WHO Essential Drug list

Application for inclusion of miconazole nitrate 10 mg muco-adhesive buccal tablet

1. **Summary statement of the proposal for inclusion/change/deletion**
   The following is a formal application to the WHO Essential Drug list requesting the inclusion of miconazole nitrate 10 mg muco-adhesive buccal tablet for the treatment of oro-pharyngeal candidiasis. Although fluconazole is mentioned on the Essential Drug list, as an example of the therapeutic "azole" group, we are requesting special mention of the muco-adhesive tablet containing miconazole, based on the substantial patient advantages in terms of user friendliness and safety. The product offers a safe and effective alternative to systemic treatment in immune-compromised populations in resource-poor settings.

2. **Name of the focal point in the WHO department or program submitting the application**
   Dr. T. Turmen (Executive Director, WHO Family, Community and Health Programme)

3. **Name of the organization consulted and supporting the application**
   WHO (see copy of the Home Based Care and Community Care proposals sponsored by the Belgian and Italian governments in Tanzania, Burundi, Mozambique and Uganda in Attachment 1)
   MSF (see copy of treatment guidelines in Attachment 2)
   IDA (see copy of newsletter in Attachment 3)
   PLHIV/AIDS: testimonials available upon request

4. **International Nonproprietary Name of the drug:**
   miconazole nitrate 10 mg muco-adhesive buccal tablet

5. **Category of listing requested**
   Section 6: Anti-infective Drugs
   6.3Antifungal drugs
   °fluconazole capsule, injection and oral suspension is listed as an example of a therapeutic group (the "azoles"). Various drugs can serve as alternatives.
   Griseofulvin (capsule or tablet)
   Nystatin (tablet, lozenge or pessary)
   Complementary drugs (Flucytosine (B), potassium iodide (A))

6. **Information supporting the public health relevance (epidemiological information on disease burden, target population, cost)**

Epidemiological information on disease burden

HIV/AIDS with an estimated 5million new cases for 2001 of which 3.4million for the Africa continent alone has become the major global health challenge. Oral candidiasis is

one of the most frequently occurring opportunistic infections in HIV/AIDS. Repeated infections (2-3 occurrences per year) are estimated in patients with CD4 counts below 200. Oropharyngeal candidiasis is almost invariably linked to the oral condition and oesophageal candidiasis becomes a frequent problem with CD4 counts below 50. Among hospitalised African AIDS patients point prevalences of 45% have been reported. (AIDS epidemic update – December 2001, UNAIDS website; Sonnet J, Taelman H. Clinical and biological profile of African AIDS. In Stacquet M, Hemmer R & Baert A (eds): Clinical aspects of AIDS and AIDS related complex. Oxford University Press, Oxford 1986: 78-89.)

The 'Guidelines for the clinical management of HIV infection in adults',WHO/GPA, recommend to use Nystatin 100,000 IU orally 3 times daily for 7 days or gentian violet as first line treatments for oropharyngeal candidiasis. Ketoconazole 200mg twice daily for 2 weeks was recommended for the treatment in cases of suspected oesophageal candidiasis. (Global Programme on AIDS. Guidelines for the clinical management of HIV infection in adults. WHO, Geneva, 1991. WHO/GPA/IDS/HCS91.6.) In a cost-effectiveness comparative study sponsored by WHO/GPA, it was concluded that in different treatment regimens including nystatin, miconazole, ketoconazole and ketoconazole+acid, the cure rates were not significantly different from each other while ketoconazole+acid was significantly better than the Nystatin group. It was suggested that from a purely economic viewpoint, nystatin should be recommended as first line treatment for oro-pharyngeal candidiasis. (Perriens J, Dally G, Katabira E. A comparison of different treatment regimens for oropharyngeal candidiasis: a multi-centre cost-effectiveness study in African HIV seropositive subjects. In preparation.) However it should be stressed that in this study, the unfavourable reputation of nystatin amongst patient population hindered recruitment.

