

## HISTORICALLY ACCEPTED USE

### Tertiary and Quaternary Committee

#### Executive Summary

**Date:** June 2023

**Medicine (INN):** Methotrexate

**Medicine (ATC):** L04AX03

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

#### Efficacy estimates:

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

- Methotrexate:
  - » A double-blind, controlled, multicenter study evaluating weekly methotrexate injections versus placebo in patients with chronically active Crohn's disease (despite a minimum of corticosteroid therapy) in 141 patients (2:1 ratio), found that after 16 weeks, 39.4% of patients in the methotrexate group compared to 19.1% in placebo group were in clinical remission ( $p=0.025$ , RR 1.95, 95% CI 1.09 to 3.48). The methotrexate group utilised less prednisone overall ( $p=0.026$ ) and mean score on Crohn's disease activity index after 16 week was significantly lower ( $p = 0.002$ ).<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>• Methotrexate effective and used for alleviating signs of steroid dependent Crohn's disease and for maintaining remission (conditional recommendation, low 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>• Methotrexate may be used for the maintenance of remission of Crohn's disease, and the dose should be at least 15 mg weekly. Subcutaneous administration has better bioavailability than oral, particularly at higher doses (GRADE: weak recommendation, moderate-quality evidence. Agreement: 88.4%).</li> </ul>
European Crohn's and Colitis organization (ECCO), 2020 <sup>6</sup>	<ul style="list-style-type: none"> <li>• Methotrexate administered parenterally recommended for the maintenance of remission in patients with steroid dependent Crohn's disease [weak recommendation, moderate-quality evidence].</li> </ul>
American Gastroenterological Association, 2021 <sup>7</sup>	<ul style="list-style-type: none"> <li>• In adult outpatients with moderate to severe CD, suggest the use of subcutaneous or intramuscular methotrexate monotherapy over no treatment for the induction and maintenance of remission. (conditional, moderate).</li> <li>• In adult outpatients with moderate to severe CD, the AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission. (conditional, very low).</li> </ul>

### 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.	<p>YES                      NO</p> <p><input type="checkbox"/>                      <input checked="" type="checkbox"/></p>	<i>Included but not for this specific indication.</i>
2	The medicine is currently registered by SAHPRA for the indication.	<p>YES                      NO</p> <p><input checked="" type="checkbox"/>                      <input type="checkbox"/></p>	SAHPRA indicates registered product since 1986
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.	<p>YES                      NO</p> <p><input checked="" type="checkbox"/>                      <input type="checkbox"/></p>	Comment:
4	New safety or efficacy concerns.	<p>YES                      NO</p> <p><input type="checkbox"/>                      <input checked="" type="checkbox"/></p>	Comment:
5	Is budget impact expected to have an incremental increase, that a de novo review is justified?	<p>YES                      NO</p> <p><input type="checkbox"/>                      <input checked="" type="checkbox"/></p>	<p><i>MHPL – May 2023</i></p> <p><i>Methotrexate 2.5 mg tablets, 100 tablets: R157.26</i></p> <p><i>Methotrexate 50mg/2ml injection: R47.39</i></p>
6	Equitable access across the country is essential, and is limited only by the availability of adequately trained staff and availability of equipment.	<p>YES                      NO</p> <p><input checked="" type="checkbox"/>                      <input type="checkbox"/></p>	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 methotrexate 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> Feagan BG, Rochon J, Fedorak RN, Irvine J, Wild G, Sutherland L, et.al. Methotrexate for treatment of Crohn's Disease. *NEJM*. 1995, 332:292-297.
- <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.