IPAR

Public Assessment Report for a Medicinal Product for Human Use

Scientific discussion

Canespor 1% w/w cream

BIFONAZOLE

PA1410/083/001

Instructions for use: Choose relevant text and delete alternative. Follow instructions in italic text and then delete.

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

This is a Decentralised application submitted under Article 8(3) of Directive 2001/83/E, as amended, for Canespor 10 mg/g cream. The applicant has therefore submitted quality, non-clinical and clinical data in support of this application.

Canespor 10 mg/g cream contains an antifungal acvtive substance called bifonazole. Bifonazole is a halogen-free imidazole derivative with the chemical designation 1-(4-bisphenyl)-phenyl-methyl-1H-imidazole (ATC code D01AC10). Bifonazole is not considered to be a new active substance as medicinal products containing bifonazole have been authorised in Europe since 1982.

As part of this procedure the applicant also proposed to switch the classification for supply of this bifonazole 10 mg/g cream product from a “prescription only” medicine to OTC pharmacy only supply in Ireland. The applicant has therefore included an OTC Switch addendum to the Clinical Overview of this application.

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Canespor 10mg/g Cream for Bayer Limited on 9th March 2018.

The legal basis of the application is considered acceptable by HPRA.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA’s website at http://www.hpra.ie/

Name of the product	Canespor 1% w/w Cream
Name(s) of the active substance(s) (INN)	BIFONAZOLE
Pharmacotherapeutic classification (ATC code)	D01AC10 BIFONAZOLE
Pharmaceutical form and strength(s)	1% w/w Cream
Marketing Authorisation Number(s) in Ireland (PA)	PA1410/083/001
Marketing Authorisation Holder	Bayer Limited
MRP/DCP No.	IE/H/470/001/DC
Reference Member State	IE
Concerned Member State	FI

II QUALITY ASPECTS

II.1. Introduction

This application is for Canespor 1% w/w Cream

II.2 Drug substance

The active substance is Bifonazole, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Contains bifonazole 1% w/w. 1 g of cream contains 10 mg bifonazole.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for cream, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Canespor 1% w/w Cream.

III NON-CLINICAL ASPECTS

III.1 Introduction

Bifonazole is a widely used and well-known active substance. The applicant has not provided additional nonclinical safety studies and has based the nonclinical overview on the original nonclinical studies performed to support marketing application of the drug in the early 1980's as well as relevant published literature. This is considered appropriate.

All studies derived from the literature as well as studies submitted by the applicant were performed before the principle and guidelines of Good Laboratory Practice (GLP) had been established. Though the studies might not have been performed in strict compliance with current GLP conditions, there is no reason to believe that repetition of these studies under GLP conditions would produce results different results.

III.2 Pharmacology

Biofonanzole is an azole antimycotic with a broad spectrum antifungal activity. Efficacy has been demonstrated in vitro and in vivo in preclinical studies against a number of dermatophytes and yeasts which are known causative agents of superficial fungal infections including some of the fungal skin indications proposed for this product. A number of secondary pharmacodynamic effects have been associated with bifonazole including anti-inflammatory effects. No safety pharmacology studies have been performed and for a topically applied cream with low systemic absorbance this is acceptable.

III.3 Pharmacokinetics

The dermal absorption of bifonazole has been primarily investigated in clinical trials. These have demonstrated low absorption from healthy skin which is increased to a maximum of 5% from inflamed or damaged skin. Importantly from the perspective of the toxicology package evidence has been presented to demonstrate that in rats 90% of orally administered bifonazole is absorbed. Bifonazole is widely distributed after systemic exposure including into the milk of lactating rats, a fact that has been accurately reflected in the SmPC. A large fraction of bifonazole after oral administration is metabolised during the first passage through the liver and the metabolite profile between the species used in the toxicology programme and humans is qualitatively similar. Excretion occurs predominantly via the faeces. No new non-clinical pharmacokinetic studies have been conducted by the applicant in support of this current application, and none are required.

