriasis, Enstilar®. Enstilar® contains the same active ingredients (calcipotriol and BDP) as the marketed products, Daivobet® gel and Daivobet® ointment. Enstilar® is currently not marketed in EU, but almost 900 people have already applied Enstilar® in clinical trials.

Daivobet® ointment

Daivobet® ointment is approved for once daily treatment of psoriasis on the body. The marketing approvals were based on 8 trials testing the benefit (efficacy) and the safety of the product. The 3 most important trials included a total of 3,471 patients with psoriasis on the body who applied Daivobet® or another product (for comparison) once or twice for 4 weeks. The efficacy was evaluated in the 3 trials by letting the trial doctor assess if the psoriasis improved (severity and extent) and if the symptoms of the patients' disease had disappeared or improved to be very mild after 4 weeks' treatment. In that case, the patients were 'responders'. The results showed that there were more responders after 4 weeks' treatment with Daivobet® ointment compared to the other tested products, and Daivobet® ointment applied once daily as well as twice daily was therefore the most efficient treatment option.

Daivobet® ointment is approved for repeated treatment of psoriasis on the body, meaning that the recommended treatment period is 4 weeks, but if necessary, treatment may be extended or restarted after medical review and under regular medical supervision. The marketing approval was based on 8 trials testing the efficacy and the safety of the product. The 2 most important trials included a total of 1,135 patients with psoriasis on the body who applied Daivobet® ointment or another product (for comparison) once daily for 4 weeks or longer. The efficacy was evaluated as for the trials with Daivobet® ointment described above. The results showed that Daivobet® ointment was the best treatment option regardless of the length of treatment period.

Daivobet® gel

Daivobet® gel is approved to be used for treatment of psoriasis on the scalp and on the body. The marketing approvals were based on 16 trials that tested the benefit (efficacy) and safety of the product. The 3 most important of the trials included a total of 3,286 patients with psoriasis on the scalp (2 trials) or the body (1 trial) who applied Daivobet® gel or another product (for comparison) for 8 weeks. The efficacy was evaluated as for the trials with Daivobet® ointment described above.

The 2 most important trials for approval of Daivobet® gel for treatment of scalp psoriasis included 2,922 patients with psoriasis on the scalp who were treated once daily for 8 weeks with Daivobet® gel or another product for comparison. The results showed that there were more responders after 8 weeks' treatment with Daivobet® gel once daily on the scalp compared to the other tested products, and a satisfactory effect was seen already after 4 weeks.

The most important trial for the approval of once daily treatment with Daivobet® gel on the body included 364 patients who were treated once daily for 8 weeks with Daivobet® gel or

another product for comparison. The results showed that Daivobet® gel is the best treatment option both after 4 weeks and after 8 weeks, but a better effect is seen after 8 weeks than after 4 weeks.

Development product - Enstilar®

Enstilar® is a new product developed by LEO Pharma for topical treatment of psoriasis in adults. Enstilar® contains the same active ingredients (calcipotriol and BDP) as the marketed products Daivobet® gel and Daivobet® ointment described above, but Enstilar® is a cutaneous foam. It is expected that Enstilar® will be better liked by its users than the already approved Daivobet® products since it should be a more efficient and user-friendly product.
So far, 7 trials have tested the efficacy and safety of Enstilar®. The Enstilar® marketing application will mainly be based on three clinical trials that included a total of 1,104 patients with psoriasis vulgaris on the body who applied Enstilar® or another product (for comparison) once daily for 4 weeks. The efficacy was evaluated as for the trials with Daivobet® described above. The results showed that 4 weeks' treatment with Enstilar® once daily is the best treatment option.

Daivonex®

Daivonex® cream and Daivonex® ointment are approved for treatment once or twice daily of psoriasis on the body in adults and children 6 years old or older. Daivonex® scalp solution is approved for twice daily treatment of psoriasis on the scalp in adults. Overall, Daivonex® products have shown to be safe and efficient for treatment of psoriasis on the body and on the scalp, both in adults and in children above 6 years of age (Daivonex® cream and Daivonex® ointment). Daivonex® products have been on the market all over the world since the 1990'es and they are still widely used for topical treatment of psoriasis. This extensive experience obtained after the products initially were approved, together with knowledge obtained from the clinical trials with Daivonex® products have shown Daivonex® to be a safe and effective treatment of psoriasis.

VI.2.3 Unknowns relating to treatment benefits

Daivobet® and Enstilar®

The trials submitted to the authorities for approvals of the Daivobet® products and Enstilar® were done in adults of both sexes and of any ethnic origin. Apart from what is known from the trials, there is also substantial experience and knowledge of the benefits with Daivobet®, which have been on the market for many years. There are at present no important unknowns relating to the treatment benefit in the target population.

