

South African National Department of Health

HISTORICALLY ACCEPTED USE REVIEW: Para-aminosalicylic acid (PAS)

Executive Summary

Date: July 2026

Medicine(s) (INN): Para-aminosalicylic acid (PAS) (4-aminosalicylic acid)

Medicine(s) (ATC): J04AA01

Indication/s (ICD10 code/s): Drug-resistant TB (DR-TB) (U50, U50.9, U50.91)

Patient population/s: Children and adults with DR-TB with limited treatment options requiring individualised and/or rescue regimens.

Prevalence of condition/s:

Level of Care: individualised regimens as advised by the National clinical advisory committee (NCAC), then down referred to PHC for ongoing care

Prescriber Level: Doctor initiated

Current Standard(s) of Care: PAS is included in the NDoH TB guidelines for use in individualised DR-TB regimens when other medicines are unlikely to be effective because of resistance and/or are not tolerated.

Background:

The Tuberculosis (TB) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) are being updated, with a focus to align with the National Department of Health (NDoH) TB Guidelines and Recommendations.

Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023).¹ PAS is classified as a Group C medication by the World Health organisation². The Group C medications are medications added to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective because of resistance and/or are not tolerated.

Group A	Levofloxacin or moxifloxacin
	Bedaquiline
	Linezolid
Group B	Clofazimine
	Cycloserine or terizidone
Group C	Ethambutol
	Delamanid
	Pyrazinamide
	Imipenem-cilastatin or meropenem
	Amikacin (or streptomycin)
	Ethionamide or prothionamide
	P-aminosalicylic acid

PAS has historically been used in the management of TB since the 1940s.³ PAS is listed on the Current Master Health Product list as non-EML, although it has never been considered for EML inclusion.

Methods:

The WHO Drug-Resistant TB (DR-TB) Guidelines will be evaluated to understand the evidence supporting the use of PAS in individualised DR-TB regimens.

Summary of Evidence:

Specific indications for PAS have been included in WHO TB guidelines for management of DR-TB since 1997.⁴

Clinical Practice Guideline (CPG) recommendations:

Guideline	Recommendations	AGREE II assessment
World Health Organisation: Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care - 2025	Recommendation 3.1. In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. <i>(Conditional recommendation, very low certainty of evidence)</i>	97% <i>See annexure 1</i>
	Recommendation 3.13. P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. <i>(Conditional recommendation against use, very low certainty of evidence)</i> This recommendation has been in place since 2019 <i>(PAS showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible)</i>	

Historically accepted use Criteria

SECTION A		
	Criteria	Comment
1	The medicine is included in the World Health Organization (WHO) Model Essential Medicines List, either as a core or complementary item, for the indication requested.	YES NO ☒ X ☐
2	The medicine is currently registered by South African Health Products Regulatory Authority (SAHPRA).	YES NO ☒ X ☐

3	A documented rapid literature review identified no new safety concerns or new evidence of lack of efficacy.	YES NO X <i>PAS is associated with <u>known</u> higher incidence of adverse reactions. Data from the Individual Patient Data Meta-Analysis (iPD) found that 12.2% of patients had adverse effects attributed to PAS.⁵</i> Use of PAS remains limited to exceptional individualised regimens where safer alternatives are not clinically appropriate.
4	The anticipated costs and usage are not likely to result in a substantial impact on the budget.	YES NO X <i>Comment:</i> <i>PAS 4g sachets (30s); R1250*</i> <i>*MHPL July 2026</i> Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)⁶ and already being used to manage patients with DR-TB and limited treatment options requiring individualised regimens. We therefore do not anticipate any incremental budget impact.
SECTION B		
1	There is evidence prior to 2007* of safety and efficacy for the recognised indication (a systematic review/meta-analysis, or at least one critically appraised controlled trial.) <i>Information after 2007 would need to be subject to standard review processes for a new inclusion.</i>	YES NO X <i>See above: Used to treat TB since 1940s.</i>
OR		
2	It is included as part of standard of care in a critically appraised clinical practice guideline (CPGs) of adequate quality, for the particular indication.	YES NO X <i>See above: CPG recommendations</i>
AND		
3	It is currently use in practice for this indication.	YES NO X <i>Comment:</i> Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)

