SUMMARY OF RISK MANAGEMENT PLAN

Isotretinoin Actavis

Version 7.1, 29.3.2016

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

There are several types of acne and some severe forms can cause psychosocial suffering and can lead to physical scarring.

Acne vulgaris is a common skin disease that affects an estimated 80% of Americans at some time during their lives. Twenty percent will have severe acne, which results in permanent physical and mental scarring.
Persons of some races are affected more than others. Cystic acne is prevalent in the Mediterranean region from Spain to Iran. Acne is common in North American whites. Spanish persons tend to more commonly develop cystic acne. African Americans have a higher prevalence of pomade acne, likely stemming from the use of hair pomades (oily and waxy hair products).
Acne is not limited to adolescence. Twelve percent of women and 5% of men at age 25 years have acne. By age 45 years, 5% of both men and women still have acne.

Acne conglobata is an uncommon disease. Acne conglobata can produce pronounced disfigurement. Severe scarring produces psychological impairment; individuals with acne conglobata are often shut out from social groups, or they may feel excluded. Acne conglobata has also been responsible for anxiety and depression in many patients. The disease affects males more frequently than females. The onset of acne conglobata usually occurs in young adults aged 18-30 years, but infants may develop this condition as well.

VI.2.2 Summary of treatment benefits

Because of the risk of adverse effects, which may be severe, the drug should be reserved for patients who are unresponsive to conventional acne therapies, including oral and/or topical anti-infectives.

In one study, 20 patients with extensive acne conglobata affecting the face, chest and back, were treated for a period of six months with isotretinoin at a dosage of 1 mg/kg/day. In all cases, the acne conglobata cleared up completely. With the exception of symptoms produced by drying of mucosa and skin, no side effects were observed. The laboratory parameters were all within normal limits during the anti-acne treatment phase and there was no recurrence of the disease within a period of one year after cessation of treatment.

In another study, the efficacy of isotretinoin was investigated at 0.5 to 1.0 mg/kg per day in the treatment of acne. A number of 638 patients, both male and female, with moderate acne were enrolled and treated with isotretinoin at 20 mg/day for 6 months.
At the end of the treatment phase, good results were observed in 94.8% of the patients aged 12 to 20 years, and in 92.6% of the patients aged 21 to 35 years. Failure of the treatment occurred in 5.2% and 7.4% of the two groups, respectively, and twenty-one patients dropped out of thedue to

because of side effects.
In summary, it can be concluded that six months of treatment with low-dose isotretinoin (20 mg/day) was found to be effective in the treatment of moderate acne, with a low incidence of severe side effects and at a lower cost than higher doses.

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, for the treatment of severe forms of acne, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important indentified risks

Risk	What is known	Preventability

Risk of malformation and formation of a compound (isotretinoin), which may be harmful to an unborn child (Teratogenicity)	If pregnancy does occur in spite of precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the foetus. The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial malformations, cleft palate, external ear abnormalities (absence of external ear, small or absent external ear canals),eye abnormalities (microphthalmia), abnormalities of the heart and blood vessels (conotruncal malformations such astetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.	Yes, by providing educational material to reinforce the warnings about the teratogenicity of isotretinoin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing. Also this medicinal product is on restricted medical prescription to 30 days and 7-day validity. If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met: she has severe acne, she understands the teratogenic risk (risk of malformations in the fetus), she understands the need for rigorous follow up, on a monthly basis, she understands and accepts the need for effective contraception, even if she has amenorrhea (absence of menstrual period) she must follow all of the advice on effective contraception, she should be capable of complying with effective contraceptive measures, she is informed and understands the potential consequences of pregnancy , she understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment, she has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

Psychiatric Disorders - including depression, suicidality and anxiety	Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms and, very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.	Yes, by monitoring for early symptoms. Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary.
Eye disorders including corneal opacities, reduced night vision and keratitis (inflammation of the cornea) (The cornea is the transparent structure on the front of the eyeball)	Patients may experience dry eye, corneal opacities and keratitis during the treatment with isotretinoin. Dry eyes can be helped by application of a lubricating eye ointment or by tear replacement therapy. Intolerance to contact lenses may occur, which may necessitate the use of glasses during treatment. Caution when driving or operating machines at night is warranted due to decreased night vision that can happen suddenly. Blurred vision, colour blindness, cataract, intolerance to contact lenses, corneal opacities decreased night vision, keratitis, photophobia, visual disturbances have been reported in patients treated with isotretinoin. Sensitivity to light may increase.	Yes, by monitoring for early symptoms and by wearing sunglasses to protect the eyes from bright sunlight.
Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis (breakdown of muscle tissue) (Connective tissue is any type of biological tissue that supports, binds together, and protects organs.	Isotretinoin can cause muscle and joint pain. Arthritis, bone disorders (delayed growth, extra growth and changes to bone density), calcium deposits in soft tissue, sore tendons, pain in joints, muscles and back have been reported in patients treated with isotretinoin Breakdown of muscle tissue (rhabdomyolysis) which can appear as muscle pain and change in colour of the urine has also been reported.	The doctor may also periodically monitor the bones, as isotretinoin may cause bone changes. Patients are adviced to refrain from intensive exercise and physical activity.

