VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Severe forms of psoriasis including: erythrodermic psoriasis, local or generalized pustular psoriasis; (chronic severe skin disease characterized by red patches on the skin, often accompanied by silvery-white scales of dead skin cells)

Psoriasis is a long term skin problem affecting about 2–4% of the population in western countries. Caucasians are more prone than other ethnic groups.[1]

Psoriasis tends to run in families but can also be triggered or worsened by smoking, obesity, alcohol consumption, diet, infections, medications, and stressful life events.[2]

Although psoriasis is usually non-life threatening (benign), it is a lifelong illness with remissions and flare-ups. Sometimes it is not responsive to treatment. In severe cases it can progress to inflammation of the joints. About 17-55% of patients experience improvement of psoriasis of varying lengths.[5]

Severe disorders of keratinization such as: Congenital ichthyosis, Pityriasis rubra pilaris, Darier's disease, Other disorders of keratinization which may be resistant to other therapies (severe disorders with dry skin and scaling)

Congenital ichthyosis

Ichthyosis vulgaris is an inherited skin disorder in which dead skin cells accumulate in thick, dry scales on the skin surface. It occurs in about 1 in 300 people in the US, occurs equally in men and women and in all racial groups.

The condition generally first becomes apparent during the first year of life and in most cases by 5 years of age. The extent of scaling usually increases up to puberty and then the symptoms generally decrease with age. This is a long-term condition (chronic) and often requires continuous therapy. [6]

Pityriasis rubra pilaris

Pityriasis rubra pilaris is a rare skin disorder that causes constant inflammation and shedding of the skin. Persons of any race can be affected and it occurs equally among men and women. The disorder may begin in childhood (for inherited form) or adulthood (for acquired form). Patients with pityriasis rubra pilaris can have painful and disabling abnormal thickening of the palms and soles. The state of being for these patients is related to the possible generalization of redness of the skin. [7]

Keratodermia palmoplantaris
Hereditary keratodermia palmoplantaris is a skin disorders characterized by thickening of the palms and soles and it was reported to occur rarely (5.2 per 10,000 population) more frequently in men than women. The condition may either be hereditary or acquired and in the form of associated syndrome(s), PPK being its predominant component. Hereditary forms may be localized to the hands and feet or associated with more generalized skin disorders.[42]

Darier's disease
Darier's disease is quite rare and usually appears in late childhood to early adulthood. It is an inheritable disease and males and females are equally affected. Patients may experience itchy skin and sometimes pain in the affected areas. Patients with this disease are more sensitive to getting skin infections.[8]

Lichen planus
Lichen planus occurs commonly in middle-aged men and women. The disease can appear on the skin, in the mouth or genitaly. While risk of cancer is low for skin disease, in the mouth the occurence is higher. However, in general the risk is low (less than 2%).[43]

VI.2.2 Summary of treatment benefits
A total of 12 clinical studies have shown that acitretin doses of 25 to 35mg/day are suitable for treating psoriasis. Results of these studies showed complete alleviation of psoriasis in 31.5% of patients, a marked improvement in 16.5% of patients, only slight improvement in 12.5% of patients and 8.5% of patients experienced no change or worsening of their condition. The results also showed that best results were achieved with the more severe and rarer forms of psoriasis (pustular and erythrodermic) than with the more common plaque-type psoriasis. [39]

A study performed on 30 patients (26 males and 4 females, age 18-70 years) with severe disorders of keratinization who were treated with acitretin 35 mg during 4 weeks followed by doses of 20-50 mg/day showed that remission or marked improvement was obtained in 23 out of 30 patients. Scaling, redness, itching and abnormal thickening of the palms and soles were beneficially influenced. The study managed to prove that acitretin is effective in various disorders of keratinisation in which systemic retinoids are currently the only drugs that provide significant improvement.[40]

Sixty-five patients with lichen planus were included in an 8-week study. The patients treated with 30 mg/day acitretin (64%) showed marked improvement compared with those that did not receive any treatment (13%). Furthermore, during the following 8-week, 83% of previously untreated patients responded favourably to acitretin therapy. This study showed that acitretin is an effective and acceptable therapy for severe cases of lichen planus.[44]