III.4 Toxicology

The toxicology package originates from the initial marketing authorisation. Most of the described studies were performed in the 1970s and predate GLP regulations. In light of the > 30 years clinical experience with the active substance this is considered acceptable. The single dose studies performed by oral administration suggest that bifonazole is a low toxicity compound. The repeat dose toxicity studies were performed in rats and dogs via oral administration and are of sufficient duration to support the proposed duration of treatment. No toxicokinetic data is available, however, pharmacokinetic studies suggest that the systemic exposure, at least in rats, is significantly higher after oral administration than what is seen via the intended dermal route (90% via oral route versus 5% via dermal route). Genotoxicity studies suggest a lack of genotoxic potential. Although no carcinogenicity studies have been performed this is considered acceptable given the non-genotoxic nature of the drug and its low dermal absorption levels. In the reproductive toxicity studies no effects were seen on fertility levels in either males or females. Embryo-foetal studies reveal that although not teratogenic in either rats or rabbits, at the highest dose used in rabbits of 30 mg/kg significant embryotoxic effects were seen. The lack of toxicokinetic data renders the interpretation of the clinical significance of these findings difficult. No juvenile toxicity testing have been performed. Local tolerance studies with gel and cream formulations of 1% bifonazole suggest that it is well tolerated upon dermal application.

III.5 Ecotoxicity/environmental risk assessment

Bifonazole PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, bifonazole is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

Bifonazole is a widely used and well-known active substance and its pharmacodynamic, pharmacokinetic and toxicological properties are well known. The information provided by the applicant is sufficient to support the MAA from a non-clinical perspective.

IV CLINICAL ASPECTS

Pharmacokinetics

Introduction
Bifonazole is a locally acting antimycotic agent that is applied to the external layers of the skin. Locally applied, locally acting medicinal products should not have any appreciable systemic absorption. Therefore the applicant has evaluated absorption of this product through the external layer of skin, distribution within skin layers, as well as systemic absorption, distribution, metabolism and elimination of bifonazole following topical application. PK trials of this product were first initiated in the 1980s.

Absorption
Bifonazole penetrates well into infected skin layers. 6 hours after administration concentrations in the various skin layers reach from 1000 µg/cm
3 in the top layer of the epidermis (stratum corneum) to 5 µg/cm3 in the stratum papillare.
Pharmacokinetic investigations after topical application to intact human skin have shown that only a small amount of bifonazole is absorbed systemically (0.6-0.8% of the dose). The resulting serum concentrations were usually below the detection limit (i.e. < 1 ng/mL). Higher absorption was observed after application to inflamed skin (2-4% of the respective dose).

Conclusions on pharmacokinetic data
Comparing pharmacokinetic results in patients to those for healthy volunteers, it would seem as though there may be increased absorption in mycotically infected or broken skin and/or under occlusion. A warning has therefore been included in the patient information to state that occlusive bandages should not be used as this could result in increased systemic absorption.

The applicant has presented limited data on use of bifonazole in elderly patients and other special populations. It is possible that greater amounts of bifonazole may be absorbed due to skin thinning in elderly patients. However, the applicant has marketed this product since 1982 with limited evidence of systemic adverse effects. It is noted that there is some evidence that imidazoles may cause increases in INR when used with oral anticoagulants such as warfarin and a warning to this effect has been included in the patient information.

Pharmacodynamics

Introduction
The mechanism of action of bifonazole is not yet comprehensively understood. No clinical pharmacodynamic studies were performed by the sponsor.

Dermatophytes
The *in vitro* pharmacodynamic data presented by the applicant appears to support an indication for use of bifonazole in dermatophyte skin infections as activity has been demonstrated against the common causative agents.

The applicant has discussed primary and secondary resistance to bifonazole and no concerns are raised in relation to this matter.

Clinical efficacy

Introduction

The applicant has presented placebo-controlled, active-controlled and uncontrolled company studies as well as drawn upon references from the published literature that are relevant to this substance to support the indications applied for.

Tinea pedis

The applicant has presented 2 small placebo-controlled, 3 small active comparator-controlled (miconazole, tioconazole or ketoconazole) and 3 uncontrolled studies of bifonazole in this indication. The applicant has also presented 5 controlled studies from the published literature examining bifonazole use in tenia pedis. While negative culture rates were generally not as high as those presented in the company studies, results are still generally positive. The most recent study presented (Watanabe et al, 2006) was a large study (n=489). It showed a negative culture result of 50% in the bifonazole group but negative microscopy results were more favourable at 75.9%.

