

# Amphotericin B: Deoxycholate and Liposomal Usage



National Department of Health

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Affordable Medicines Directorate  
Essential Drugs Program

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Adult Hospital Level Standard Treatment  
Guidelines and Essential Medicines List



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# Amphotericin B: The Journey to better care



## Agenda

- Previous standard treatment guidelines
- Review leading to change in guidelines
- NEMLC recommendation and new standard treatment guideline
- Contingency plans
- Liposomal amphotericin B and renal impairment
- Take home messages



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# PREVIOUS Standard Treatment Guidelines for Cryptococcal Meningitis



## Induction Phase

7 days	<b>Ampho B deoxycholate &amp; Flucytosine</b>	14 days	<b>Ampho B deoxycholate AND Fluconazole 1200mg PO daily</b>
+ 7 days	<b>THEN Fluconazole 1200mg PO daily</b>		



## Maintenance phase

**Fluconazole 800mg PO daily**



## Consolidation phase

**Fluconazole 200mg PO daily**

*Flucytosine dose: 25mg/kg/day PO*

*Amphotericin B deoxycholate dose: 1mg/kg/day IV*



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National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Amphotericin B for Cryptococcal Meningitis. <http://www.health.gov.za/>.  
[Liposomal-Amphotericin-B-for-cryptococcal-meningitis\\_Adult-review\\_Updated-24-Jan-2024\\_final-approved.pdf](#)



# Medicine Review: Liposomal Amphotericin B for Cryptococcal Meningitis



## Ampho B deoxycholate toxicities

- nephrotoxicity
- electrolyte disturbances
- haematological effects
- hepatotoxicity

## Liposomal Ampho B

- Less toxic formulation
- Lower uptake by somatic cells
- Greater uptake by fungal cell
- High doses needed

## Ampho B deoxycholate vs Liposomal Ampho B

	deoxy	liposomal
Mortality at 10 wks	28.7% (24.4% to 33.4%)	24.8% (20.7% to 29.3%)
Fungal clearance	-0.40 log <sub>10</sub> CFU/day	-0.42 log <sub>10</sub> CFU/day
Grade 3/4 AEs In first 21 days	62.3%	50.0%

Jarvis, JN (2022) *The New England journal of medicine*



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# Other data looking at Liposomal Amphotericin B vs Amphotericin B deoxycholate



Study	Study	Outcome	Finding	Figures
Jarvis et al	RCT	Creatinine increase grade 3 Creatinine increase grade 4 Mean Cr increase from baseline at D7	L-AMB < D-AMB L-AMB > D-AMB L-AMB < D-AMB	4% vs 5.2% 1.2% vs 0.7% 20.2 vs 49.7
Mistro et al 2012	SR + MA	Nephrotoxicity	L-AMB < D-AMB	15% vs 33%
Johnson et al 2002	RCT	<b>Severe dissem. histoplasmosis</b> Clinical success Mortality	L-AMB > D-AMB L-AMB < D-AMB	88% vs 64% 2% vs 13%
Walsh et al 1999	RCT	<b>Neutropenic fever</b> Clinical success Breakthrough fungal infections Infusion-related fever/chills/rigors Nephrotoxicity	L-AMB = D-AMB L-AMB < D-AMB L-AMB < D-AMB L-AMB < D-AMB	50% vs 49% 3.2% vs 7.8% 17% vs 44% 19% vs 34%



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# Liposomal Amphotericin B for Cryptococcal Meningitis



## NEMLC Recommendation



NEMLC recommends the use of liposomal amphotericin B on the EML for the management of cryptococcal meningitis in line with the treatment regimen included in the cost analysis. The Committee supported this recommendation on the basis of the better safety profile of liposomal amphotericin B compared to amphotericin B deoxycholate as well as the potentially lower overall cost with liposomal amphotericin B. The committee however, acknowledged the limitations of modelling the benefits of the better safety profile of liposomal amphotericin B in the cost analysis.

**Rationale:** The current evidence of moderate risk of bias, shows that liposomal amphotericin B is as efficacious as amphotericin B deoxycholate in the management of cryptococcal meningitis. Safety outcomes reflect the superiority of liposomal amphotericin B regarding infusion related reactions, nephrotoxicity, hypokalaemia, and anaemia versus amphotericin B deoxycholate.