Severe skin reactions	Five-six months after the end of the treatment, the risk of hypertrophic scarring (raised scars) in atypical areas and more rarely postinflammatory hyper or hypopigmentation (dark or light damages to the skin after the inflammation has cleared) in treated areas, is increased. For at least a period of 6 months after treatment the risk of skin tearing is also increased. Isotretinoin is likely to cause dryness of the skin and lips. Local irritation may increase due to concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne (substances used to soften and peel the outer layer of the skin). There have been post-marketing reports of severe skin reactions (e.g. erythema multiforme (EM), Stevens- Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) associated with isotretinoin use. As these events may be difficult to distinguish from other skin reactions that may occur, patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If a severe skin reaction is suspected, isotretinoin treatment should be discontinued.	Yes, by monitoring for early symptoms. Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used. Aggressive chemical dermabrasion (technique used to remove scars with abrasive materials) and skin laser treatment should be avoided in patients on isotretinoin for a period of 5-6 months after the end of the treatment. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment. Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment. Concurrent administration of isotretinoin with topical keratolytic or exfoliative antiacne agents (substances used to soften and peel the outer layer of the skin) should be avoided.
Benign intracranial hypertension (increased pressure around the brain)	Cases of benign intracranial hypertension (increased pressure around the brain) have been reported, some of which involved concomitant use of tetracyclines (special group of antibiotics). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema (swelling of the optic disc in the eye). Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.	Yes, by monitoring for early symptoms and contraindicating the association with tetracyclines.

Severe increase in blood lipid (triglyceride) levels, sometimes associated with acute inflammation of the pancreas	Isotretinoin has been associated with an increase in plasma triglyceride levels (blood lipids). Isotretinoin should be discontinued if hypertriglyceridaemia (high levels of blood lipids) cannot be controlled at an acceptable level or if symptoms of pancreatitis occur. Levels in excess of 800mg/dL or 9mmol/L are sometimes associated with acute inflammation of the pancreas (pancreatitis), which may be fatal.	Yes, by monitoring the plasma triglyceride levels.
Severe allergic reactions	Isotretinoin contains refined soya-bean oil and partially hydrogenated soyabean oil. Therefore, isotretinoin is contraindicated in patients allergic to peanut or soya. Anaphylactic reactions have been rarely reported, in some cases after previous topical exposure to retinoids. Allergic skin reactions are reported infrequently. Serious cases of allergic vascultitis (inflammation of blood vessels), often with purpura (bruises and red patches) of the extremities and skin abnormalities have been reported. Severe allergic reactions require interruption of therapy and careful monitoring.	Yes, by monitoring for early symptoms and contraindicating isotretinoin in patients with allergy to the active substance or to any of the excipients.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Gastrointestinal disorders including inflammatory bowel disease (group of inflammatory conditions of the colon and small intestine)	Severe abdominal pain with or without bloody diarrhoea have been reported in patients treated with isotretinoin.

Important missing information

Risk	What is known
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VI.2.5 Summary of risk minimisation measures by safety concen

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 bbreviated 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:

Teratogenic (causing malformations of an embryo or fetus) effects

Risk minimization measure(s)
Objective and rationale: Patients and Healthcare professionals to understand the risk of teratogenic effects and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.
Proposed action: Pregnancy Prevention Programme to emphasize the need of monthly prescriptions, monthly pregnancy testing and dispensing recommendations, Acknowledgement (Informed Consent) form to be signed off by female patients of childbearing age at the beginning of treatment. List of components: 1.Doctor's guide to prescribing isotretinoin 2.Doctor's checklist to prescribing isotretinoin to female patients 3.Pharmacist's guide to dispensing isotretinoin 4.Patient guide when using isotretinoin 5.Acknowledgement form for female patients 6.General acknowledgement form for patients

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for isotretinoin.

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

Version	**Date**	**Safety Concerns**	**Comment**
4.0	03-09-2013	Important Identified Risks: -Severe skin reactions -Teratogenic effects -Psychiatric Disorders- including depression, aggressive and/or violent behaviours -Benign intracranial hypertension -Severe increase in triglyceride levels, sometimes associated with acute pancreatitis -Severe allergic reactions	First version approved.

5.0			Relevant sections completed for a hybrid application.
6.0	04-03-2016	***Important identified risks:*** -Teratogenicity -Psychiatric Disorders - including depression, suicidality and anxiety -Eye disorders including corneal opacities, reduced night vision and keratitis -Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis -Severe skin reactions (including SJS and TEN) -Benign intracranial hypertension -Severe increase in triglyceride levels, sometimes associated with acute pancreatitis -Severe allergic reactions ***Important potential risks:*** -Gastrointestinal disorders including inflammatory bowel disease ***Important missing information:*** NA	The following three new safety concerns were included in order to be in line with PSUSA outcome (Procedure No.: PSUSA/00001795/201505) -Eye disorders including corneal opacities, reduced night vision and keratitis -Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis - Gastrointestinal disorders including inflammatory bowel disease Some risks have been renamed.

7.0	29-03-2016	***Important identified risks:*** -Teratogenicity -Psychiatric Disorders-including depression, suicidality and anxiety -Eye disorders including corneal opacities, reduced night vision and keratitis -Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis -Severe skin reactions (including SJS and TEN) -Benign intracranial hypertension -Severe increase in triglyceride levels, sometimes associated with acute pancreatitis -Severe allergic reactions ***Important potential risks:*** -Gastrointestinal disorders including inflammatory bowel disease ***Important missing information:*** NA	Minor updates/corrections in section V.1 due to RMS Day 190 Draft Assessment Report on RMP version 6.0 for isotretinoin, dated 04-03-2016, received from Icelandic Medicines Authority.