HISTORICALLY ACCEPTED USE

Tertiary and Quaternary Committee

Executive Summary

Date: June 2024

Medicine (INN): Itraconazole

Medicine (ATC): J02AC02

Indication/s (ICD10 code/s): In patients with Histoplasmosis (B39) as maintenance therapy following induction with amphotericin B.

Patient population/s: HIV-positive patients with disseminated histoplasmosis.

Prevalence of condition: An analysis of electronic pathology laboratory data in South Africa from 2010 to 2020 found 133 patients with proven/probable or possible laboratory-diagnosed histoplasmosis over this 10-year analysis period. [1]

Level of Care: Tertiary and Quaternary

Prescriber Level: Specialist

Current standard of Care: Only amphotericin B available, no oral management.

Background: Itraconazole for histoplasmosis was reviewed by the Tertiary and Quaternary Expert Review Committee in 2008. At this time, it was not supported (due to cost and limited data) and weekly amphotericin B was proposed as management. Review indicators were listed as; new evidence of efficacy compared to amphotericin B, increase in incidence of the condition and significant price changes.

Methods

An updated search was conducted to assess changes in evidence since last review. See Annexure C: Search strategy. Updated pricing was calculated.

As this agent was first registered in South Africa in 1991, the historically accepted use review template was utilised.

One applicable systematic review was identified (Murray et.al. 2020[2]), while no randomised controlled trials, or other applicable clinical and observational trials were identified.

Evidence

The Cochrane review by Murray et.al.2020 found that there was very low certainty evidence to inform comparisons between amphotericin B formulations and itraconazole:

- One retrospective cohort study compared all forms of amphotericin B to triazole therapy (including itraconazole) for histoplasmosis in patients with cell-mediated immunodeficiency including HIV. Treatment success for triazoles was 83% (95%CI 62% to 95%), however there was no stratification for severity. The failure rates were similar whether patients received initial amphotericin B or triazole therapy.[3]
- One single arm trial of itraconazole in mild to moderate progressive disseminated histoplasmosis reported treatment success rate of 85% (95% CI 73% to 93%). [4]
- Two single arm studies reported low relapse rates of approximately 0.5% with itraconazole.[5,6]

Evidence based guideline recommendations:

Guideline	Recommendations
Infectious Disease Society of America: Clinical Practice Guidelines for the Management of Patients with Histoplasmosis, 2007.[7]	• For moderately severe to severe disease, *liposomal* amphotericin B (3.0 mg/kg daily) is recommended for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months). *(A - I: Good evidence to support recommendation, evidence from ≥ 1 properly randomized, controlled trial).* • For mild-to-moderate disease, itraconazole (200 mg 3 times daily for 3 days and then twice daily for at least 12 months) is recommended. *(A - II: Good evidence to support recommendation, Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic; from multiple time-series; or from dramatic results from uncontrolled experiments).*

Historically accepted use Criteria

	Criteria	Comment
1	The medicine is included in the WHO Model Essential Medicines List, either as a core or complementary item, for the indication requested.	YES: X / NO: Antifungal medicines (6.3) *For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by T. marneffei and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by T. marneffei in AIDS patients*
2	The medicine is currently registered by SAHPRA for the indication.	YES: X / NO: Registration since 1991, SAHPRA Database
3	There is evidence of long-established (prior to 1996*) safe and effective use of the medicine for the recognised indication in the public health sector.	YES: X / NO: Comment: Registered in 1991 and included in management guidance for histoplasmosis
4	There have been no new reported safety or efficacy concerns (Please mark 'yes' if in agreement with statement).	YES: X / NO:
5	The budget impact is not expected to have an incremental increase, that a de novo review is justified (Please mark 'yes' if in agreement with statement).	YES: X / NO: Comment: See Annexure B: Cost analysis
6		YES / NO

	Equitable access across the country is essential, and is limited only by the availability of adequately trained staff and availability of equipment.	X	Comment

** The Essential Drugs Programme (EDP) of South Africa was established in terms of the National Drug Policy (NDP) which was implemented in 1996*

Recommendation

Oral itraconazole is an efficacious intervention for patients with disseminated histoplasmosis and provides a more practical treatment strategy than requiring patients to attend a hospital for weekly amphotericin B infusions. The evidence has not become more robust since the last evaluation, and there are no new safety concerns; however, there is unlikely to be further randomised controlled trials comparing itraconazole to amphotericin B in this indication.

