PUBLIC ASSESSMENT REPORT
Scientific Discussion

LORAMYC 50 mg muco-adhesive buccal tablets
Miconazole

FR/H/329/01/MR

Applicant: BIOALLIANCE PHARMA

Date of the PAR: September 2008


1. INTRODUCTION

The applicant submitted an application for a national marketing authorisation in France in 2005. Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for LORAMYC 50 mg, muco-adhesive buccal tablet from BioAlliance Pharma on the 10th of October 2006.

The product is indicated for:
"Treatment of oropharyngeal candidiasis in immunocompromised patients"

A comprehensive description of the indications and doses is given in the SPC.

As miconazole is a well-known active substance, no additional animal studies or microbiology studies were performed with this new formulation of miconazole due to an extensive series of nonclinical studies conducted in support of the original approval of topical agents containing miconazole.

A potential serious risk to public health concerns was raised by one Concerned Member State regarding the possible drug-drug interactions with Loramyc. Finally, it was agreed to grant a marketing authorisation with a post-approval commitment not to market the product in this CMS until an in-depth analysis of all published data about the clinical relevance of the listed drug-drug interactions. This part will have to be provided through a type II variation to be submitted within 3 months.

2. QUALITY ASPECTS

2.1 Introduction

The proposed medicinal product is presented in the form of a muco-adhesive buccal tablet containing 50 mg of miconazole.

The tablet presents a round and a flat side faces: the flat face is positioned facing the cheek mucosa; the round face is placed on the upper gum above the incisor tooth in order to adhere on it.

The excipients of the formulation are hypromellose, maize starch, lactose, sodium laurilsulfate, magnesium stearate and milk protein concentrate.

The tablets are packaged in HDPE bottle with a child-resistant closure containing a desiccant.

2.2 Drug substance

The drug substance, miconazole is described in the European Pharmacopoeia. It is a white to almost white powder, freely soluble in methyl alcohol, ethyl alcohol, acetone, chloroform, propylene glycol, soluble in ether; practically insoluble in water.

The manufacturer of the drug substance has submitted an ASMF.

The specifications are those of the Ph. Eur. monograph supplemented by an identity test by UV and by limits for 2,4-dichlorobenzylchloride, individual unknown impurities and residual solvents.
The specifications for impurities and residual solvents are in line with the recommendations of guidelines ICH Q3A and ICH Q3C. The retest period proposed is of 5 years when the drug substance is stored at a temperature below 25°C in a polyethylene bag closed inside a second polyethylene/aluminium bag inside a fibre drum. This is supported by the stability data provided.

2.3 Medicinal product

The objective of the development was to obtain a tablet with an oral extended release of miconazole that would be used as local treatment of candidiasis with little to no systemic absorption. The preliminary formulations were selected regarding dissolution, tablet swelling characteristics, tablet adhesivity properties. The formulation was optimized improving the release of miconazole.

The manufacturing process has been sufficiently described including process operating parameters, list of equipment, in-process controls performed at each stage. The manufacture is validated at the declared manufacturing site on three pilot batches. A protocol has been submitted for the validation at full-scale batch size.

All excipients are described in the current Ph. Eur except for milk protein concentrate (MPC). MPC is controlled according to in-house specifications. MPC is a well-known and extensively used excipient in the food industry. It is composed primarily of casein and lactose, both of which are GRAS. Other minor components of MPC include milk-derived proteins (albumin and globulins), as well as fat, water, and minerals. The only materials of animal origin are lactose and MPC. Satisfactory TSE statements have been provided.

The specifications of Loramyc tablets are considered appropriate to control the quality of the finished product in relation to its intended purpose. They include testing for identity, uniformity of dosage units, dissolution, water content, assay, related substances and microbial purity. Analytical methods have been described and validated. The stability data provided support the shelflife claimed in the SPC: 18 months when the product is stored at a temperature below 30°C, in the bottle tightly closed to protect from moisture.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

The non-clinical aspects of this product are based on clinical evidence of the safety and efficacy of miconazole, which is used in Europe, the United States, Japan and other countries for 30 years with various formulations. The non-clinical overview of this application contains a summary of all information obtained from the literature. However, local tolerance studies were performed with miconazole in animals. These local tolerance studies (jugal mucosa of hamster and sensitization LLNA assay in mice) did not show any toxicity.

