

miconazole, 50mg muco-adhesive buccal tablets (Loramyc®)
No. (517/08)

SpePharm UK Ltd

07 November 2008

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

miconazole muco-adhesive buccal tablets (Loramyc®) are not recommended for use within NHS Scotland for the treatment of oropharyngeal candidiasis in immunocompromised patients.

Miconazole muco-adhesive buccal tablets were shown to be non-inferior to another locally-acting miconazole preparation in the treatment of oropharyngeal candidiasis in patients with cancer of the head and neck who had received radiotherapy.

There are no data comparing miconazole buccal tablets to treatments currently used in practice in NHS Scotland.

The manufacturer did not present a sufficiently robust analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients.

Dosing information

Application of one muco-adhesive buccal tablet once daily for 7 to 14 days depending on clinical response.

Product availability date

10 July 2008

Summary of evidence on comparative efficacy

Miconazole is an imidazole antifungal drug with broad-spectrum activity against the most frequent species of *Candida* involved in oropharyngeal candidiasis (OPC). It acts by inhibiting ergosterol biosynthesis in the fungal cell membrane. It has been formulated as a muco-adhesive buccal tablet to be applied to the upper gum, providing local antifungal activity with low systemic bioavailability of miconazole (25-30%).

The evidence comes from an open-label, randomised, non-inferiority trial in adult patients with cancer of the head and neck who had received radiotherapy. The patients had OPC, (first episode or relapse following treatment), diagnosed by clinical criteria and direct microscopic examination or positive fungal culture with >100 colonies.

Patients were randomised in a 1:1 ratio to receive 14 days treatment with a miconazole 50mg buccal tablet applied once daily to the upper gum and retained in the oral cavity until completely dissolved, or miconazole 500mg oral gel daily divided into four equal doses of 125mg. The gel was to be kept in the mouth for as long as possible before being swallowed.

The primary endpoint was clinical success (complete or partial response) at day 14 in the modified intention to treat (mITT) population i.e. all randomised patients who received at least one treatment dose and had one efficacy evaluation after randomisation. Complete response was defined as the complete disappearance of OPC lesions and partial response as improvement compared with baseline score of at least 2 points on the Murray Scoring Scale (a 4 point scale used to evaluate the extent of OPC lesions, where 0=none, 1=single localised, 2=multiple localised, 3=extensive or confluent). All other responses were considered failures. The non-inferiority margin was 20%. An amendment, implemented after the inclusion of 59 patients, introduced blind assessment of the primary endpoint by an independent healthcare member unaware of study drug allocation.

At day 14, the success (complete or partial response) rate in the mITT population of 282 patients was numerically higher in the buccal tablets group, 56% (n=79/141), compared with the oral gel group, 49% (n=69/141), (95% confidence interval: -19%; 4.8%). Non-

inferiority of miconazole buccal tablets to miconazole oral gel was demonstrated. The proportions of complete responders at day 14 were 52% versus 45% for the buccal tablets and oral gel groups, respectively, a statistically significant difference. Improvements in clinical symptoms and oral lesions were similar between treatment groups.

Recurrence rates for complete responders were not significantly different between the buccal tablets and oral gel groups: 19% versus 12%, and 22% versus 17%, at days 28 and 60, respectively.

At day 7, (unblinded evaluation), clinical success rates were 14% versus 20% in the buccal tablets and oral gel groups, respectively.

The buccal tablets were still adherent to the gum in 91% and approximately 60% of patients at least 6 hours and 12 hours after application, respectively.

Summary of evidence on comparative safety

The adverse event (AE) profiles of miconazole buccal tablets and miconazole oral gel were similar. Adverse events considered by the investigator to be treatment-related were more frequent in the buccal tablets group than in the oral gel group (18% and 14%, respectively). Very few of the treatment related AEs reported were severe (2.7% in the buccal tablets group, 1.4% in the oral gel group).

Oral discomfort and dysgeusia were the most frequent AEs reported by patients. The frequency of oral discomfort was similar between treatment groups; four patients (2.7%) in the buccal tablets group and five patients (3.4%) in the oral gel group. Dysgeusia, was reported only in the buccal tablets group (nine patients [6.1%]). It was reported only in one radiotherapy centre and no patients discontinued the trial for this reason.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Miconazole buccal tablets were shown to be non-inferior to miconazole oral gel in treating OPC in patients with head and neck cancer who had undergone radiotherapy. However the choice of comparator may not be appropriate. The daily dose of miconazole in the oral gel used in the trial was 500mg, whereas the UK licensed dose range is 480 to 960mg. SMC expert opinion suggests that miconazole oral gel is not widely used in Scotland for this indication. Although there is no standard treatment for OPC in immunocompromised patients, SMC experts have advised that nystatin and fluconazole are the first-line choices in Scotland. There are conflicting views concerning the use of topical or systemic antifungals as first-line treatment. The British National Formulary advises that topical therapy may not be adequate in immunocompromised patients and that an oral triazole antifungal is preferred.

Efficacy was limited. After seven days treatment only 14% of patients receiving miconazole buccal tablets achieved complete or partial response. This rose to 56% after 14 days treatment.

Results of a pharmacokinetic study demonstrated significantly higher salivary concentrations of miconazole in patients taking miconazole buccal tablets compared to miconazole oral gel, however there was not a corresponding improvement in efficacy in the pivotal trial.

