HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

28 March 2007

LORAMYC 50mg, muco-adhesive buccal tablets
B/14, code CIP: 377 236-4

Applicant : BIOALLIANCE PHARMA

Miconazole

List I

Date of Marketing Authorisation: October 10, 2006

Reason for request: Inclusion on the list of medicines approved by National Insurance and approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Miconazole

1.2. Background
LORAMYC is a muco-adhesive buccal tablet containing miconazole.

1.3. Indications
Treatment of oropharyngeal candidiasis in immunocompromised patients, in particular those with head and neck cancer after radiotherapy and for HIV infected patients.

1.4. Dosage
For adults only:

Application of one muco-adhesive buccal tablet once a day for 7 to 14 days depending on the patient's response. The tablet should be applied in the morning, after brushing the teeth.

In case of complete clinical response (defined as complete resolution of disease signs and symptoms) after 7 days of treatment, the use of LORAMYC may be discontinued.

If there is no improvement after 7 days, the treatment should be continued for another 7 days.

Method of administration

LORAMYC should be applied to the upper gum just above the incisor:

- Once the tablet is removed from the bottle, it should be used immediately.
- The rounded side of the tablet should be applied on the upper gum above the incisor. Hold the tablet in place for 30 seconds with a slight pressure of the finger over the upper lip.
- If the tablet does not adhere properly, it should be repositioned.
- If the tablet falls off or is accidentally swallowed within the first 6 hours, it should be replaced immediately.
- With each application of LORAMYC, the tablet should be applied to alternate sides of the upper-gum.

LORAMYC can be used by the elderly.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

A : Digestive and metabolic systems
01: Stomatological preparations
A: Stomatological preparations
B: Anti-infectives and antiseptics for local oral treatment
09: Miconazole

2.2. Medicines in the same therapeutic category

These consist of imidazole antifungal medicines administered by oral route:

- fluconazole : TRIFLUCAN 50, 100 and 200mg, capsules and 2mg/ml, 50 mg/5 ml, 200mg/ml powder for oral suspension
- itraconazole : SPORANOX 10 mg/ml, oral solution

2.3. Medicines with similar therapeutic aim

These consist of other local antifungal medicines, administered by oral route:

- amphotericin B: FUNGIZONE,
- nystatin: MYCOSTATIN.
- miconazole: DAKTARIN 2%, oral gel.

3 ANALYSIS OF AVAILABLE DATA

The laboratory has submitted three studies:

- A pharmacokinetic study compared to Daktarin oral gel (BA2000/01/01), which will not be detailed in this opinion
- A comparative study versus Daktarin oral gel (BA2002/01/02) in patients with upper aerodigestive tract (UAT) cancer,
- A study conducted on HIV+ patients with sequential analysis (BA2002/01/03).

3.1. Efficacy

3.1.1. Study in patients with upper aerodigestive tract cancers (BA2002/01/02)

Objective: to evaluate the efficacy and safety of LORAMYC 50 mg compared to DAKTARIN oral gel in the treatment of oropharyngeal candidiasis in 282 patients treated with radiotherapy for a cancer of the upper aerodigestive tracts.

Methodology: Open-label, non-inferiority study compared to DAKATARIN oral gel, conducted on 282 patients treated for 14 days.

Inclusion criteria: adult patients with oropharyngeal candidiasis clinically diagnosed (presence of lesions ± symptoms) and mycologically diagnosed (number of cultures > 100 colonies) who have received radiotherapy for cancer of the upper aerodigestive tract.

Non-inferiority was accepted if the lower margin of the confidence interval for the observed difference did not exceed a limit set at -20%.

Exclusion criteria: systemic candidiasis or located in a non-oropharyngeal area, hepatic impairment, antifungal treatment administered in the 14 days prior to inclusion, concomitant treatments likely to interfere with miconazole activity (AVK, hypoglycaemic sulfamides, cisapride, astemizole, phenytoin, etc.).

Treatment:

- LORAMYC 50 mg, one application daily (n=141),
- DAKTARIN oral gel, 4 applications daily (n=141).

Primary efficacy endpoint: The percentage of responders at end of treatment (D14) with complete responses (complete resolution of lesions) and partial responses (decrease by at least 2 extension score points for oral lesions assessed on Murray[1] scale).

Secondary endpoints: The percentage of responders at D7, percentage of improvement of symptoms at D14 (partial response), disappearance of symptoms (complete response) at D7 and D14, rate of relapse at D7 and D14 and time to relapse onset in responders at D14, mycological response, observance, safety.

[1] 0= no lesions, 1= single localised lesion, 2= multiple localised lesions, 3= extensive or confluent lesions

Results:
The analysis in modified ITT was conducted on 282 patients and the *per-protocol* analysis on 213 patients.

Table 1: Primary efficacy endpoints: Percentage of responders (Complete Response + partial response) at D14

	LORAMYC 50 mg number (%)	**DAKTARIN oral gel** Mean (SD)	Mean difference 95% CI	P
Responders PP Analysis	N=107 62 (57.94%)	N=106 58 (54.72%)	 -3.22% [-16.7%; 10.3%]	<0.0001
Responders Modified ITT analysis	N=141 79 (56.03%)	N=141 69 (48.94%)	 -7.09% [-19%; 4.8%]	<0.0001

After 14 days of treatment, the upper margin of the confidence interval for the observed difference was 10.3%, below the limit established in the protocol (20%); hence, the non-inferiority of LORAMYC 50 mg compared to DAKTARIN oral gel was demonstrated.
The modified ITT analysis confirmed the *per-protocol* observed results.

An additional analysis with adjustment of the results for the extent of lesions and xerostomia at baseline was undertaken by the laboratory. This analysis was conducted on sub-groups defined post-factum, and therefore only confers an investigational value to the results.