Environmental risk

The potential environmental risks from the use and excretion of miconazole have been evaluated by an environmental risk assessment. The PEC in the surface water (PECSW) is 0.09 µg/L. The PECSW being significantly above the 0.01 µg/L limit concentration, this justified further analysis to be performed (Phase II environmental fate and effect).
4. CLINICAL ASPECTS

4.1 Introduction

Miconazole is a synthetic, imidazole, antifungal agent, which exerts its antifungal activity by inhibition of ergosterol biosynthesis in the cell membrane of the pathogenic organism. Miconazole is a fungicidal agent.

The drug substance is a well-known product, which has been marketed as various pharmaceutical formulations in more than 100 countries and approved in several European countries since 1973 under the trade name of Daktarin® (miconazole gel for oral candidiasis and tablets for gastro-intestinal fungal infections) and in the United States since 1974 under the name of Monistat® (miconazole nitrate for fungal vaginal infections). Tens of millions of patients in many countries, including Europe and the United States, have been treated with products containing miconazole. Therefore, miconazole is considered as a well-known active substance with established efficacy and safety profile.

For the treatment of oropharyngeal candidiasis, therapeutic options may vary from topical formulations (delivery of drug up to 5 times daily) to systemic formulation with a drug delivery allowing a single-dose administration. Topical agents are efficient and preferred in the treatment of oropharyngeal candidiasis (Pappas, 2004; Benson, 2004) due to their low systemic exposure and reduction of potential risk of drug-drug interactions. The main cause of therapeutic failure with topical agents is loss of treatment adherence. Indeed, the drug rapidly disappears from the oral cavity (transient concentration and short duration of concentration greater than the minimum inhibitory concentration [MIC]), and thus, the topical formulation has to be applied several times daily (5 times daily for the clotrimazole troches [Mycelex®], 4 times daily for the miconazole oral gel [Daktarin®], and several times daily for mouthwashes containing chlorhexidine, nystatin, and amphotericin B in suspension). As a consequence, poor treatment adherence could lead to microbial resistance. The other drawbacks which may limit the use of topical agents include inconvenient formulation (e.g., mouthwash, gel, and troches), bad taste and high level of sugar to hide the unpleasant taste. Some systemic azole antifungal agents lose gradually their potency due to the emergence of drug resistant yeasts.

Local treatment of oropharyngeal candidiasis in immunocompromised patients is the indication claimed by the applicant for this new muco-adhesive tablet formulation of miconazole.

4.2 Discussion on the clinical aspects

No additional specific pharmacodynamic properties with the new muco-adhesive tablet formulation of miconazole were performed by the applicant. This is acceptable insofar as the pharmacodynamic properties of the miconazole are already well characterized.

Clinical efficacy

Efficacy data derived from one well designed pivotal study in patients with head and neck cancer and undergoing chemotherapy, and comparing the new tablet formulation with miconazole buccal gel. The primary endpoint was the clinical efficacy on the oropharyngeal candidiasis at day 14 using success rate as evaluation criterion defined as the rate of complete or partial response at the end of treatment.

All patients had been treated by radiation therapy. More than half (66.7% of the modified Intent-To-Treat population and 70% of the Per Protocol population) had received chemotherapy, among them almost all patients had been treated with regimen containing platinum derivatives chemotherapy.
The analysis in the PP population showed that the rate of partial or complete responses was:

- In the muco-adhesive tablet group: 57.94% (62/107)
- In the reference group: 54.72% (58/106)

The point estimate of the difference (reference group rate minus bio-adhesive tablet group rate) with its 95%CI was: -3.22% [-16.7%; 10.3%].

The upper limit of the 95% confidence interval was compatible with a non inferiority demonstration (more stringent than the large pre-defined 20% non inferiority margin). Therefore, the two formulations can then be viewed as providing a similar rate of partial or complete responses. The point estimate was even in favour of the bio-adhesive formulation.

In addition the applicant has provided the results of an open-label, non comparative, study to enlarge the targeted population to HIV infected patients. This population was already included in the indication of the gel formulation.

The primary endpoint was the rate of complete or partial response at the end of the treatment (D15). A follow-up visit was scheduled on day 45 (i.e. up to 30 days after the end of the treatment), in all partial or complete responder patients.