VI.2.3 Unknowns relating to treatment benefits
Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Increased risk of malformation due to non-compliance with restriction of alcohol use and formation of a compound (etretinate), which may be harmful to an unborn child (Teratogenicity, increased risk due to non-compliance with alcohol restriction (conversion to etretinate))	Acitretin causes malformation in an unborn child (defects of bones of cranium and face, heart, vascular and brain malformations, skeletal defects). Blood donations from patients treated with acitretin to pregnant women are also exposing an unborn child to high risk of causing malformation. Concurrent ingestion of acitretin and alcohol may result in formation of a compound (etretinate), which may be harmful to an unborn child, and if formed it takes a rather long time for it to be totally excreted from the body.	Pregnancy prevention measures and pregnancy tests are necessary during treatment and for 3 years after completion of treatment with acitretin. Women of childbearing potential must not receive blood from patients who are or have been treated with acitretin within 3 years. Women of childbearing potential may not consume alcohol (in drinks, food or medicines) during treatment with acitretin and for 2 months after cessation of therapy. Female at a fertile age must use an effective birth control (contraception) without an interruption for at least 4 weeks before starting taking acitretin, while taking it, and for 3 years after stoping taking it. Primary contraceptive method is a combination hormonal contraceptive product or an intrauterine device and it is recommended that a condom or diaphragm (cap) is also used. Minipills are not recommended. The doctor should ask a pregnancy test up to 3 days before starting treatment, which must be negative. Acitretin must be started after the negative pregnancy test, on the second or third day of the next menstrual period. Regular pregnancy tests at 28 days intervals must be performed while taking acitretin. Before each renewal of prescription, the doctor must request a negative pregnancy test. The test should not be older than 3 days. After stopping the treatment with acitretin, pregnancy tests should be performed at 1-3 monthly intervals for a period of 3 years after last dose is given.
Breastfeeding; toxicity in the infant	The elimination of acitretin in human milk was studied and it was determined that 1.5% from maternal dosage	Breastfeeding is contraindicated during acitretin treatment.

Risk	What is known	Preventability
	passes into milk.	
Increased pressure in the skull - Drug interaction with tetracyclines leading to increased pressure in the skull (Benign intracranial pressure increased; Drug interaction with tetracyclines leading to increased risk)	Acitretin can cause increased pressure in the skull. The symptoms may consist of: severe headache, nausea, vomiting and visual problems.	The appearance of suggestive symptoms should be checked as soon as possible by the doctor. The combined use of acitretin and other drugs that may cause increased pressure in the skull (tetracyclines) is contraindicated.
Liver problems- drug interaction with methotrexate leading to increased risk of inflamation of the liver (Hepatic dysfunction; Drug interaction with methotrexate leading to increased risk of hepatitis)	Acitretin may cause yellowing of the skin and the whites of your eyes, which may be a sign of jaundice (very rare - may affect up to 1 in 10,000 people) or inflammation of the liver (uncommon - may affect up to 1 in 100 people). Other symptoms may include loss of appetite, fever, general feeling of being unwell, nausea, dark urine and abdominal discomfort.	The liver function in the blood should be checked before starting treatment and then regularly during treatment. Patients with severely impaired liver function (contraindicated) are at special risk. Combination of methotrexate with acitretin is also contraindicated due to increased risk of inflammation of the liver.
Fat(lipids) levels in the blood (Hypercholesterolemia and hypertriglyceridemia)	During treatment with high doses of acitretin, reversible elevation of fat (lipid) levels in the blood has occurred, especially in high-risk patients and during long-term treatment.	The fat (lipids) levels in the blood should be checked before starting treatment and then regularly during treatment. Acitretin is contraindicated in patients with chronic abnormally elevated blood lipid values.
Abnormal formation of new bone on the surface of bones (exostosis) in adults, especially elderly after long-term treatment (Ossification abnormalities in adults, especially elderly after long-term treatment) Bone changes in children seen with etretinate	Acitretin may cause changes in bone growth, meaning formation of new bone on the surface of the bones.	The doctor may also periodically monitor the bones, as acitretin may cause bone changes, especially in children and elderly receiving long-term treatment.
Modifications in glucose tolerance (Alterations in glucose metabolism)	In diabetics, retinoids can either improve or worsen glucose tolerance.	Blood-sugar levels must therefore be checked more frequently than usual at the beginning of treatment.

