VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Acitretin Orifarm is indicated as treatment for severe skin problems where the skin has become thick and may be scaly. Acitretin Orifarm is used to treat severe forms of psoriasis and other skin diseases characterized by disorders of the formation of new skin e.g. Darier's disease.

Psoriasis is estimated to affect about 2–4% of the population in western countries (Stern et al., 2004; Gelfand et al., 2005b; Kurd and Gelfand, 2009). Important factors in the variation of the prevalence of psoriasis include age, gender, geography, and ethnicity, probably due to genetic and environmental factors. Higher prevalence rates have been reported at higher latitudes, and in Caucasians compared with other ethnic groups (Farber and Nall, 1998).
Psoriasis can present at any age and has been reported at birth and in older people of advanced age. Accurate determination of the age of onset of psoriasis is problematic, as studies which do so typically rely on a patient's recall of the onset of lesions or determine the onset from the physician's diagnosis as recorded on the initial visit. The mean age of onset for the first presentation of psoriasis can range

from 15 to 20 years of age, with a second peak occurring at 55–60 year (Langley et al, 2005).There seems to be no noticeable difference between men and women.

The worldwide prevalence of Darier disease is unknown. The prevalence of Darier disease is estimated to be 1 in 30,000 people in Scotland, 1 in 36,000 people in northern England, and 1 in 100,000 people in Denmark.[6] The disease affects both sexes and all ethnic groups.[7]

VI.2.2 Summary of treatment benefits

Acitretin is a systemic treatment for psoriasis, with both favourable and unfavourable characteristics. Acitretin enhances cellular differentiation and maturation and does not have immunosuppressive effects. As acitretin does not put a patient at increased risk of developing infections or skin or internal malignancies, it is suitable for the treatment of HIV-positive or other immune-compromised patients with psoriasis.
Acitretin may be used in combination therapy as a means of enhancing the effects of other medications while reducing their toxicitye.g. phototherapy.

Acitretin is usually less effective when used as monotherapy as opposed to combination therapy for plaque psoriasis. Acitretin can be successfully used as monotherapy in the elderly or patients with other subtypes of psoriasis erythrodermic or pustular psoriasis.

Acitretin 10 mg and 25 mg capsule is shown effective for the treatment of various forms of psoriasis alone or in combination with other drugs. Clinical studies support the claimed effects. If used appropriately (according to the SPC) it is a safe drug.

VI.2.3 Unknowns relating to treatment benefits

None.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
• Causing malforma-tions of an unborn child (Teratogeni-city), increase risk due to conversion to the substance etretinate (non-compliance with alcohol restriction)	Acitretin may cause birth defects. It must not be used in women who might become pregnant during or within 3 years after stopping treatment. The risk of giving birth to a deformed child is exceptionally high if acitretin is taken before or during pregnancy, no matter for how long or at what dosage. The substance etretinate can be formed if taking acitretin and alcohol in the same time. Etretinate is highly teratogenic (can cause malformations in the unborn child). Women of childbearing age must therefore not consume alcohol (in drinks, food or medicines) during treatment with acitretin and for 2 months after stopping acitretin therapy. Birth control and pregnancy tests must also be taken for 3 years after completion of acitretin treatment.	Acitretin Orifarm should only be prescribed by doctors, who have experience in treatment with systemic retinoids and who are aware of the teratogenic risk associated with acitretin treatment. You must exclude pregnancy before starting treatment with Acitretin Orifarm. Effective birth control (preferably 2 complementary methods) must be used without interruption for four weeks before, during and for 3 years after the discontinuation of treatment with acitretin. During treatment a monthly pregnancy test should be performed.