The study patients were suffering from AIDS for about 10 years on average (119.8 ± 80.3 months). Despite highly active antiretroviral therapy (HAART), they were significantly immunosuppressed with a mean CD4+ cell count of 190/mm3, and one third of the patients had less than 50 CD4+ cells. The mean viral load was about 100,000 copies/mL. These patients presented other active viral diseases, such as hepatitis C (48% of co-infection) and hepatitis B virus (12% of co-infection).

Overall, in addition to the pharmacokinetic exploration of the new tablet as compared to the gel formulation, the clinical demonstration of the efficacy of this new formulation of miconazole for the treatment of oropharyngeal candidiasis was considered acceptable.

Clinical safety

The safety profile of Loramyc has been established based on:
- A pharmacokinetic study conducted in healthy volunteers (Study BA2000/01/01), N=18 patients
- Two Phase III clinical trials (Studies BA2002/01/02 and BA2002/01/03), N=172 treated with miconazole muco-adhesive tablet.

The safety database was considered acceptable.

The safety profile of the muco-adhesive tablet is somewhat different to that of the gel formulation on a qualitative point of view, with specific reports of dysgeusia.

An acceptable adherence to the muco-adhesive tablet was reported from the clinical studies.

However, as accidental swallowing of the muco-adhesive occurred frequently during clinical trials, it has been requested to the applicant to monitor the patients and reinforce information in the SPC with a specific warning as well as the package leaflet.

Pharmacovigilance System

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Minimisation Plan
As highlighted above, one of possible issues with this new formulation is the potential consequence of adhesion of the Loramyc tablets on the oesophagus. Indeed, the formulation adhered satisfactorily to the gum for about 78% of tablet applications. But, it should be mentioned that 45 patients (26.2%) swallowed a total of 132 tablets, and 75 patients (43.6%) expectorated a total of 309 tablets. The rates of discomfort, pain, burning, or bad taste were slightly more frequent and more severe in cases of expectoration or swallowing (no specific data provided).

The accidental swallowing of the tablet has been reported quite frequently in the clinical trials (6% of the applied tablets). A special attention of prescribers and patients on this risk of accidental swallowing is indicated in the SPC. However, the safety mention will have to be further reinforced in a forthcoming revision of the SPC. Moreover, the applicant will have to perform a specific review of the Adverse Events reported in patients who experienced an accidental ingestion compared to those who did not.

4.3 Pharmacokinetics

The muco-adhesive tablet exhibits a better pharmacokinetic profile as compared to the gel formulation gel with higher miconazole concentrations in saliva and a higher and longer exposure. The length of time with miconazole salivary concentrations above the Candida albicans MIC (1µg/mL), was indeed higher than the one obtained with the buccal gel: 7h vs 0.6h.

Data showed that miconazole concentrations in saliva were above 1 µg/ml for several hours. This allows a once daily application which represents a significant advantage over the buccal gel to be administered 4 times daily.

Regarding the duration of adhesion, the applicant was asked to provide the miconazole concentrations in saliva for patients with duration of adhesion lower than the mean value (15 h) in order to ensure that these patients were not exposed to sub-optimal concentrations of miconazole according to Candida albicans MIC (i.e. 1 µg/ml). Data showed that miconazole concentrations in saliva were above 1 µg/ml during several hours in these patients.

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Satisfactory chemical-pharmaceutical documentation has been provided in the dossier, assuring consistent and sufficient information on the quality of the product.

The muco-adhesive formulation provides a better pharmacokinetic profile as compared to the gel formulation reference of miconazole, especially with higher miconazole concentrations in saliva and a higher and longer exposure.

In patients suffering from oropharyngeal candidiasis, a similar response rate was achieved between the two formulations. In line with this PK profile improvement, the point estimate of the difference in terms of response rates between both formulations favours the mucoadhesive tablet.

The SPC, Package Leaflet (PL) and packaging are in the agreed template.

Several post-approval commitments were made during the procedure. The Member States mutually recognised the French evaluation of the marketing authorisation.
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

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ANNEX I – Repeat Use Procedure (FR/H/329/01/E/01)

The Repeat Use Procedure started on December 22\textsuperscript{nd}, 2009. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The Concerned Member States (AT, BG, CZ, EE, EL, HU, LT, LV, PL, PT, RO, SI, and SK), on the basis of the data submitted, recognised the French evaluation of the marketing authorisation. The repeat-use procedure was finished on March 22\textsuperscript{nd}, 2010.

The date for the first renewal will be: 10 October 2011.