Recently attention has been drawn on the relationship between HIV and TB whereas worldwide approximately one-third of people with HIV have TB, with in some countries up to 70% of TB patients being HIV-infected (STOP TB. News, issue 4, Summer 2001 www.stoptb.org.) TB is the leading cause of death in people with HIV and up to half of HIV-infected people will develop TB. (Harries A., Hargreaves N., Kemp j., Jindani A., Enarson D., Maher D., Salaniponi F. Deaths from tuberculosis in Sub-Saharan African countries with a high prevalence of HIV-1. Lancet 2001; 357: 1519-1523.)
For the avoidance of potential drug interactions, the CDC recommends the use of alternatives to systemic antifungal azoles: ketoconazole, itraconazole and fluconazole, in patients taking TB drugs (Prevention and Treatment of Tuberculosis among patients infected with HIV. Principles of therapy and revised recommendation. MMWR Vol 47/No. RR-20 pg 34 Oct. 30 1998.).

Target population:
Miconazole nitrate 10mg muco-adhesive buccal tablet is positioned as first line treatment for oropharyngeal candidiasis. The target population is considered to be patients presenting with oropharyngeal candidiasis.

Topical treatment, with the miconazole nitrate muco-adhesive buccal tablet is considered an ideal alternative to systemic azoles based on its equivalent efficacy, and its negligible systemic bioavailability.

Cost:
The miconazole muco-adhesive tablet is available in a generic, bulk package of 50 patient treatments. Currently the price is 1 € per blister of 7 tablets or 1€ per full treatment of 7 days. This is part of a not-for-profit programme aiming for treatment at the lowest possible cost.

7. **Treatment details (dosage regimen, duration; reference to existing WHO and other relevant clinical guidelines; need for special diagnostic or treatment facilities and skills) (See also Summary of Product Characteristics in Attachment 6).**

   Dosage regimen: 1 tablet daily (apply in the morning)

   Duration: 7 days

   Reference to WHO and other clinical guidelines:
   (Clinical AIDS Care Guidelines For Resource-poor Settings, Médecins Sans Frontières, Belgium-Luxemburg, First Edition, March 2001, chapter 11 pg 11.6.) (Attachment 2)

   Need for special diagnostic or treatment facilities and skills: None

8. **Summary of comparative effectiveness in a variety of clinical settings** (See attachment 4 "Clinical Research report CR-TTT/GUM-C103). A Phase IIIb study in Uganda compared topical therapy (miconazole nitrate 10 mg mucoadhesive tablet once daily) to systemic treatment with ketoconazole 400 mg once daily in 357 patients with HIV infection. The study design was based on a previously conducted WHO/GPA study, comparing 4 antifungal treatment regimens.
   - Specification of the comparator treatment: Ketoconazole was the comparator treatment in the pivotal Phase IIIb study conducted in Uganda. Ketoconazole was the WHO reference drug the time of protocol preparation (late 1999), and was the standard of care at the clinical study site, Makerere Hospital in Uganda. Ketoconazole was since replaced by fluconazole on the WHO essential drug list (12/99), although ketroconazole is an accepted alternative to fluconazole. Ketoconazole was also found to be more effective than nystatin in the WHO/GPA study, and was therefore thought to be a more rigorous reference drug.
   - Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data): A study by WHO/GPA compared 4 treatments for oral candidiasis in HIV infected patients in Uganda, nystatin (3x/d), miconazole oral gel (4x/d), ketoconazole (od) and ketoconazole + acid (od). The results indicated that nystatin, although less effective, should be considered as first line therapy for oral candidiasis based on lower cost (see

Attachment 5: study report). The design of the study comparing the miconazole nitrate 10 mg muco-adhesive tablet and ketoconazole was based on upon the WHO trial design in Attachment 5 (inclusion/exclusion criteria were identical), to allow for cross-referencing of historical data. Similar methods for analysis of study data were employed.

- Summary of data (appraisal of quality, outcome measured, summary of results) The study was conducted according to GCP/ICH guidelines.
  Results indicated non-inferiority of topical therapy versus systemic therapy in the treatment of oro-pharyngeal candidiasis with and without dysphagia, the former being the clinical diagnosis of oesophageal candidiasis in immunocompromised HIV patients.