It is thus recommended that itraconazole be included as an essential medicine for use as maintenance therapy in HIV-positive patients with disseminated histoplasmosis following amphotericin B induction therapy. *See protocol below.*

Annexure A: Protocol

Protocol for treating disseminated histoplasmosis in people with HIV

» Amphotericin B deoxycholate 1 mg/kg/day IV for 14 days*
THEN
» Itraconazole 200 mg 8 hourly for 3 days (loading dose)
FOLLOWED BY
» Itraconazole 200 mg 12 hourly for a total of at least 12 months (continue until CD4 count has increased to >200)

**If liposomal amphotericin B is used then dosing is 3 mg/kg/day.*

Important drug interactions with ARVs

- When a ritonavir-boosted protease inhibitor is used the maintenance dose of itraconazole should be reduced to 200 mg daily.
- Efavirenz induces the metabolism of itraconazole – co-administration is NOT recommended (unless therapeutic drug monitoring can be done).

Annexure B: Cost analysis

Cost per patient per course of therapy (as per above protocol)

	Cost per 100mg tablet*	Number of tablets per day	Number of days	Cost	Total cost
Loading 200mg 8 hourly for 3 days	R43.34	6	3	R780.13	R61,110.24
200mg 12 hourly for 12 months	R43.34	4	348	R60,330.11	

**Based on most affordable generic product – Single Exit Price Database – April 2024*

Estimated budget impact.

Based on estimated patient numbers of 133 over 10 years, an annual average of 13 patients would result in an annual budget impact of **R832 746.21.** This is a direct cost and not offset against the costs of amphotericin B and its administration (not a true incremental cost). Currently Liposomal Amphotericin B is on tender at a price of R600.00/vial (MHPL June 2024), at a weekly dosing regimen this would account to R31200 annually just for medicine costs (not including staff time, any fluid administration, consumables, hospital bed, patient transport etc.).

Note: The National Institute for Communicable Diseases indicates that the true burden of histoplasmosis in African is unknown largely due to the diagnosis being rarely considered of confirmed.[8]

Annexure C: Search Strategy

PubMed – SEARCH RUN 18 June 2024

Search	Query	Search Details	Results
#5	Histoplasmosis and guidelines	("histoplasmosis"[MeSH Terms]) AND (practiceguideline[Filter])	6
#4	Limit to any clinical study and after 2008	("itraconazole"[MeSH Terms] AND "histoplasmosis"[MeSH Terms]) AND ((clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR observationalstudy[Filter]) AND (2008:2024[pdat]))	1
#3	Limit to RCTs	("itraconazole"[MeSH Terms] AND "histoplasmosis"[MeSH Terms]) AND (randomizedcontrolledtrial[Filter])	0
#2	Limit to systematic review and meta-analyses	("itraconazole"[MeSH Terms] AND "histoplasmosis"[MeSH Terms]) AND (meta-analysis[Filter] OR systematicreview[Filter])	5
#1	Itraconazole and histoplasmosis	"itraconazole"[MeSH Terms] AND "histoplasmosis"[MeSH Terms]	381

Excluded studies and guidelines.

