South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: HIV and AIDS

MEDICINE REVIEW

- **Executive Summary**

Date: 15 November 2018
Medicine (INN): Flucytosine
Medicine (ATC): J02AX01
Indication (ICD10 code): Cryptococcal meningitis B20.5 + (B45.1 + G02.1*)
Patient population: HIV-infected adults with cryptococcal meningitis
Level of Care: Adult Hospital level (secondary and regional level)
Prescriber Level: Secondary level
Current standard of Care: Two weeks Amphotericin B plus Fluconazole during the induction phase in the treatment of cryptococcal meningitis in adults with HIV infection
Efficacy estimates: (preferably NNH):

- 2-weeks AmBd/5FC vs. 2-weeks AmBd/FLU = (320/1000 vs. 355/1000) = 40
- 1-week AmBd/5FC vs. 2-weeks AmBd/FLU = (239/1000 vs. 412/1000) = 8
- 2-weeks 5FTC/FLU vs. 2-weeks AmBd/FLU = (350/1000 vs. 412/1000) = 24

Motivator/reviewer name(s): S Takuva, JM Nabyoma, T Kredo
PTC affiliation: n/a

- **Name of author(s)/motivator(s)**

Primary reviewer(s): S Takuva[1] and JM Nabyoma[2]
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- **Author affiliation and conflict of interest details**

Affiliation:
1: Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Adult Hospital Level Committee (2017-2020).
2: North West Department of Health, Department of pharmacy, Lehurutshe hospital; Adult Hospital Level Committee (2017-2020).
3: South African Medical Research Council; National Essential Medicines List Committee.

Conflict of interest:
1: ST is employed full time by the NIH-funded HIV Vaccine Trials Network as a medical monitor for HIV vaccine candidate clinical trials partially sponsored either by GSK Biologics, Sanofi Pasteur, Janssen Pharmaceuticals and Vaccines and Novartis Vaccines.
2: None declared
3: None declared

- **Indication:** Treatment of cryptococcal meningitis as part of a combination antifungal regimen during the induction phase in adults with HIV infection.

- **Introduction/ Background**

Cryptococcal meningitis mainly affects persons with severe immunodeficiency. The recent global burden estimates for cryptococcal is at 223,100 cases with sub Saharan Africa accounting for 162,500 cases in sub-Saharan Africa causing 181,100 deaths annually of which 135,900 deaths occur in sub-Saharan Africa.

It is estimated that cryptococcal meningitis accounts for 15%-20% all deaths related to AIDS globally of which three quarters are in sub-Saharan Africa. (1) Mortality from cryptococcal meningitis at 3 months among HIV – infected persons is estimated to be 70%. (1)

Current international guidelines including the World Health Organization (WHO) recommend combination Amphotericin B and Flucytosine in the induction phase of treatment. (2) Flucytosine is unavailable in South Africa and local guidelines recommend a 2-week induction phase course of Amphotericin B plus Fluconazole. As a result of emerging evidence, the WHO recently updated its guidelines in 2018 recommending an even shorter 1-week course of Amphotericin B plus Flucytosine as the regimen of choice for the induction phase in the treatment of cryptococcal meningitis. (2) The guideline further recommends an alternative oral 2-week course of Flucytosine and Fluconazole where Amphotericin B is either unavailable or where intravenous therapy cannot be administered.

Purpose/Objective: This medicine review will examine if 1 week or 2-week Amphotericin B plus Flucytosine is equivalent in terms of efficacy and safety to the current standard of care in South Africa – 2-week Amphotericin B plus Fluconazole during the induction phase in the treatment of cryptococcal meningitis in adults with HIV infection.
A second question is examined in which a 2- week course of oral Flucytosine plus Fluconazole in the induction phase was compared to the current standard of care in South Africa – 2-week Amphotericin B plus Fluconazole.

PICO framework

Population	HIV infected adult patients with cryptococcal meningitis (CM)
Intervention	Flucytosine as combination antifungal therapy with amphotericin B (1 or 2 weeks) as an induction therapy for CM. **OR** Flucytosine plus Fluconazole (2-week oral course) as an induction therapy for CM
Comparison	Fluconazole as combination antifungal therapy with amphotericin B for 2 weeks as an induction therapy for cryptococcal meningitis (Current SOC)
Outcomes	*Efficacy*: Mortality, Cerebrospinal Fluid sterilization *Safety*: Nephrotoxicity, anaemia, hypokalemia, other

- **Methods:**

a) Data sources and search strategy

- MEDLINE (accessed via PubMed) and Embase up to November 2018.

