

Re-submission

miconazole, 50mg, muco-adhesive buccal tablet (Loramyc[®])
SMC No. (517/08)

Therabel Pharma UK Ltd

14 January 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a re-submission

miconazole muco-adhesive buccal tablet (Loramyc[®]) is not recommended for use within NHS Scotland.

Indication under review: The treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients.

Miconazole muco-adhesive buccal tablets were shown to be non-inferior in the treatment of OPC to another locally-acting miconazole preparation in patients with cancer of the head and neck who had received radiotherapy, and to another locally-acting anti-fungal in HIV-positive patients. There are no data comparing miconazole buccal tablets to treatments currently used in practice in Scotland in this patient group.

Overall the manufacturer did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

The treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients.

Dosing Information

Application of one muco-adhesive buccal tablet once a day for 7 to 14 days depending on the patient's clinical response.

It is preferable to apply the tablet in the morning, after brushing of the teeth. It can be administered with food and drink.

In case of failure to improve after 7 days, the treatment should be continued for 7 additional days. In the event of complete clinical response (defined as complete resolution of disease signs and symptoms) after 7 days of treatment, treatment can be stopped.

Product availability date

May 2008

Summary of evidence on comparative efficacy

Miconazole is an imidazole antifungal drug with broad-spectrum activity against the most common *Candida* species involved in 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 manufacturer has requested that SMC consider the use of miconazole muco-adhesive buccal tablets in a restricted patient population, for the treatment of immunocompromised patients in whom first-line treatment with fluconazole was not successful.

Evidence for the efficacy of miconazole muco-adhesive buccal tablets came from two comparative randomised controlled studies, one in HIV-positive patients and one in patients being treated for head and neck cancer.

In a phase III, non-inferiority study, 578 HIV-positive adult patients with clinically diagnosed OPC and a Eastern Cooperative Oncology Group (ECOG) score <2 were randomised in a double-blind manner to either once daily 50mg miconazole muco-adhesive buccal tablets or clotrimazole 10mg troches (lozenges) five times daily, both for 14 days. Patients who had had recent systemic or local anti-fungals or who were taking concomitant treatments likely to interfere with miconazole were excluded. The primary endpoint was clinical cure at the test-of-cure visit (day 17 to 22), where clinical cure was defined as the complete resolution of the signs and symptoms of OPC. Both signs and symptoms were assessed on 4-point scales, where 0=absent and 3=severe. A clinically relevant non-inferiority margin of 15% was selected.

The clinical cure rates at the test-of-cure visit were 65% (187/287) for the clotrimazole group and 61% (176/290) for the miconazole group, in the ITT population, with a treatment difference between the two groups of -4.5% (95% confidence interval (CI): -12.4 to 3.4). Similar findings were reported for the per protocol (PP) population, with clinical cure rates of 74% (175/236) and

68% (164/240) for the clotrimazole and miconazole groups, respectively. Treatment difference between the two groups was -5.9% (95% CI: -14.0 to 2.2). Thus, the non-inferiority of miconazole muco-adhesive buccal tablets once daily to clotrimazole troches five times daily was demonstrated. Secondary outcomes reported in the ITT population included the percentages of patients clinically cured on day 7, which were 25% (71/287) of clotrimazole patients and 23% (67/290) of miconazole patients, and the rate of relapse at day 35, which was 27% (53/197) of clotrimazole patients and 28% (51/183) of miconazole patients, both non-significant differences.

A phase III, non-inferiority, open-label study recruited 306 adults with cancer of the head and neck, who had received radiotherapy, with clinically diagnosed OPC. Exclusion criteria included concomitant medication likely to interact with miconazole and patients who had recently used anti-fungal treatment. Patients were randomised to 14 days treatment with a miconazole 50mg muco-adhesive buccal tablet applied once daily or miconazole 500mg oral gel daily divided into four equal doses of 125mg. The primary endpoint was clinical success (complete or partial response) at day 14 in the modified intention to treat (mITT) population. Complete response was defined as the complete disappearance of OPC lesions and partial response as improvement compared with baseline score of at least two points on the Murray Scoring Scale (a 4 point scale, 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%.

At day 14, the clinical success rate in the mITT population was numerically (though not statistically significantly) higher in the buccal tablets group, 56% (n=79/141), compared with the oral gel group, 49% (n=69/141). Non-inferiority of miconazole muco-adhesive buccal tablets to miconazole oral gel was demonstrated. Secondary outcomes included the proportions of complete responders at day 14, which were 52% versus 45% for the buccal tablets and oral gel groups, respectively, and relapse rates for complete responders for the buccal tablets and oral gel groups, which were 19% versus 12%, and 22% versus 17%, at days 30 and 60, respectively.

Summary of evidence on comparative safety

Miconazole muco-adhesive buccal tablets were well tolerated overall. The adverse event (AE) profiles observed for miconazole muco-adhesive buccal tablets, clotrimazole troches and miconazole oral gel were similar. No drug-related serious adverse events (AEs) were reported.