- Summary of estimates of comparative effectiveness: Results indicated statistically significant non-inferiority of miconazole nitrate 10 mg muco-adhesive buccal tablet o.d. versus ketoconazole 400 mg o.d. after 7 days of treatment.

9. **Summary of comparative evidence on safety (estimate of total patient exposure, description of adverse effects/ reactions, identification of variation in safety due to health systems, patient factors, summary of comparative safety against comparator treatment).**

General safety experience with miconazole nitrate:

Miconazole nitrate has been used extensively as a treatment for superficial and mucosal infections for more than two decades. Experience has shown that it is effective and well tolerated. A safety update report from Janssen Pharmaceutica on the experience with the miconazole oral gel (20mg/g; daily dose of about 200mg) and tablets (250mg/tablet; daily dose of 1000mg) during the period from 02-05-1997 to 14-08-1999) is available upon request. Over a period from 1981 to 14 August 1999, more than 79 million tubes of oral gel, accounting for 60,701kg active ingredient had been sold. If one assumes a daily dose of 200mg and a duration of a treatment of 14 days, this accounts for **21.6 million** treatments. The report concluded that there were no new relevant safety items identified during the period, and that the benefit-risk balance of miconazole oral gel remained adequate.

Taking into account the large number of units sold, the rarity of reported adverse events (0,0013%) and the fact that no new relevant safety issues could be identified, indicates that this relatively high-dosage formulation and its treatment scheme is well-tolerated and can be considered safe for the indicated use. In addition, the breadth of safety experience with the miconazole gel provides substantial support as to the safety of the miconazol compound.

The miconazole nitrate muco-adhesive buccal tablet formulation allows for a daily dosage reduction from 200mg with the gel to 10mg, providing an additional margin of safety compared to the miconazole gel.

Phase IIIB study in Uganda:

In the Phase IIIb study conducted in Uganda, the following safety conclusions were made:

- Miconazole nitrate mucoadhesive buccal tablet was not associated with any serious or unexpected adverse events. No local irritation was observed.
- There were fewer drug related adverse events associated with the use of miconazole nitrate muco-adhesive buccal tablet versus ketoconazole.
- There was a higher incidence of vomiting during use of ketoconazole (8%) versus miconazole (1%).

10. Summary of comparative cost and, where feasible, cost-effectiveness within the same therapeutic group

- Range of costs of the proposed drug

  Tibotec-Virco is providing the miconazole nitrate to non-governmental agencies and not-for profit distributors, such as IDA for 1 Euro per treatment (blister of 7 tablets). We anticipate that mark-ups by governments, non-governmental agencies, and not-for-profit distributors will range from 10% to 30% by the time the product reaches the end user.
- Comparative cost-effectiveness presented as (range of) cost per routine outcome

  The total costs of initial treatment and rescue treatment (in case of failure) were calculated per treatment group, assuming the following treatment scenario:

  After a visit to the clinic, subjects started 7-days treatment with 10 mg miconazole nitrate o.d. or 400 mg ketoconazole o.d. Subjects who were not cured after 1 week of treatment, had to return to the clinic and received a second week of treatment with the same drug. If not cured after the second week of treatment, subjects returned to the clinic and received a third week of treatment with fluconazole rescue medication. No visit was planned after the third week as no fluconazole treatment failures are assumed.

  These costs were calculated based on the daily costs of the treatment (drug costs and visit costs (including transport costs)), the duration of treatment and the cure rates.
  The cure rates for miconazole nitrate and ketoconazole were retrieved from the intent-to-treat population. For fluconazole rescue medication, a 100% cure rate after 1 week was assumed.

  A nystatin arm was not included in this trial, but an extrapolation for a hypothetical nystatin group was added based on the previous study conducted by WHO using the same study design and comparing the following 4 groups: nystatin, miconazole gel, ketoconazole and ketoconazole+acid). The following probability of not being cured (and 95% CI) were used for nystatin (historical control (6)) after 7 days: 27.7% (18.5%; 37.0%) and after 14 days: 15.7% (8.1%; 23.4%).