A brief outline of the search strategy – combined the concepts 1, 2, 3 below with "AND"

1."HIV"[Mesh] OR "HIV Infections"[Mesh] OR "HIV-1"[Mesh]

2. ("Cryptococcal Meningitis "[Mesh] OR Meningitis)

3. (Treatment OR Therapy OR Management)

This returned 248 articles. The search was further limited to Randomized Control Trials, Systematic Reviews and Meta-analysis resulting in 69 articles. Age restriction applied to consider adults only – 51 articles. Further excluded studies that were non-fungal treatment, conducted outside Sub-Saharan Africa or Asia leading to 25 articles. These articles were scanned, and we included one updated Cochrane systematic review and meta-analysis - this review examined 13 studies that made

direct comparisons to antifungal agents in the management of cryptococcal meningitis. We also identified the WHO guideline for review.

- **Systematic reviews and RCTs:**

  An updated Cochrane Review and Network Meta-Analysis published in 2018 predominantly examining studies in resource limited settings was identified for inclusion in the medicine review. (1) This review included all the RCTs identified in the search and so these trials are not analysed individually as they are already part of the review.

- **Guidelines:**
  The WHO Guideline 2018 was identified (2): Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018.

b) Evidence synthesis

Systematic Review and Network Meta-Analysis:

An up to date, high quality Cochrane Review by Tenforde et al (2018) was examined.(1) We assessed the internal validity of this review using the AMSTAR II questionnaire for critical appraisal tool for systematic reviews. See Table 2. This review was commissioned by WHO and informed their guideline panel.

Twenty-one interventions were compared in the pairwise meta-analysis from 13 eligible studies that enrolled 2426 adult participants. In the network meta-analysis 46 combinations were compared. Most studies (eleven) were conducted in resource-limited settings, including 11 of 12 studies with 10-week mortality data. This review was largely driven by findings from the ACTA trial.

Key findings from the review:

One week of combined amphotericin B deoxycholate and flucytosine probably results in lower risk of mortality than longer treatment with two weeks of combination amphotericin B deoxycholate and flucytosine. The shorter treatment likely results in similar clearance of the infection with less toxicity due to lower adverse effects. Where amphotericin B deoxycholate cannot be given, two weeks of combined flucytosine with fluconazole is likely a good treatment option.

The authors concluded "*that in resource-limited settings, one-week AmBd- and 5FC-based therapy is probably superior to other regimens for treatment of HIV-associated cryptococcal meningitis. An all-oral regimen of two weeks 5FC and FLU may be an alternative in settings where AmBd is unavailable or intravenous therapy cannot be safely administered*". There was no mortality benefit seen with the combination two weeks AmBd and FLU compared to AmBd alone. The key characteristics of this review are shown in Table 1 below.

Table 1: Summary of Characteristics of Included Systematic Review and Meta-Analyses

Systematic review	**Characteristics**
Tenforde et al, 2018	**Question**: directly relevant to the PICO and included studies with direct head to head comparisons of flucytosine with the current standard of care. **Search comprehensive**: Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE(PubMed), Embase (Ovid), LILACS (BIREME), African Index Medicus, and Index Medicus for the

	South-East Asia Region (IMSEAR); and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov, and the ISRCTN registry; and abstracts of select conferences **Date of search**: 1980 to July 2018 **RCTs**: 13 **Study participants**: n = 2426 **Inclusion**: adults, first episode of HIV-associated CM, any anti-fungal regimen **Settings**: 11 out of 13 from sub-Saharan Africa, 1 from North America and 1 from Netherlands & Australia **Intervention and Comparison**: 21 regimen comparisons **Outcomes**: *Efficacy* - Mortality at 2, 10 weeks and 6 months; Early anti-fungicidal activity. *Safety* - DAIDS grade three/four laboratory toxicities (Anaemia, renal dysfunction, ALT abnormalities, Hypokalaemia)

Table 2: Strengths and Limitations of the Systematic Review using AMSTAR II

We assessed the internal validity of systematic reviews using the AMSTAR 11 question critical appraisal tool for systematic reviews. (3) Using AMSTAR, this review rated as moderate quality. See Appendix 1.