Secondary endpoints:
A complete response at D14 was observed in:

- 57/107 patients (53.27%) under LORAMYC treatment *versus* 55/106 (51.89%) under DAKTARIN oral gel treatment (difference -1.4, CI [-15.1%; 12.3%]): *per-protocol* analysis.
- 74/141 (52.48%) *versus* 64/141 (45.39%), (difference –7.09, CI [-19%; 4.8%]): modified ITT analysis.

The rates of relapse at D30 and D60 and their time to onset, as well as the other results observed on the other secondary endpoints, did not vary among the groups.

3.1.2. Study conducted on HIV+ patients (BA2002/01/03)
This study assessed the efficacy and safety of LORAMYC 50 mg in the treatment of oropharyngeal candidiasis in 25 HIV+ patients.
The percentage of responders (complete response + partial response) was 84% (21/25 patients) with 52% for complete response (13/25) and 32% for partial response (8/25).
32% of patients had a relapse at 45 days.

3.2. Adverse events

The adverse events observed during the studies were similar to those described in the SPC for LORAMYC.

In study BA2002/01/02, the frequency of adverse events was similar in both groups. The most frequently observed events were: gastrointestinal disorders, including abdominal pain, nausea, vomiting, and dysgeusia.

Nine patients discontinued their treatment due to adverse events: 3 in the LORAMYC group (one of which was product-related) and 6 in the miconazole oral gel group, 2 of which were product-related.

3.3. Conclusion

In study BA2002/01/02, after 14 days of treatment the upper margin of the confidence interval for the observed difference was 10.3%, below the limit established in the protocol (20%); hence the non-inferiority of LORAMYC 50 mg compared to DAKTARIN oral gel was demonstrated.

Safety was satisfactory, comparable to the safety profile for LORAMYC validated in the SPC.

The Committee regrets the absence of any direct comparative study with TRIFLUCAN and FUNGIZONE.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Oropharyngeal candidiasis is a disorder that may result in degradation of general condition (pain, dietary intake disorder, denutrition, etc.).

This medicinal product is intended as a curative treatment.

The efficacy/safety ratio of this medicinal product is average.

LORAMYC is a first-line therapy.

There are medicinal treatment alternatives.

> Public health benefit
> The burden on public health imposed by oropharyngeal candidiasis in immunocompromised patients (in particular those with head and neck cancer after radiotherapy and HIV infected patients), despite their potential severity, is low due to the scarcity of these disorders in the general population.
> Managing these disorders does not constitute an identified public health priority in light of the available treatments.
> Given the available data, it is not expected that LORAMYC will have an impact in reducing the morbidity of these patients or on their quality of life.
> Therefore, LORAMYC is not expected to have a public health benefit in this indication.

The actual benefit provided by LORAMYC in the treatment of oropharyngeal candidiasis in immunocompromised patients, in particular patients with upper aerodigestive tract cancer after radiotherapy and in HIV infected patients is substantial.

4.2. Improvement in actual benefit

LORAMYC, a muco-adhesive buccal tablet containing miconazole, does not provide improvement in actual benefit compared to miconazole oral gel (IAB V).

Nevertheless, the Committee emphasizes that this new pharmaceutical formulation represents a useful treatment option for patients.

4.3. Therapeutic use

HIV patients:

Per the Yeni 2006[2] report, the first episodes of oral candidiasis are treated with local antifungal agents: nystatin, miconazole or amphotericin B. In severe cases or in case of frequent relapse, fluconazole 100 mg/day in a single administration, or itraconazole solution 200 mg/day, is employed until resolution of the clinical symptoms (7 to 10 days).

Cancer patients

Treatment of oropharyngeal candidiasis in non-HIV+ immunocompromised patients is considerably less regulated but follows the same protocol. In practice, LORAMYC may be a viable alternative to local treatments used as first-line therapy in limited and/or less recurrent forms. The efficacy of LORAMYC in oesophageal candidiasis has not been shown[3,4].

[2] "Prise en charge médicale des patients infectés par le VIH", rapport Yeni 2006.
[3] Koletar, S.L., et al., Comparison of oral fluconazole and clotrimazole troches as treatment for oral candidiasis in patients infected with human immunodeficiency virus. Antimicrob Agents Chemother, 34: p. 2267-8. 1990.

4.4. Target population

The target population comprises patients with upper aerodigestive tract (UAT) cancer after radiotherapy and HIV infected patients developing oropharyngeal candidiasis. This may be estimated from the following data:

HIV+ patients

- Per the Yeni 2006 report, the prevalence of AIDS is approximately 130,000 patients in France.
- Of these patients, 5% are at risk of developing an oral candidiasis, which represents approximately 6,500 patients (specialist opinion).

Patients with upper aerodigestive tract cancer (UAT)

The number of new cases of upper aerodigestive tract cancer was estimated at approximately 22,000[5,6] in 2000.

According to the specialists, 50% of these patients are eligible for combination radiotherapy + chemotherapy and approximately 3,000 patients can only be treated through radiotherapy, i.e. 14,000 patients.

Among these, approximately 30% are likely to develop oropharyngeal candidiasis, i.e. approximately 4,000 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services.

Packaging: Appropriate for the prescription conditions

The Committee recommends that a box of 7 tablets be made available in addition to the 14-tablet box.

Reimbursement rate: 65%

[4] Flynn, P.M., et al., Oropharyngeal candidiasis in immunocompromised children: a randomized, multicenter study of orally administered fluconazole suspension versus nystatin. The Multicenter Fluconazole Study Group. J Pediatr, 127: p. 322-8. 1995.

[5] Rapport de la Commission d'orientation sur le cancer, INVS 2003

[6] Remontet L, Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. INVS 2003