Daivonex®

Daivonex® has been marketed for more than 23 years and there is therefore extensive "real-

life" experience with its use which, together with the trials that investigated the efficacy and safety of Daivonex®, gives a substantial knowledge of the product. Due to this extensive experience, there are at present no important unknowns relating to the treatment benefit in the target population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Thinning of the skin (Skin atrophy)	Thinning of the skin can appear if Daivobet®/ Enstilar® are used for a long time due to the content of steroid in the product.	Avoid using the product for a long time on the same treatment area.
Depressed function of the adrenal glands (HPA axis suppression)	Excessive prolonged use of Daivobet®/ Enstilar® can cause your adrenal glands to stop working properly (the adrenal glands are found near the kidneys and produce hormones).	Avoid using doses higher than recommended in the Product Information Leaflet for a long time.
A worsening of psoriasis after ended treatment (Rebound phenomenon)	Your psoriasis may worsen after stopping treatment with Daivobet®/ Enstilar®.	Avoid using the product for a long time on the same treatment area.
Skin infections	Daivobet®/ Enstilar® may increase the risk of skin infections in the treated areas because your immune system, which fights infections, may be suppressed or weakened.	Avoid using the product on skin affected by skin infections caused by virus, a fungus, bacteria or parasites.
Increased level of calcium in the blood (Hypercalcaemia)	Excessive use of Daivobet®/ Enstilar®/Daivonex® may cause a problem with calcium in your blood, which usually normalises when discontinuing treatment.	Avoid using doses higher than recommended in the Product Information Leaflet.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Potential enhancement of UV radiation induced skin cancer	Studies in mice have shown that calcipotriol may enhance the effect of UV radiation to induce skin tumours. The clinical relevance of this finding is unknown. It is considered an important potential risk as this is observed in animal studies, only.

Missing information

Risk	What is known
Safety and efficacy in children below 12 years	Children below 12 years are not included in the clinical development program for Daivobet®. Therefore information about safety and efficacy of Daivobet® in children below 12 years is missing.
Safety and efficacy in children below 18 years	Children below 18 years are not included in the clinical development program in EU for Enstilar®. Therefore information about safety and efficacy of Enstilar® in children below 18 years is missing.
Safety and efficacy in patients with very poor kidney function (severe renal insufficiency) or severe hepatic disorder	Patients with severe renal insufficiency or severe hepatic disorder are not included in the clinical development program for Daivobet®/ Enstilar®. Therefore information about safety and efficacy of Daivobet®/ Enstilar® in patients with severe renal insufficiency or severe hepatic disorder is missing.

VI.2.5 Summary of additional 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 directions for use described in these documents are known as routine risk minimisation measures.

The SmPC and PL for Daivobet®, Enstilar® and Daivonex® can be found in the product's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
NIS-DAIVOBETOIN-1163 Post-marketing survey in Japan	Evaluate the safety and efficacy of Dovobet® ointment in patients under long therapy on the actual status of the usage in post-marketing phase.	Important items for investigation is the important identified risk of Hypercalcaemia	Ongoing	Interim report planned September 2017. Final study report planned September 2020

Studies which are a condition of the marketing authorisation

NIS-DAIVOBETOIN-1163 is a condition of the marketing authorisation, since this post-marketing survey is a local Japanese requirement in connection with the NDA of Dovobet® Ointment in Japan.

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

Table 1 Major changes to the Risk Management Plan (RMP) over time

Version	Date	Safety Concerns	Comment
Daivobet® gel Version 2.0	24-Oct-2008	- HPA axis suppression - Hypercalcaemia - Skin atrophy	These safety concerns were included in the first version of the RMP.
Xamiol® gel Version 2.0	08-Dec-2008	- HPA axis suppression - Hypercalcaemia - Skin atrophy	These safety concerns were included in the first version of the RMP.
Calcipotriol + BDP and calcipotriol containing products Version 1.0	12-Sep-2012	One RMP was written to cover all calcipotriol + BDP and calcipotriol containing products 'Potential Enhancement of UV Radiation Induced Skin Cancer' (for Calcipotriol containing Products) was added as an important potential risk.	The potential risk was included based on pre-clinical data.
Calcipotriol + BDP and calcipotriol containing products Version 2.0	Jan-2015	New Template. No additional risks have been identified and added to the RMP.	
Calcipotriol + BDP and calcipotriol containing products Version 3.0	Jan-2016	Rebound phenomenon and secondary skin infection have been added as important identified risks for BDP containing products. Safety and efficacy in children below 12 years has been added as missing information for BDP containing gel and ointment. Safety and efficacy in children below 18 years has been added as missing information for BDP containing foam. Safety and efficacy in	Requested by the authorities during approval of Enstilar® in EU

Version	Date	Safety Concerns	Comment
		patients with severe renal insufficiency or severe hepatic disorder has been added as missing information for calcipotriol + BDP containing products..	