Strengths	Limitations
• Research questions, objectives, inclusion criteria, and exclusion criteria were clearly described • A literature search strategy including seven named databases was conducted, with key word and search strategy provided • Data extraction was performed in duplicate and data was reviewed by a group and additional authors, with discrepancies reconciled by discussion until achieving consensus • List of included and excluded studies was provided in adequate detail • Risk of bias was assessed in individual studies for allocation • concealment, random sequence generation, blinding of outcome assessment, participants and personnel, incomplete outcome data, selective reporting and other bias • Sources of funding for individual studies was provided and an investigation into publication bias was conducted • Robust sensitivity analyses conducted • Authors reported no competing interests	• One RCT conducted across nine centres in Malawi, Zambia, Tanzania, and Cameroon provided majority of data these comparisons (ACTA trial). (4) While this may be a meta-analysis the major inferences are driven by a single RCT (1) • High degree of heterogeneity in the majority of analyses • Authors were unable to conduct assessments for reporting bias for the pairwise comparisons and network meta-analysis • Results of the network meta-analysis and associated SUCRA rankings should be interpreted with caution due to the limited number of studies and participants contributing to each node and high imprecision • The SUCRA rankings may not directly correlate with clinically meaningful effects so these should be interpreted cautiously. It is more of a mathematical analysis. • The certainty of the evidence for all comparisons using modified GRADE for network meta-analysis was low or very low

Summary of Pairwise Meta-Analysis

1. **Two weeks of AmBd + 5FC versus two weeks of AmBd + FLU**

Mortality: Four studies examined mortality. There was no statistically significant difference in mortality outcomes at both 2 weeks, 10 weeks and 6 months.

Early fungicidal activity: greater clearance of the AmBd+5FC compared to local SOC and this was statistically significant.

DAIDS grade 3/4 toxicities: there were no statistically significant difference in the occurrence of severe grade and potentially life-threatening toxicities. (4–6)(7)

Table 3: Two weeks of AmBd + 5FC versus two weeks of AmBd + FLU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 2 weeks	4	538	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.16]
1.2 10 weeks	4	538	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.69, 1.17]
1.3 6 months	1	199	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.53, 1.06]
2 Early fungicidal activity	4	474	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.14, -0.05]
3 DAIDS grade 3/4 toxicities	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Anaemia	3	507	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.89, 1.55]
3.2 Renal dysfunction	3	507	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.31, 1.37]
3.3 Neutropenia	3	507	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.61, 1.98]
3.4 Hypokalaemia	3	507	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.63, 2.27]
3.5 ALT abnormality	2	308	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.60]

The two-week course of AmBd plus 5FC compared to 2 weeks of AmBd plus FLU probably has little or no effect on medium and long-term mortality risk. With regards to severe or potentially life-threatening toxicities there was no significant difference in risk of these events when using the 2-week course of AmBd plus 5FC compared to 2 weeks of AmBd plus FLU.

2. **One week of AmBd + 5FC versus two weeks of AmBd + FLU**

Mortality: Only 1 study investigated directly compared one week of AmBd and 5FC with AmBd and FLU. There was over 40% reduction in mortality risk at both 2 weeks, 10 weeks. These were statistically significant. There was no 6 months data.

Early fungicidal activity: greater clearance of the AmBd+5FC compared to local SOC and this was statistically significant.

DAIDS grade 3/4 toxicities: The risk of the occurrence of severe grade and potentially life-threatening anaemia, renal dysfunction and neutropenia was less in the one-week regimen of AmBd and 5FC versus the 2-week regimen of AmBd and FLU. Estimates for hypokalaemia and ALT abnormalities were largely similar. (4)

Table 4: One week of AmBd + 5FC versus two weeks of AmBd + FLU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 2 weeks	1	227	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.97]
1.2 10 weeks	1	227	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.39, 0.86]
2 Early fungicidal activity	1	192	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.14, -0.00]
3 DAIDS grade 3/4 toxicities	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Anaemia	1	227	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.18, 0.71]
3.2 Renal dysfunction	1	227	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.10, 0.85]
3.3 Neutropenia	1	227	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.49, 2.51]
3.4 Hypokalaemia	1	227	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.42, 2.45]
3.5 LFT abnormality	1	227	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.34, 3.03]

The shortened one-week amphotericin B deoxycholate and flucytosine regimen was non-inferior in efficacy and had a lower risk of grade 3 or 4 anaemia and renal dysfunction toxicities compared with two weeks of amphotericin B deoxycholate and flucytosine.