  Two analyses were done: a primary analysis using the IDA price indicator list (November 2000) without transport costs (expressed in Euro) and a secondary analysis using the local drug units costs (expressed in UgSh). Results of these

analyses are presented in table 1. In Table 1, the cumulative total costs at week 3, i.e., the total costs to cure all patients, is presented for the 3 treatment groups.

The following assumptions are made:

- N = number of subjects to be treated during that week = 100 in week 1
- IDA International Drug Unit costs are utilised:
  - 1 ketoconazole tablet is 0.0945€ or 0.189 €/day
  - 1 miconazole 10mg buccal tablet is 0.1679€/day
  - 1 nystatin 100 000 Unit tablet is 0.020€ or 0.06€/day
- Visit costs = €6,27 per visit (transport costs included)
- Exchange rate: 1 Euro = 1500UgSh and 1US$ = 1,1€.

The total costs to cure all patients (primary analysis) was similar for miconazole nitrate and ketoconazole and was about one fifth higher in the nystatin arm. Results of the secondary analysis showed that cumulative costs at week 3 were about one third lower in the miconazole nitrate arm compared to the two other treatment arms.

Table 1: Cumulative costs at week 3

Treatment group	Primary analysis (Euro)		Secondary analysis (UgSh)	
	Estimate (lower bound – upper bound)			
miconazole nitrate[1]	1070	(910; 1212)	2073297	(1616682; 2462425)
ketoconazole	1030	(894; 1149)	3200600	(2765955; 3579245)
nystatin	1267	(1009; 1500)	3191120	(2420835; 3882000)

[1] As miconazole nitrate is not yet on the market in Uganda as a buccal slow-release adhesive tablet, local price was simulated.

In conclusion: topical treatment with miconazole nitrate 10mg muco-adhesive buccal tablet is a cost-effective alternative to systemic treatment with ketoconazole for oropharyngeal candidiasis.

11 Summary of regulatory status of the drug (country of origin, preferably in other countries as well)

Regulatory Status

Country	Decision	Date submitted to Ministry	Approval Date
EU:			
Belgium	Approvable letter	3/00	2/2002
Ireland	MAA pending	7/00	
non-EU:			
Benin	Pending	3/00	
Botswana	Pending	4/00	
Burkina Faso	Approval	1/01	7/01
Burundi	Approval	3/00	3/00
Central African Republic	Approval	10/01	2/02
Democratic Rep of Congo	Pending*	1/02	1/02
Ethiopia	Pending	4/00	
Ghana	Approval	3/00	11/00
Israel	Pending	7/00	
Kenya	Approval	11/99	11/01
Malawi	Approval	3/00	05/00
Mozambique	Pending*	10/00	
Niger	Pending	2/02	
Namibia	Pending	3/00	
Nigeria	Pending	3/00	
Rwanda	Approval	8/00	10/00
Senegal	Pending	11/01	
Tanzania	Approval	11/99	08/00
Thailand	Withdrawn 2/02**	12/99	
Togo	Pending	9/01	
Uganda	Approval	12/99	11/01
Zambia	Pending*	9/00	
Zimbabwe	Approval	3/00	5/01

NA = not applicable; MAA = Marketing Authorisation Application

*= Provisional approval

**Withdrawn pending Certificate of Free Sales

12 Availability of pharmacopoeal standards (USP, BP, International Pharmacopoea)

See attached certificate of suitability (Attachment 7).

13 Proposed (new/adapted) text for the WHO Model Formulary

Section 6: Anti-infective Drugs

6.3Antifungal drugs

*Fluconazole capsule, injection and oral suspension is listed as an example of a therapeutic group (the "azoles"). Various drugs can serve as alternatives.

Miconazole nitrate muco-adhesive buccal tablet

tablet, 10 mg (first line treatment for oropharyngeal candidiasis)

Griseofulvin (capsule or tablet)

Nystatin (tablet, lozenge or pessary)

Complementary drugs (Flucytosine (B), potassium iodide (A))