The number of adverse events considered by the investigator to be treatment-related was similar between drugs in both studies. In the study in HIV-positive patients, these occurred in 24% of patients receiving miconazole muco-adhesive buccal tablets and 23% of those receiving clotrimazole troches. In the study in patients with head and neck cancer, 18% of patients receiving miconazole muco-adhesive buccal tablets reported treatment-related AEs and 14% of those in the miconazole oral gel group. Very few of the treatment related AEs reported were severe (2.7% in the miconazole muco-adhesive buccal tablet group and 1.4% in the miconazole oral gel group).

The most frequently reported treatment-emergent AEs with the buccal tablets were headache, nausea, diarrhoea and dysgeusia. Apart from dysgeusia, the number of AEs reported was similar to the other treatments groups. Dysgeusia was reported in 2.4% of patients in the miconazole muco-adhesive buccal tablet groups, in 1.0% of those taking clotrimazole troches and in no patients using the miconazole oral gel. Oral discomfort was reported by 1.3% of

miconazole muco-adhesive buccal tablet patients, 0.3% of clotrimazole troche patients and 1.4% of miconazole oral gel patients.

Summary of clinical effectiveness issues

Miconazole buccal tablets have been shown to be non-inferior to miconazole oral gel in treating OPC in patients with head and neck cancer who had undergone radiotherapy and to clotrimazole troches in treating OPC in HIV-positive patients.

The manufacturer has requested that SMC consider the use of miconazole muco-adhesive buccal tablets for the treatment of immunocompromised patients in whom first-line treatment with fluconazole was not successful. However, this patient population was not identified in either study and so the effect of the buccal tablets in this patient group has not been established. Indeed, in the two studies submitted, recent prior use of anti-fungal treatment was an exclusion criterion. The extrapolation of data from first-line use to second-line use in presumably more resistant disease is implausible. The British National Formulary advises that topical therapy may not be adequate in immunocompromised patients and that an oral triazole antifungal is preferred. Experts support this advice, suggesting that a topical agent would usually not be an appropriate second line treatment after failure of first line systemic treatment.

There are a number of limitations in the evidence base. With regard to the comparators used in the studies, one was a different formulation of miconazole and the other was a topical treatment not available in the UK. These comparators are unlikely to represent treatment selection for the positioning sought by the company. Different endpoints were used in the studies: one used an endpoint of a combination of complete and partial success, while for the other, the endpoint was complete cure. Response rates were low, with only 61% of the HIV-positive patients and 52% of patients with head and neck cancer achieving complete cure.

There were differences between treatment groups in the two comparative studies with regard to baseline OPC severity. In both studies, patients in the miconazole muco-adhesive buccal tablets groups were more severely affected.

None of the studies reviewed investigated patient acceptability or satisfaction with the treatments assigned to them although patient compliance was measured.

The company has suggested that itraconazole is commonly used after failure of fluconazole and that the oral solution of itraconazole is the appropriate comparator for miconazole buccal tablets. However, the oral solution is not always acceptable for patients, due to its reported unpleasant taste. There are no head-to-head data comparing miconazole muco-adhesive buccal tablets and itraconazole in immunocompromised patients and so the manufacturer undertook an adjusted indirect comparison using the Bucher method. There were many inconsistencies between the studies used, including drug doses, duration of treatment, drug formulations, study endpoints and date of assessment of relapse. Adjusted relative risks calculated suggested that there was no significant difference between miconazole muco-adhesive buccal tablets and itraconazole in terms of clinical cure rate or relapse rate. However, the indirect comparison was not considered robust enough to accept this conclusion.

Summary of comparative health economic evidence

The manufacturer presented a cost-effectiveness analysis comparing miconazole muco-adhesive buccal tablets to itraconazole oral solution in a subset of immunocompromised patients in whom first line treatment with fluconazole was not successful. The time horizon for the analysis was 45 days, to correspond with a two-week treatment period and a follow-up period to allow for any relapses. The analysis was structured around a decision-tree which allowed for patients to have successful or unsuccessful treatment and for patients who had initially successful treatment to relapse. Patients treated with miconazole who had unsuccessful treatment were assumed to switch to treatment with itraconazole oral solution whereas patients in the comparator arm were assumed to switch to treatment with posaconazole.

There was an absence of clinical data to support the positioning proposed by the manufacturer and also a lack of direct trial evidence for miconazole versus itraconazole. As such, the manufacturer conducted an adjusted indirect comparison to derive effectiveness estimates to drive the economic model. Costs in the model related to drug acquisition costs and costs associated with extra consultant appointments for patients who failed on treatment or relapsed.

The results of the analysis indicated that miconazole was associated with cost savings but was also less effective than itraconazole oral solution. Miconazole was associated with a saving of £64.59 per patient but was also 11.4% less effective to give a cost-effectiveness ratio of £566.82 per patient successfully treated. Note however, that this is a cost-effectiveness ratio in the south-west quadrant (new medicine less effective and less expensive) rather than the more usual north-east quadrant (i.e. new medicine more effective and more expensive) of a cost-effectiveness diagram. Sensitivity analysis indicated that the results were most sensitive to the relative risks estimated from the indirect comparison.