Onychomycoses

The applicant has presented one published randomised, blinded, placebo-controlled clinical trial to support this indication. The randomised controlled trial presented shows promising statistically significant results for most parameters assessed up to 3 months assessment. At 6 months, these promising results are not maintained. This may reflect the fungistatic action of bifonazole and the chronic nature of this condition. No active (topical) comparator randomised, blinded trials have been presented.

The remaining studies that the applicant has presented are mostly identical in design. These studies were open label, uncontrolled observational studies with small numbers of participants in various geographical regions. They involved the use of a urea-based topical product to remove the nail, followed by (mostly) 4 weeks of treatment with bifonazole 1% topically.

The published reviews presented by the applicant indicate that general dermatology practice involves treatment with a topical antifungal post nail avulsion, despite the evidence base not being extremely compelling. The general consensus is that topical agents work better in early, limited disease and when the proximal portion of the nail is not affected. The available efficacy data indicate that combined oral and topical antifungal therapy achieve better results than treatment with topical therapies alone.

Overall conclusions on efficacy studies

Treatment of tinea pedis (Athlete's foot)

Considering the totality of the data presented and taking into account the non-clinical PD data presented, it would appear as though bifonazole 1% cream is superior to placebo in dermatophyte skin infections such as tinea pedis. There is also some data to indicate that bifonazole 1% cream is comparable to the commonly used active comparators. Therefore, there is evidence to support the use of bifonazole 1% cream in dermatophyte skin infections and therefore the indication of tinea pedis is approvable. The applicant has justified why a 3 week duration of treatment is proposed for tinea pedis.

Treatment of an exposed nailbed following keratolytic removal of the nail

Onychomycosis of the toenail is a difficult condition to treat and eradicate. The available efficacy data indicate that combined oral and topical antifungal therapy achieve better results than treatment with topical therapies alone. However, some patients cannot tolerate oral antifungal therapies (E.g. liver or renal impairment, congestive cardiac failure). Taking into account the pharmacodynamic data presented, the large randomised controlled trial presented as well as supporting small open label trials and expert opinion, the indication "*treatment of an exposed nailbed following keratolytic removal of the nail"* may be accepted. The applicant has justified why a 4 week duration of treatment is proposed for treatment of an exposed nailbed following keratolytic removal of the nail.

Clinical safety

Preparations containing bifonazole 1% have been licensed and marketed in Europe since 1982. The majority of clinical trials were conducted between 1979 and 1989. Therefore, the levels of exposure to this product since it was developed are considered sufficient to ascertain if the benefit risk balance is positive.

The pattern of adverse events seen in the clinical trial programme are generally not a cause for concern and the relevant adverse events have been included in the Summary of Product Characteristics and Patient Information Leaflet. However, it is noted that these trials are old and that the clinical trial setting is an artificial clinical environment for evaluating the safety of a medicinal product. The applicant has therefore provided a discussion of post-marketing adverse event reports in the dossier. The majority of adverse events reported were allergic reactions that resolved when the medicinal product was withdrawn. Review of the post-marketing pharmacovigilance data does not alter the benefit-risk balance for this product.

Method of Sale and Supply

Based on the data provided by the applicant, the HPRA considers this product to be suitable for OTC Pharmacy sale in Ireland in the indications "*treatment of tinea pedis including treatment of an exposed nailbed following keratolytic removal of the nail*". The product information has been worded to suit this method of sale and supply.

V OVERALL CONCLUSIONS

Based on the review of the data and the Applicant’s response to the questions raised by the Reference Member State (Ireland) and Concerned Member State (Finland) on quality, safety and efficacy, the RMS considers that the application for Canespor in the treatment of tinea pedis including treatment of an exposed nailbed following keratolytic removal of the nail, is approvable.

Topical bifonazole has been licensed in the European Union and worldwide for treatment of fungal skin infections since 1982 and so this active substance is well-characterised.

The posology and method of administration are considered acceptable and are supported by data presented in the dossier.

In conclusion, based on the information provided by the applicant, the risk/benefit profile of this medicinal product is to be positive.

VI REVISION DATE

08.11.2017