

## HISTORICALLY ACCEPTED USE

### Tertiary and Quaternary Committee

#### Executive Summary

**Date:** June 2023

**Medicine (INN):** Azathioprine

**Medicine (ATC):** L04AX01

**Indication (ICD10 code):** Crohn's disease (K50.9)

**Patient population:** Patients diagnosed with Crohn's disease

**Prevalence of condition:** the prevalence of Crohn's disease for medical aid beneficiaries over the age of 20 years was reported at about 0.2 per 1000.<sup>1</sup> Incidence reported to be 2.6/100 000 per year.<sup>2</sup>

**Level of Care:** Tertiary and Quaternary

**Prescriber Level:** Specialist

**Current standard of Care:** *Azathioprine forms part of standard regimen for management of Crohn's in the public sector and has been for the past three decades.*

#### Efficacy estimates:

*Azathioprine has been shown to be effective in Crohn's disease since the early 1990's.*

- Azathioprine:
  - » A double-blind controlled study evaluating azathioprine (with a 12 week diminishing doses of prednisone) versus placebo in 63 patients with active Crohn's disease found that remission rates at 15 months were significantly different, 42% in those receiving azathioprine versus 7% in those receiving placebo, p =0.001.<sup>3</sup>

#### Evidence based guideline recommendations:

Guideline	Recommendations
American College of Gastroenterology, 2018 <sup>4</sup>	<p><u>Moderate to severe disease/moderate/high risk</u></p> <ul style="list-style-type: none"> <li>• Thiopurines (azathioprine, 6-mercaptopurine) effective and steroid sparing (strong recommendation, low level of evidence).</li> <li>• Thiopurines for maintenance of remission (strong recommendation, moderate level of evidence).</li> </ul>
British Society of gastroenterology, 2019 <sup>5</sup>	<p><u>Induction of remission in mild to moderate disease ileocolonic disease:</u></p> <ul style="list-style-type: none"> <li>• Azathioprine or mercaptopurine can be used as monotherapy in the maintenance of remission in Crohn's disease (GRADE: strong recommendation, low-quality evidence. Agreement: 100%).</li> <li>• Recommend that for patients with moderate to severe Crohn's disease responding to prednisolone, early introduction of maintenance therapy with thiopurines (GRADE: strong recommendation, low-quality evidence) or methotrexate (GRADE: strong recommendation, moderate-quality evidence) should be considered to minimise risk of flare as prednisolone is withdrawn (Agreement: 93.3%).</li> </ul>
European Crohn's and Colitis organization (ECCO), 2020 <sup>6</sup>	<ul style="list-style-type: none"> <li>• Suggest thiopurines as monotherapy for the induction of remission of moderate-to severe luminal Crohn's disease [weak recommendation, very low-quality evidence].</li> <li>• Thiopurines are recommended for the maintenance of remission in patients with steroid-dependent Crohn's disease [strong recommendation, moderate-quality evidence].</li> </ul>

American Gastroenterological Association, 2021 <sup>7</sup>	<ul style="list-style-type: none"> <li>In adult outpatients with quiescent moderate to severe CD (or patients in corticosteroid-induced remission), suggest the use of thiopurines over no treatment for the maintenance of remission. (conditional low).</li> </ul>
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### 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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
2	The medicine is currently registered by SAHPRA for the indication.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/> First registered in 1974
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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/> Comment:
4	New safety or efficacy concerns.	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/> Comment:
5	Is budget impact expected to have an incremental increase, that a de novo review is justified?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/> <i>MHPL – May 2023</i> <i>Azathioprine 50 mg tablets, 100 tablets: R102.35</i>
6	Equitable access across the country is essential, and is limited only by the availability of adequately trained staff and availability of equipment.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/> 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

It is recommended that azathioprine be included on the Tertiary Essential Medicines List for use in patients with Crohn's disease.

## REFERENCES

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- <sup>1</sup> Council for Medical Schemes. Trends in chronic disease prevalence in SA medical aid schemes: 2006-2011. November 2013. [https://www.medicalschemes.com/files/Research%20Briefs/CD2006\\_2011\\_20131115.pdf](https://www.medicalschemes.com/files/Research%20Briefs/CD2006_2011_20131115.pdf)
- <sup>2</sup> Wright JP, et al. The epidemiology of inflammatory bowel disease in Cape Town 1980-1984. *S Afr Med J*, 1986;70(1):10-5.
- <sup>3</sup> Candy S, Wright J, Gerber M, Adams G, Gerig G, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut*. 1995. 37:674-378.
- <sup>4</sup> Lichtenstein GR, et.al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018; 113: 481-517.
- <sup>5</sup> Lamb CA et.al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019, 68: s1-s106.
- <sup>6</sup> Torres J, et.al. ECCO Guidelines on therapeutics in Crohn's disease: medical treatment. *Journal of Crohn's and Colitis*. 2020, 4-22.
- <sup>7</sup> Feuerstein JD, et.al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe luminal and perianal fistulizing crohn's disease. *Gastroenterology*, 2021, 160: 2496-2508.