Important potential risks

Risk	What is known
Mood changes (including irritability, aggression and depression)	High dose treatment with acitretin can cause mood changes (including irritability, aggression and depression);

Missing information

Risk	What is known
Risk in relation to life-long administration	Acitretin may cause changes in bone growth, meaning formation of new bone on the surface of the bones after long-term treatment. Reversible elevation of fat (lipid) levels in the blood has occurred, especially in high-risk patients and during long-term treatment. At the present time, not all the consequences of life-long administration of acitretin are 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). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.
These additional risk minimisation measures are for the following risk:

Risk of malformation and formation of a compound (etretinate), which may be harmful to an unborn child

➢ **Distribution of Direct Healthcare Professional Communication (DHPC)**
Objective and rationale The objective is to highlight the main key issues directly to prescribing physicians
Summary description of main additional risk minimisation measures The DHPC will highlight the risks associated with concomitant alcohol consumption, blood-donation, and risk of teratogenicity.
➢ **Healthcare Professional and patient education**
Objective and rationale The objective is to ensure safe use of acitretin in relation to pregnancy and unborn child exposure. It describes measures for women of childbearing potential to avoid pregnancy and for other patient groups to decrease the risk of foetal exposure. The additional RMMs are needed to better inform the doctors and patients on this important risk with severe consequences upon the unborn child.
Summary description of main additional risk minimisation measures Distribution of education material in order to emphasize the need for contraception during treatment with acitretin, the need for monthly testing of pregnancy before renewing the prescription, consent forms to be signed off by women of child bearing potential. Pregnancy prevention programme in consists of: -Doctor's guide to prescribing acitretin

➢ **Distribution of Direct Healthcare Professional Communication (DHPC)**
Objective and rationale The objective is to highlight the main key issues directly to prescribing physicians
Summary description of main additional risk minimisation measures The DHPC will highlight the risks associated with concomitant alcohol consumption, blood-donation, and risk of teratogenicity.
➢ **Healthcare Professional and patient education**
-Doctor's checklist for prescribing to female patients -Pharmacist's guide to dispensing acitretin -Patient's guide when using acitretin -Acknowledgement form for female patients -Acknowledgement form for male patients

VI.2.6 Planned post authorisation development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Multi-national, observational, and cross-sectional in design, survey	This study aims to evaluate the impact of the Pregnancy and Foetal Exposure Prevention Programme on patient knowledge and potential behaviour regarding the need to avoid pregnancy during treatment with acitretin and for 3 years after cessation of treatment.	Teratogenicity, increased risk due to non-compliance with alcohol restriction (conversion to etretinate)	Planned (synopsis attached)	Not established

Studies which are a condition of the marketing authorisation
None of the above studies are conditions of the marketing authorisation.

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

Version	Date	Safety Concerns	Comment
1.0	29-08-2014	Identified Risks Teratogenicity and conversion to	First version prepared only for France

Version	Date	Safety Concerns	Comment
		etretinate Breastfeeding Benign intracranial pressure increased; Drug interaction with tetracyclines leading to increased intracranial pressure Hepatic dysfunction Drug interaction with methotrexate leading to increased risk of hepatitis Serum cholesterol and triglyceride levels increased Ossification abnormalities in adults, especially elderly after long-term treatment Bone changes in children seen with etretinate <u>Potential Risks</u> Psychiatric events (mood changes including irritability, aggression and depression) known for high dose retinoids <u>Missing information</u> Risk in relation to life-long administration	
2.0	20-11-2014	<u>The same important risks</u>	The RMP covers all Actavis products, nonclinical and clinical trial data were added.
3.0	03-02-2016	<u>One risk was added:</u> <u>Important identified risk: Alterations in glucose metabolism</u> <u>A survey was proposed as measure of evaluation of effectiveness of PPP.</u> <u>PPP changes were done according to CHMP recommendation to recommend 3 years of contraception period instead of 2 years after acitretin discontinuation.</u>	RMP changes due to Preliminary Assessment Report.