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# Liposomal Amphotericin B for Cryptococcal Meningitis



## Standard Treatment Guideline

### MEDICINE TREATMENT

#### Induction phase

If liposomal amphotericin B and flucytosine are available:

LoE:IVb<sup>xliii</sup>

- Liposomal amphotericin B, slow IV infusion over 2 hours, 10 mg/kg in dextrose 5%, single dose.

#### AND

- Flucytosine, oral 25 mg/kg 6 hourly for 14 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (see Appendix II for preventing, monitoring and management of toxicity).

#### AND

- Fluconazole, oral 1200 mg daily for 14 days
  - Fluconazole requires dose adjustment in renal failure.

LoE:IIa<sup>xliv</sup>



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# Don't Panic!



## If liposomal amphotericin B is not available:

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5% over 4 hours for 7 days.
  - Ensure adequate hydration to minimise nephrotoxicity (see Appendix II for preventing, monitoring and management of toxicity).

## **AND**

- Flucytosine, oral 25 mg/kg 6 hourly for 7 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (see Appendix II for preventing, monitoring and management of toxicity).

## **THEN** (i.e. days 8-14 of induction phase):

- Fluconazole, oral 1200 mg daily for 7 days.

LoE:IVb<sup>xlv</sup>

## If flucytosine is not available:

- Fluconazole, oral 1200 mg daily for 14 days.

## **AND**

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5% over 4 hours for 14 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (see Appendix II for preventing, monitoring and management of toxicity).

LoE:IIa<sup>xlvi</sup>



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# Renal Impairment



	L-AMB available	L-AMB unavailable
CrCl 30-50ml/min	<p>*unchanged regimen</p>	<p>*unchanged regimen</p> <p>D-AMB 1mg/kg/day for 1 week AND flucytosine FOLLOWED BY 1 week fluconazole</p>
<p>CrCl &lt;30ml/min</p> <p>*dose adjust flucytosine and fluconazole according to CrCl</p>	<p>L-AMB 10mg/kg slow IV infusion in 5% dextrose AND flucytosine FOLLOWED BY 1 week fluconazole</p>	<p>Two weeks of fluconazole and flucytosine</p> <p>If no flucytosine: D-AMB 0.7mg/kg stat AND fluconazole daily Continue D-AMB alt days if CrCl static</p>



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# Liposomal Amphotericin B for Cryptococcal Meningitis



## Take away points

- Efficacy: L-AMB  $\approx$  D-AMB
- Adverse events: L-AMB  $>$  D-AMB
- Superior does not mean risk free
- L-AMB is cost effective but drug costs are much higher
- When availability is low- there is a backup plan.



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# Issues in Procurement



“New” Product

VS

“Old” Product



The ‘new’ Liposomal Amphotericin B is available on tender:

- Tender name: HP02-2023A1
- National Stock Numbers (NSN - *i.e.*, *the reference number used in placing orders with the pharmaceutical Depot*): 180188046



The ‘old’ Amphotericin B deoxycholate is not available on tender, however some provinces may be buying it off tender via Equity Pharmaceuticals

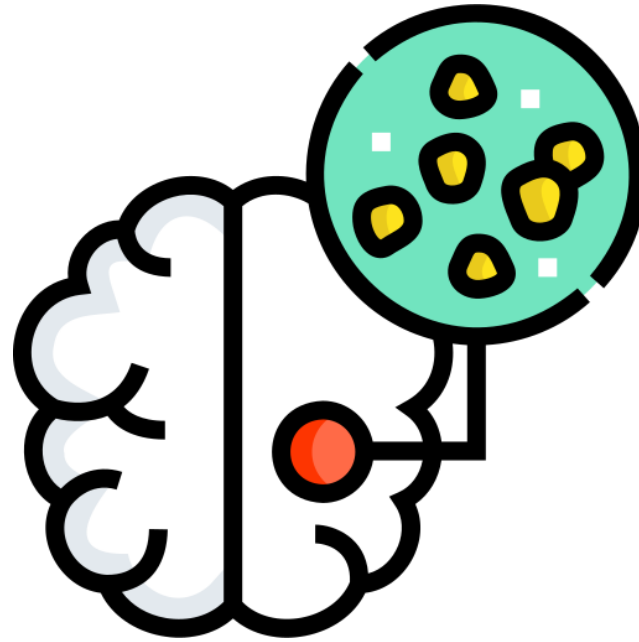
- Archived NSN = 189710723



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**THANK YOU!**



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