Part VI: Summary of the risk management plan

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Fungal infections of the skin, nail bed and scalp are among the most frequent human infections affecting more than 20% of the world's population. Their frequency is reported to be increasing.[67] The occurrence of different types of fungal infection varies with geographical region and is influenced by many factors including type of population, weather conditions, lifestyle, migration patterns, cultural practices, socioeconomic conditions, and other medical conditions that make individuals susceptible to infection (e.g. HIV), or drug therapy that can weaken a patient's immune system (e.g. chemotherapy or medicine to prevent transplant rejection).[68]

Erythrasma (a skin disease that causes brown, scaly skin patches) is caused by *Corynebacterium minutissimum*. Erythrasma occurs in approximately 4% of the population (i.e. 4 in every 100 people). This infection is observed all over the world, but more frequently in subtropical and tropical areas. [69] Erythrasma is more common in individuals who are overweight or have diabetes.

VI.2.2 Summary of treatment benefits

Topical bifonazole is used for the treatment of superficial fungal skin infections caused by dermatophytes, yeasts or moulds, and treatment of erythrasma. Bifonazole works by causing damage to the membrane of fungi and to certain bacterial cells.

Depending on the specific infection, a course of treatment of between 3 and 4 weeks is sufficient in most cases to achieve a lasting cure. The treatment benefits of bifonazole are well established, as demonstrated in numerous clinical trials and as reflected in the continuing approval of the products by multiple regulatory authorities.

VI.2.3 Unknowns relating to treatment benefits

There are no unknowns related to treatment benefits.

VI.2.4 Summary of safety concerns

In clinical trials bifonazole was well tolerated when applied to the skin. Very few side effects were reported by patients and, when they occurred, they were usually mild to moderate in severity.

Only a very small amount of bifonazole is absorbed into the body after application to the skin, so systemic effects (those due to the drug entering your body) are unlikely.

Some important identified and potential risks are known which are summarized below.

Important identified risks

Risk	What is known	Preventability
Hypersensitivity (allergic) reaction	Allergic reactions occur in approximately 1 in every 1000 patients (0.1%).	Allergic reactions may be prevented by not taking bifonazole if you know you are allergic to it or any other ingredient in the medicine, or if you have previously had an allergic reaction to a similar antifungal medicine. The package leaflet included with the medicine contains information about this.

Important potential risks

Risk	What is known
Risk of drug exposure of a foetus (unborn baby)	In studies in pregnant animals some harm to the foetus was seen at doses of bifonazole that were harmful to the mother (doses very much higher than you or your baby would be exposed to). There is very limited information available from humans about this risk. Therefore, Canespor Cream is not recommended to be used during pregnancy or in women trying to conceive unless appropriate contraception measures are taken.
Risk of systemic (throughout the body) exposure of babies and toddlers to bifonazole during lactation (breast feeding)	In lactating female rats treated by injection with bifonazole, the drug has been found in their milk. It is not known whether bifonazole is also excreted in human breast milk. Because systemic bifonazole has been shown to affect liver function in animals, so there is a potential risk for humans, female patients who are breast-feeding should not use bifonazole.
Risk of systemic exposure of babies and toddlers during their treatment with bifonazole	In newborn babies with nappy (diaper) rash being treated with topical bifonazole, a small amount of bifonazole entered the body after it was applied to the skin. If newborn babies were given multiple doses over a long duration, sufficient absorption could occur to potentially harm the liver, which is underdeveloped liver at this stage of life. In clinical studies, no cases of such harm to children have been seen to date, however no in-depth studies have been performed in children. While there is no indication that harmful effects should be anticipated in infants and toddlers, the medicinal product should only be used under medical supervision.
Risk of misdiagnosis	If bifonazole is used to treat an infection that has been misdiagnosed (i.e. an infection against which the drug does not work), used to treat more than one infection at the same time, or to treat another skin condition such as eczema which might appear similar to an infection, it will not work.
Risk of development of resistance (where the drug no longer works)	Reports of resistance to the drug are very rare.
Risk of drug interaction with warfarin	Bifonazole is known to inhibit (slow down) an enzyme that metabolises (breaks down) warfarin (a drug used to prevent blood clotting). It is unlikely, when used in line with the package leaflet, that the amount of bifonazole absorbed from the skin into your body would be sufficient to have this effect. However, if bifonazole is used for a long time, or on covered areas of the body such as the groin which can increase absorption, or if the patient is a slow metaboliser of warfarin, it is possible that the effect of warfarin if taken at the same time will be prolonged, leading to longer blood clotting time.

Missing information

None.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) (a label) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks associating with using the medicine, and the recommendations for minimising them. A shortened version of this, written in lay language is provided in the form

of the Package Leaflet (PL). The risks associated with the medicine can be minimized by reading and carefully following the labeling instructions.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

Not applicable – there is no post-marketing development plan.

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

This is the second version of the country Risk Management Plan (RMP) for Finland for 1% topical bifonazole.

Version	Date	Safety Concerns	Comment
1.1	October 04, 2016	***Important identified risk:*** Hypersensitivity reactions ***Important potential risk:*** Risk of drug exposure of foetus during treatment in the first trimester of pregnancy Risk of systemic exposure of neonate, infants and toddlers during lactation Risk of systemic exposure of neonate, infants and toddlers during their treatment Risk of misdiagnosis Risk of development of resistance Risk of drug interaction with warfarin	Version submitted during Decentralised Procedure RMS Day 70 Preliminary Assessment Report of June 21, 2016 The Assessor required the original core RMP to be revised to include the agreed indications specifically antimycotic treatment of the nail bed after keratolytic removal of the nail. The RMP was then issued a as country specific RMP for Finland version 1.1.
1.2	September 04, 2017	***Important identified risk:*** Hypersensitivity reactions ***Important potential risk:*** **Risk of drug exposure of foetus** Risk of systemic exposure of neonate, infants and toddlers during lactation Risk of systemic exposure of neonate, infants and toddlers during their treatment Risk of misdiagnosis Risk of development of resistance Risk of drug interaction with warfarin	RMP updated per request of Decentralised Procedure RMS Day 120 Draft Assessment Report, August 10, 2017 Ireland Health Authority's National Assessment requested Sponsor to slightly modify the important potential risk statement changing to Risk of drug exposure of foetus. Change adopted for Finland. The Ireland Health Authority also requested the RMP to align with the proposed revised Canespro SPC and package leaflet statements included to manage the risks. The first version aligned with the Core CCDS. Change

Version	Date	Safety Concerns	Comment
			adopted for Finland. In response to the Ireland Health authority request, the following sections were updated: Part II sections SIV, SV, SVI, SVII, SVIII, Part III, Part V, and Part VI. Change adopted for Finland. Added additional section to V.1 Risk Minimisation Measures by Safety Concern which reviews the effectiveness of risk minimiaiton activities since the last version of the RMP [version 1.1 (Finland)] was submitted. Updated safety information in all relevant sections to the DLP of latest PBRER 01-Dec-2016. Updated post marketing exposure data to DLP of last PBRER 01-Dec-2016. No important changes due to new safety information were made during this update.

[67] Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. Mycoses 2008;51 (Suppl 4):2 -15.

[68] Ameen M. Epidemiology of superficial fungal infections. *Clin Dermatol* 2010;28(2):197 201.

[69] Sarkany I, Taplin D, Blank H. Incidence and bacteriology of erythrasma. *Arch Dermatol* 1962;85:578-82.