The summary of product characteristics for miconazole buccal tablets advises that the demonstration of efficacy in HIV positive patients cannot be considered robust. The only evidence is from 26 patients who participated in a non-comparative open-label study.

The pivotal trial did not compare patient acceptability and compliance with miconazole buccal tablets or miconazole oral gel

It has been postulated that the use of miconazole buccal tablets may lead to a reduction in the use of systemic antifungals, with potentially less antifungal resistance, however there is no evidence to support this.

Summary of comparative health economic evidence

The manufacturer presented a simple drug budget impact analysis rather than a formal economic analysis. This compared miconazole buccal tablets with a number of alternative treatments for OPC. The pivotal clinical trial demonstrated that miconazole buccal tablets were non-inferior to miconazole oral gel and this was the main comparison in the submission. The manufacturer indicated that treatment with miconazole buccal tablets instead of miconazole oral gel would result in a net drug cost of £32.52 per 14 day course of treatment.

There were a number of significant weaknesses with the analysis:

- The manufacturer compared miconazole buccal tablets with miconazole oral gel based on a non-inferiority trial in patients with head and neck cancer. However, SMC clinical experts have indicated that nystatin and fluconazole are the main first-line treatments. No clinical evidence was presented comparing miconazole buccal tablets with these treatments, only a comparison of the drug costs. The inappropriate choice of comparator was highlighted in the budget impact section of the submission where the manufacturer used fluconazole as the main comparator.
- No justification was given for the increased cost of miconazole buccal tablets with only non-inferiority trial evidence presented compared to miconazole oral gel. The increased cost associated with miconazole buccal tablets has not been justified by evidence of increased efficacy or improvements in quality of life. It was stated in the submission that miconazole buccal tablets could increase compliance and patient satisfaction due to once daily dosing but no evidence was presented to support these assertions.
- The choice of time horizon may not have been appropriate given the potential for patients to relapse and require re-treatment. This information was collected in the trial but was not used in the analysis. The rate of recurrence was numerically greater in the miconazole buccal tablet group.

- The clinical evidence presented was only based on patients with head and neck cancer. It is not clear if the results would generalise to all immunocompromised patients.

Due to the lack of formal economic analysis and the inappropriate choice of comparator, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A patient interest group submission was not made.

Additional information: guidelines and protocols

The World Health Organisation guidelines entitled 'HIV/AIDS Treatment and Care: Clinical protocols for the WHO European Region 2007, state that buccal miconazole is the recommended first-line treatment for oral candidiasis in patients with HIV/AIDS.

Additional information: comparators

Possible comparators are topical treatments: miconazole oral gel, nystatin oral suspension, and amphotericin lozenges, or systemic treatments: fluconazole or itraconazole. Ketoconazole is indicated for OPC that cannot be treated topically in patients resistant to or intolerant of both fluconazole and itraconazole

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
miconazole buccal tablets	One 50mg tablet applied to the gum daily for 7 to 14 days	26 to 52
Local treatments		
miconazole oral gel [#]	5 to 10ml orally four times daily until up to 2 days after clearance of symptoms*	9 to 42
amphotericin lozenges	4 to 8 lozenges dissolved in the mouth daily for 10 to 15 days ^{##}	4 to 7
nystatin	1ml orally four times daily until 2 days after clinical cure*	2 to 4
Systemic treatments		
fluconazole oral suspension	50 to 100mg orally daily for 7 to 14 days	17 to 66
fluconazole capsules		0.5 to 2
itraconazole	One 100mg capsule orally daily for 15 days (increased to two capsules in AIDS)	15 to 29

	or neutropenic patients) or 200mg in 20ml oral solution daily for one to two weeks)	49 to 97
ketoconazole	One to two 200mg tablets daily for 2 to 3 weeks**	7 to 20

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 28.08.08. #Assumed use of 80g tube oral gel *Assumed treatment duration of 7 to 14 days. ** Treatment duration recommended in British National Formulary ##Cost based on dispensing whole packs of lozenges.

Additional information: budget impact

The main comparator used in the budget impact section was fluconazole. The manufacturer estimated the cost offset of patients switching from fluconazole suspension or capsules to miconazole buccal tablets. The manufacturer estimated that switching from fluconazole oral suspension would result in savings of between £1.6k and £1.9k in year 1 rising to between £6k and £10k in year 5. Based on patients switching from fluconazole capsules, there would be a cost increase of between £5k and £7k in year 1 rising to between £21k and £36k in year 5. These figures were based on 109 to 135 patients in year 1, rising to 426 to 718 in year 5. Market share was estimated to be around 5% in year 1 rising to between 15% and 20% in year 5. SMC clinical experts have indicated that fluconazole capsules are more commonly used in practice unless the patient has difficulty swallowing.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 17 October 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

The undernoted reference was supplied with the submission.

Bensadoun RJ, Daoud J, El Gueddari B et al. Comparison of the efficacy and safety of miconazole 50mg mucoadhesive buccal tablets with miconazole 500mg gel in the treatment of oropharyngeal candidiasis. A prospective, randomised, single blind, multicentre, comparative, phase III trial in patients treated with radiotherapy for head and neck cancer. Cancer 2008; 112:204-11