3. Two weeks of FLU + 5FC versus two weeks of AmBd + FLU

Mortality: One study compared oral 5FC and FLU to AmBd and FLU for 2 weeks. There were no statistically significant differences in mortality outcomes at both 2 weeks and 10 weeks. There was no 6 months data.
Early fungicidal activity: increased clearance with the AmBd based regimen and this was statistically significant.
DAIDS grade 3/4 toxicities: Participants on the oral FLU + 5FC regimen experienced less severe grade and potentially life-threatening anaemia, hypokalaemia and renal dysfunction toxicities compared to those on the AmBd and FLU regimen and these estimates were statistically significant. (4)

Table 5: Two weeks of FLU + 5FC versus two weeks of AmBd + FLU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 2 weeks	1	339	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.53, 1.29]
1.2 10 weeks	1	339	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.13]
2 Early fungicidal activity	1	276	Mean Difference (IV, Random, 95% CI)	0.11 [0.05, 0.17]
3 DAIDS grade 3/4 toxicities	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Anaemia	1	339	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.10, 0.39]
3.2 Renal dysfunction	1	339	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.19, 0.85]
3.3 Neutropenia	1	339	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.57, 2.36]
3.4 Hypokalaemia	1	339	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.05, 0.61]
3.5 ALT abnormality	1	339	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.17, 1.54]

The 2-week oral course of 5FC plus FLU was comparable to 2-week AmBd plus FLU and this oral regimen resulted in significant reductions in risk of grade 3 / 4 anaemia, renal dysfunction and hypokalaemia.

Table 6: Summary of Relative Effects of Network Meta-Analysis

Intervention A	Intervention B	Nature of evidence	Number of studies	Relative mortality effect (A vs. B)
AmBd + FLU	AmBd + 5FC	Mixed	4	RR 1.12 (0.89 to 1.42)
AmBd + FLU	short AmBd + FLU	Mixed	1	RR 0.87 (0.67 to 1.15)
AmBd + FLU	short AmBd + 5FC	Mixed	1	**RR 1.78 (1.22 to 1.58)**
AmBd + 5FC	5FC + FLU	Mixed	1	RR 1.21 (0.93 to 2.34)

The relative effects of each treatment derived from the network meta-analysis were similar to those derived from the pairwise meta-analysis. One week of AmBd and 5FC followed by FLU on days 8 to 14 was the best induction therapy regimen when comparison with 11 other regimens for 10-week mortality in the network meta-analysis, with an overall SUCRA ranking of 88%. However, the certainty of the evidence for this and the other comparisons using modified GRADE for the network meta-analysis was low.

Guidelines

The WHO guidelines were evaluated using AGREE II instrument. (8) The WHO guideline was scored 6 out of 7 – Can be recommended for use. See Appendix 2.

Guideline	Recommendations on treatment of cryptococcal meningitis in the induction phase
WHO 2018	A short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day), followed by 1 week of fluconazole (1200mg/day for adults), is the preferred option for treating cryptococcal meningitis among people living with HIV

	The following induction regimens are recommended as alternative options depending on drug availability: • Two weeks of fluconazole (1200 mg daily for adults) + flucytosine (100 mg/kg/day, divided into four doses per day) • Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults)

7. Summary of the Key Conclusions

In resource-limited settings, moderate-certainty evidence from one study supports the use of one week of AmBd with 5FC followed by high-dose fluconazole, with improved mortality up to 10 weeks, similar CSF fungal clearance, and reduced treatment toxicity (Molloy 2018). Below is a breakdown of key conclusions from the systematic review.

Efficacy - Mortality

- Based on moderate-certainty evidence from one study, (8) mortality within 10 weeks was lower with shortened one week of AmBd and 5FC compared to two weeks of AmBd and 5FC, which was previously considered the gold standard, as well as compared to oral 5FC and FLU.
- Based on moderate-certainty evidence, no difference in mortality was observed with two weeks of oral 5FC and FLU compared to two weeks of AmBd and 5FC.
- It is unclear if the addition of FLU to AmBd improves mortality given the low certainty of the evidence contributing to this comparison.
- Low-certainty evidence suggests that FLU monotherapy may be inferior to the combination of 5FC and FLU, and there were no direct comparisons with AmBd-based regimens.

Efficacy – Fungicidal clearance

Fungicidal clearance is a surrogate marker and does not necessarily correlate with clinical outcome benefit. This end point should be interpreted cautiously when making inferences on efficacy.

- With respect to early fungicidal activity, there no difference in the rate of CSF fungal clearance with short-course AmBd and 5FC compared to two weeks of AmBd and 5FC.
- These findings support improved fungal clearance of regimens with 5FC in addition to AmBd in comparison to induction regimens containing AmBd with FLU or AmBd alone.
- Amphotericin B deoxycholate based regimens had greater fungal clearance than all-oral induction therapy with 5FC and FLU.