Modified Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☐ Small ☒ None ☐	
EVIDENCE OF HARMS	What is the size of the effect for harmful outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	PAS is associated with known higher incidence of adverse reactions. Data from the Individual Patient Data Meta-Analysis (pIPD) found that 12.2% of patients had adverse effects attributed to PAS. ⁵
QUALITY OF EVIDENCE	What is the certainty/quality of evidence? High ☐ Moderate ☐ Low ☐ Very low ☒ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect	Limited evidence in the DR-TB setting
BENEFITS & HARMS	Do the desirable effects outweigh the undesirable harms? Favours intervention ☒ Favours control ☐ Intervention = Control <i>or</i> Uncertain ☒	PAS showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and is thus proposed only when better options to compose a regimen are not possible. In these situations, desirable effects outweigh the undesirable harm.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☐ No ☒	
FEASIBILITY	Is implementation of this recommendation feasible? Yes ☒ No ☐ Uncertain ☐	Currently being used for individualised regimens only.
RESOURCE USE	How large are the resource requirements? More intensive ☐ Less intensive ☐ No impact ☒	Currently being used for individualised regimens only.. No incremental budget impact is anticipated.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	Is there important uncertainty or variability about how much people value the options? Minor ☐ Major ☐ Uncertain ☒ Is the option acceptable to key stakeholders? Yes ☒ No ☐ Uncertain ☐	Request from TB programme to list PAS in STGs to improve access. PAS is already being used for individualised regimens only by the local TB programme.
EQUITY	Would there be an impact on health inequity? Yes ☒ No ☐ Uncertain ☐	Formally updating the EML status in line with National TB guidelines will aid in facilitating equitable access.

RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
				X	
Recommendation: It is recommended that para-aminosalicylic acid be included on the EML to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective due to resistance and/or are not tolerated. Rationale: Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)⁷, recommended by the WHO, and already being used to manage patients with DR-TB and limited treatment options. Use is limited to individualised DR-TB regimens where other EML alternatives are not clinically appropriate. Level of Evidence: Very low certainty evidence Review indicator: New efficacy or safety data					
NEMLC RECOMMENDATION: NEMLC recommended the inclusion of PAS on the EML to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective due to resistance and/or are not tolerated.					
Monitoring and evaluation considerations:					
Research priorities:					

Annexure 1:

• World Health Organisation: Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care - 2025²

		Appraiser 1	Rationale	Domain total	Domain score
Scope & Purpose	Q1	7	Objectives clearly stated.	21	100%
	Q2	7	Clinical questions defined using PICO.		
	Q3	7	Target population clearly described.		
Stakeholder Involvement	Q4	7	Multidisciplinary GDG.	20	94%
	Q5	6	Patient values considered; direct involvement less explicit.		
	Q6	7	Target users identified.		
Rigour of Development	Q7	7	Systematic searches described.	55	98%
	Q8	7	Selection criteria predefined.		
	Q9	7	GRADE used to assess certainty.		
	Q10	7	EtD framework used.		
	Q11	7	Benefits and harms balanced.		
	Q12	7	Recommendations linked to evidence.		
	Q13	7	External review documented.		
	Q14	6	Updating described but interval not explicit.		
Clarity of Presentation	Q15	7	Recommendations specific.	21	100%
	Q16	7	Management options presented.		
	Q17	7	Key recommendations identifiable.		
Applicability	Q18	6	Implementation barriers partly addressed.	26	92%
	Q19	7	Implementation tools provided.		
	Q20	7	Resource implications considered.		
	Q21	6	Monitoring guidance limited in core guideline.		
Editorial Independence	Q22	7	Funding independent.	14	100%
	Q23	7	Conflicts managed transparently.		
Overall Assessment					97%

References

¹ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

² World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care. Updated 2025. <https://iris.who.int/server/api/core/bitstreams/f663f086-5d97-4355-beea-0635d47f1227/content>

³ Lehmann J. Para-aminosalicylic acid in the treatment of tuberculosis. *Lancet*. 1946, 1(6384):15.

⁴ Crofton J, Chaulet P, Maher D, et.al. Guidelines for the Management of Drug-Resistant Tuberculosis. World Health Organization. 1997. <https://iris.who.int/server/api/core/bitstreams/a0cb51ce-893e-425a-b62f-cadd522bd397/content>

⁵ Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghaei P, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018;392(10150):821–834. doi:10.1016/S0140-6736(18)31644-1.

⁶ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

⁷ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>