	Study	*Excluded*
1	Clinical, radiological and laboratory characteristics of central nervous system histoplasmosis: A systematic review of a severe disease. de Oliveira VF, Kruschewsky WLL, Sekiguchi WK, Costa SF, Levin AS, Magri MMC, Silva GD.Mycoses. 2023 Aug;66(8):659-670. doi: 10.1111/myc.13600. Epub 2023 May 3.PMID: 37132403 Review.	Does not meet research question
2	Epidemiological, clinical, diagnostic, and therapeutic features of histoplasmosis: A systematic review. Zida A, Guiguemdé TK, Sawadogo MP, Tchekounou C, Sangaré I, Bamba S.J Mycol Med. 2024 Jun;34(2):101474. doi: 10.1016/j.mycmed.2024.101474. Epub 2024 Mar 11.PMID: 38484562 Review.	Review only included previous case management
3	Isolated Colonic Histoplasmosis in Patients Undergoing Immunomodulator Therapy: A Systematic Review. Inayat F, Nawaz G, Afzal A, Ajmal M, Haider M, Sarfraz M, Haq ZU, Taj S, Ishtiaq R.J Investig Med High Impact Case Rep. 2023 Jan-Dec;11:23247096231179448. doi: 10.1177/23247096231179448.PMID: 37293945 Free PMC article. Review.	Does not meet research question
4	Fungal infection of a ventriculoperitoneal shunt: histoplasmosis diagnosis and treatment. Veeravagu A, Ludwig C, Camara-Quintana JQ, Jiang B, Lad N, Shuer L.World Neurosurg. 2013 Jul-Aug;80(1-2):222.e5-13. doi: 10.1016/j.wneu.2012.12.016. Epub 2012 Dec 13.PMID: 23247021	Does not meet research question
5	Histoplasma antigen clearance during treatment of histoplasmosis in patients with AIDS determined by a quantitative antigen enzyme immunoassay Chadi A Hage 1, Emily J Kirsch, Timothy E Stump, Carol A Kauffman, Mitchell Goldman, Patricia Connolly, Philip C Johnson, L Joseph Wheat, John W Baddley. Clin Vaccine Immunol. 2011 18(4):661-666. doi: 10.1128/CVI.00389-10. Epub 2011 Feb 9.	Does not meet research question
6	1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). [No authors listed]Infect Dis Obstet Gynecol. 2000;8(1):5-74. doi: 10.1155/S1064744900000028.PMID: 10741830 Review.	Updated IDSA guideline included
7	Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. Wheat J, Sarosi G, McKinsey D, Hamill R, Bradsher R, Johnson P, Loyd J, Kauffman C. Clin Infect Dis. 2000 Apr;30(4):688-95. doi: 10.1086/313752. Epub 2000 Apr 20.PMID: 10770731	Updated guideline included
8	Guidelines for interpreting retinal photographs and coding findings in the Submacular Surgery Trials (SST): SST report no. 8. Solomon SD, Bressler SB, Hawkins BS, Marsh MJ, Bressler NM; Submacular Surgery Trials Research Group.Retina. 2005 Apr-May;25(3):253-68. doi: 10.1097/00006982-200504000-00002.PMID: 15805900	Does not meet research question
9	Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C; CDC; National Institutes of Health; Infectious Diseases Society of America.MMWR Recomm Rep. 2004 Dec 3;53(RR-14):1-92.PMID: 15577752	Updated IDSA guideline included
10	1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. USPHS/IDSA Prevention of Opportunistic Infections Working Group. US Public Health Services/Infectious Diseases Society of America. [No authors listed]Clin Infect Dis. 1997 Oct;25 Suppl 3:S313-35.PMID: 9356832 No abstract available.	Updated IDSA guideline included

References

[1]Mapengo Re, Maphanga TG, Grayson W, Govender NP. Endemic mycoses in South Africa, 2010-2020. A decade-long description of laboratory – diagnosed cases and prospects for the future. Neglected Tropical Diseases. 2022, 16(9): e0010737.

[2] Murray M Hine P. Treating progressive disseminated histopasmosis in people living with HIV (Review). Cochrane Database of Systematic Reviews. 2020, issue 4. CD013594.

[3] Luckett K Dummer JS, Miller G, Hester S, Thomas L. Histoplasmosis in patients with cell-mediated immunodeficiency: Human Immunodeficiency Virus Infection, Organ Transplantation, and Tumor Necrosis Factor-α Inhibition. Oxford University Press on behalf of the Infectious Diseases Society of America. 2014.

[4] Wheat J, Hafner R, Korzun AH, Limjoco MT, Spencer P, Larsen RA, Hecht FM, Powderly W. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. American Journal of Medicine. 1995, 98 (4):336 – 342.

[5] Wheat_J, Hafner_R, Wulfsohn_M, Spencer_P, Squires_K, Powderly_W, et al. Prevention of relapse of histoplasmosis with itraconazole in patients with the acquired immunodeficiency syndrome. Annals of Internal Medicine 1993;118(8):610-6.

[6] Hecht_F, Korzun_A, Wheat_J, Hafner_R. Itraconazole maintenance treatment for histoplasmosis in AIDS: prospective multi-center trial. Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 1995;35:241.

[7] Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, Kauffman CA. Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by Infectious Diseases Society of America. Clinical Infectious Diseases. 2007, 45: 807-825.

[8] National Institute for Communicable Diseases – Histoplasmosis fact sheet for laboratory workers, November 2018. https://www.nicd.ac.za/wp-content/uploads/2022/04/HistoplasmosisFactSheetLabWorkers_Nov2018.pdf