Toxicities

- With respect to DAIDS grade three or four toxicities, traditional two-week AmBd-based therapy was associated with higher occurrence of AmBd-related toxicities compared to short-course therapy.
- All-oral 5FC and FLU therapy was associated with less toxicity (including anaemia, hypokalemia, and renal dysfunction) compared to several AmBd-containing regimens.

One RCT conducted across nine centers in Malawi, Zambia, Tanzania, and Cameroon provided majority of data these comparisons (ACTA trial). While this may be a meta-analysis the major inferences are driven by a single RCT. The results of the meta-analysis and RCT should be interpreted in light of the following potential limitations of this trial;

- Open label study where treatment allocations where not blinded. However, for objective outcomes, such as all-cause mortality, unblinded assessment is unlikely to bias the trial results
- The outcome was composite – all cause mortality. Other comorbidities and other causes may have contributed to the mortality outcome other than CM. However, the authors used 2-week mortality as one of the outcomes increasing the likelihood of a true CM related death.
- Participants received pre-emptive management of toxicities i.e. potassium supplementation, IV fluids as this is the standard of care. However, difference in safety was still demonstrated across the regimens.

c) EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [x] Not confident [ ] Uncertain [ ]	Moderate certainty in terms of efficacy and confident in terms of effectiveness
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	- Addition of Flucytosine to current standard of care may reduce the mortality from CM. Flucytosine added to amphotericin B had a lower mortality rate than fluconazole — 31.1% vs. 45% in the ACTA trial. (4) The shorter 1 week regimen had lower side- effect profile.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the outcomes?** Minor [ ] Major [ ] Uncertain [x] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	MSF advocacy – key stakeholder
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [x]	**Cost of medicines/ month:** **Medicine** | **Cost (ZAR)*** Flucytosine | Not available as no product is currently registered with SAHPRA. **Note:** Reports of clinicians currently accessing medicines through NGO's. Refer to the Health Economics and Budget Impact Analysis for flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV infected adults – www.health.gov.za
EQUITY	**What would be the impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [ ] No [X] Uncertain [ ]	Flucytosine is currently not available in South Africa, as it is not registered with SAHPRA.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[x]	[ ]	[ ]	[ ]	[ ]

Recommendation:
Based on the evidence review, the Adult Hospital Level Committee recommends the following, **pending SAHPRA registration:**

- One-week combination of Amphotericin B deoxycholate and Flucytosine be the preferred regimen for treatment of CM in the induction phase.
- As an alternative, where Amphotericin B is not available or intravenous therapy cannot be administered, two-week oral course of Flucytosine and Fluconazole should be the alternative regimen.

However, cost-effectiveness analysis and budget impact analysis need to be investigated to determine affordability.

Rationale: Meta-analysis evidence shows that 1-week Amphotericin B + Flucytosine is not inferior to 2 weeks Amphotericin B + Fluconazole. When flucytosine was added to amphotericin B in a large multicentre trial conducted in several African countries, flucytosine was associated with a 38% lower risk of death compared to fluconazole (4)

Level of Evidence: I Systematic Review

Review indicators: SAHPRA registration; Price

NEMLC Minutes of 11 July 2019:
Following the review of the health economics and budget impact analyses (accessible at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/411-hospital-level-adults-costings) , NEMLC recommended the following:

NEMLC Recommendation: Flucytosine be considered for inclusion to the EML, pending SAHPRA registration with a reduction in price.
Rationale: Simulation confirms that flucytosine is cost-effective as induction therapy for treatment of cryptococcal meningitis amongst HIV-infected. Incremental budget impact of flucytosine compared to current standard of care is an estimated R8 million per annum, but savings could be achieved with early discharge of patients (i.e. LOS 10 days or less).

A 60% reduction in price would result in a cost-neutral budget impact (R1500.00 per 100 flucytosine tablets) for the 1 week AmBd/5FC course and cost neutrality would be achieved at a price of R2195 per pack (42% price reduction) for the oral regimen. However, this is subject to uncertainty in the model, including the impact of reduction in LOS, uptake of flucytosine and use of different regimens and so a price reduction of around 40% is likely to be reasonable.

Level of Evidence: I RCT, Costing analyses, Expert opinion

M & E considerations:

Research priorities :

1. More studies on the non-inferiority of the oral FLU plus 5FC regimen
2. Addition of fluconazole to amphotericin alone during induction phase
3. Cheaper generic forms of flucytosine and amphotericin
4. Budget impact analysis of flucytosine to determne affordability in local context

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