The analysis had a number of limitations:

- There were no head-to-head data available and thus an indirect comparison had to be conducted.
- The clinical evidence feeding into the indirect comparison and economic analysis did not match the positioning proposed by the manufacturer for the product.
- The manufacturer presented a cost-effectiveness rather than cost-utility analysis which made it more difficult for SMC to be able to judge whether the treatment offers value for money as there are no readily available thresholds by which to judge the ratio.
- There appears to be some concerns over the indirect comparison in terms of the consistency of the studies, in terms of things like dose, duration of treatment, mode of treatment (tablet/oral solution), patient ages, ITT or PP analyses and definition of response. These could have influenced the results and the sensitivity analysis showed that the results were sensitive to the outputs of the indirect comparison.
- No comparison was provided with miconazole gel, which may be a relevant comparator.

Given these issues, the economic case was not demonstrated.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: guidelines and protocols

The “British HIV Association guidelines for the treatment of opportunistic infection in HIV-positive individuals”, published for consultation in 2010, state that “azoles and topical treatment are equally effective at treating oropharyngeal candidiasis but azole therapy is associated with a lower risk of relapse.” They continue “There are a number of newer antifungal drugs which can be considered for the treatment of fluconazole-refractory disease. These include the new azoles, voriconazole and posaconazole, and the echinocandins, caspofungin, micafungin and anidulafungin, which have shown efficacy in randomised clinical trials against oesophageal candidiasis although cost means their use should be reserved for cases where traditional fluconazole therapy is ineffective, not tolerated or where infection is due to organisms with altered susceptibility to first-line agents.” Miconazole is not mentioned as a choice.

NHS Scotland’s “Scotland’s Health on the Web” published “Oral care guidelines for palliative care patients” in 2009, and these recommend nystatin oral suspension or miconazole oral gel as first-line treatments and fluconazole capsules as second-line treatment.

The World Health Organisation guidelines entitled ‘HIV/AIDS Treatment and Care: Clinical protocols for the WHO European Region’ from 2007, state that buccal miconazole or oral fluconazole are the recommended first-line treatment for oral candidiasis in patients with HIV/AIDS, with second line treatment being oral itraconazole.

Additional information: comparators

Possible comparators are topical treatments: miconazole oral gel and nystatin oral suspension; or oral anti-fungal preparations, including fluconazole, itraconazole and posaconazole. Ketoconazole is indicated for OPC that cannot be treated topically in patients either resistant to fluconazole or itraconazole or intolerant of these agents, but it has been associated with fatal hepatotoxicity.

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
Topical treatments		
nystatin suspension	1 mL used four times daily, until 2 days after clinical cure	2 to 4
miconazole oral gel	5 to 10mL applied four times daily, for 7 to 14 days	2
Oral treatments		
posaconazole suspension	200mg for 1 day, then 100mg once daily for 13 days	491
itraconazole oral liquid	200mg daily for 1 or 2 weeks	46 to 92
itraconazole capsules	100 to 200mg daily for 15 days	7 to 14
fluconazole oral suspension	50 to 100mg daily, for 7 to 14 days	17 to 66
fluconazole capsules		1 to 5
ketoconazole	200 to 400mg daily, for 2 to 3 weeks	6 to 19

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 8 November 2010, and for posaconazole from Monthly Index of Medical Specialties October 2010. For treatment with oral gel, it is assumed that full tubes are dispensed. For treatment with liquid preparations, it is assumed that full bottles are dispensed.

Additional information: budget impact

The manufacturer estimated drug budget savings of between £36k and £45k per year if all patients were treated with miconazole muco-adhesive buccal tablets rather than itraconazole oral solution.

The estimates were based on an assumption that between 881 and 1081 prescriptions of miconazole muco-adhesive buccal tablets or itraconazole oral solution would be issued each year. It should be noted that these calculations assumed a level of relapse among treated patients of between 10% and 35% (hence the range in number of prescriptions) and that the relapse rate applied equally to miconazole and itraconazole. The baseline number of eligible patients was just over 800 per year. The projected savings assumed a 100% market share for miconazole muco-adhesive buccal tablets.

References

The undernoted references were supplied with the submission.

Clinical Study Report (BA2004/01/04). A Comparative Randomised, Double-Blind, Double-Dummy, Multicenter Study of the Efficacy and Safety of Miconazole Lauriad® 50mg Administered Once a Day and Mycelex® Troches (Clotrimazole 10mg) Administered Five Times a Day in the Treatment of Oropharyngeal Candidiasis in Immunocompromised Patients: The SMiLES study.

Clinical Study Report (BA 2002/01/02). Comparison of the efficacy and safety of miconazole Lauriad® tablets to those of miconazole gel in the treatment of oropharyngeal candidiasis. A multicentre, randomised, phase III trial in patients treated with radiotherapy for head and neck cancer.

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

This assessment is based on data submitted by the applicant company up to and including 10 December 2010.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.