Risk	What is known	Preventability
	For male patients treated with acitretin, available data indicate a minimal, if any, risk of teratogenic effects, based on the level of maternal exposure from the semen and seminal fluid.	After stopping therapy, pregnancy tests should be performed at 1-3 monthly intervals for a period of 3 years after the last dose is given. Negative pregnancy tests must be achieved. The medicine must not be passed on to other people. Women of childbearing age must not receive blood from patients being treated with acitretin.
• Breast-feeding; retinoid toxicities in the infant	Acitretin passes into the breast milk and may harm the baby. It must not be used by breast-feeding women.	There is no specific measure to prevent the occurrence. The risk can be reduced by not breast-feeding.
• Increased pressure in the head (Benign intracranial pressure) increased; drug interaction with tetracyclines leading to increased risk	There have been reports of rare cases of increased pressure in the head. Acitretin and medicine called tetracyclines, used for treating infection, can cause an increase in intracranial pressure.	There is no specific measure to prevent the occurrence. Patients with severe headache, nausea, vomiting and visual disturbances should discontinue acitretin treatment immediately and be referred for neurologic evaluation and treatment. The risk can be reduced by not taking the product together with tetracyclines.
• Liver dysfunction; When taking acitretin together with metho-trexate leading to increased risk of liver infection (Hepatic dysfunction; Drug interaction with methotrex-ate leading to increased risk of	Liver infection is a possible adverse reaction to acitretin and happens with an uncommon frequency. Acitretin and medicine called methotrexate, used for treating e.g. gout, can cause an increased risk of liver infection.	There is no specific measure to prevent the occurrence. The risk can be reduced by not taking acitretin together with methotrexate. Liver function should be checked before starting treatment with acitretin, every 1 - 2 weeks for the first 2 months after commencement and then every 3 months during treatment. If abnormal results are obtained, weekly checks should be done. If hepatic function fails to return to normal or deteriorates further, acitretin must be withdrawn. In such cases it is advisable to continue monitoring hepatic function for at least 3 months.

Risk	What is known	Preventability
hepatitis)		
• High levels of cholesterol or fat in the blood (Hypercholesterolemia and hypertrigly-ceridemia)	Acitretin may cause elevated blood levels of cholesterol and fat (triglycerides) especially in high-risk patients (patients suffering from disorders of lipid metabolism, diabetes, obesity, alcoholism). An associated risk of plague in the arteries (atherogenesis) cannot be ruled out if these conditions persist.	There is no specific measure to prevent the occurrence. Blood levels of fat (triglycerides) and cholesterol must be monitored before treatment start, one month after treatment start and thereafter every third month during treatment. For all high risk patients where cardiovascular risk indicators do not return to normal or deteriorates further dose reduction or discontinuation of acitretin should be considered. The risk can be reduced by not using the product in patients with chronic abnormal increased levels of blood fat and cholesterol.
• Abnormal Bone formation (Ossification) in adults, especially elderly after long-term treatment	Bone changes in adults, especially elderly, who receive long-term treatment, is also a possible side effect of acitretin and bone changes must be regularly monitored.	There is no specific measure to prevent the occurrence. Adults, especially elderly, who receive long-term treatment with acitretin, must be regularly monitored in view of possible ossification abnormalities. If these disturbances occur, treatment should only be continued after careful evaluation of the patient and if benefits outweigh risks.
• Bone changes in children seen with etretinate	There have been occasional reports of bone changes in children after long-term treatment with etretinate. These effects may be expected with its active break-down-product acitretin. Acitretin therapy in children is not, therefore, recommended unless, in the opinion of the physician, the benefits significantly outweigh the risks and all other alternative treatments have failed.	There is no specific measure to prevent the occurrence. If, in exceptional circumstances, such therapy is undertaken the child should be regularly monitored for any abnormalities of skeletal development and growth. Any symptoms that suggest possible bone changes (restricted mobility, bone pain) should be carefully investigated. As soon as the medical condition allows, the use of acitretin should be interrupted.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
• Psychiatric events (mood changes including irritability, aggression and depression) known for high dose retinoids	Treatment with high-dose retinoids (e.g. acitretin) can cause mood changes including irritability, aggression and depression.

Missing information

Risk	What is known
Risk in relation to life-long administration	The consequences of long-term therapy with acitretin are not yet all known.

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 special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures are for the following risk:

Teratogenicity, increase risk due to conversion to etretinate (non-compliance with alcohol restriction)

Risk minimisation measure(s)
Objective and rationale
• Summary description of main additional risk minimisation measures – Warning on labelling (box). – Internal yearly periodic safety report with a specific section concerning pregnancy/teratogenicity. – Prescription status limited to skin specialists – Pregnancy Prevention Programme (PPP)
<u>Can cause malformations in the unborn child.</u> Warning on box will warn the patient and remind of the safety concern, beyond the warnings and instructions given in the product information for both physicians and patients. An internal safety report will be done with specific focus on the safety concern and keeping track of any possible pregnancies and securing the prevention. Prescription status limited to skin specialists to secure the medical knowledge when prescribing the medicine. The Pregnancy Prevention Programme will consist of elements aligned with that of the reference product Neotigason and consist of: • Doctor's guide to prescribing acitretin • Doctor's checklist for prescribing to female patients • Pharmacist's guide to dispensing acitretin • Patient's guide when using acitretin • Acknowledgement form for patients • General acknowledgement form for patients

VI.2.6 Planned post authorisation development plan

None.

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

Not applicable as this is the initial risk management plan.