South African National Department of Health
HISTORICALLY ACCEPTED USE REVIEW TEMPLATE
ONCOLOGY EVIDENCE WORKING GROUP
of the Expert Review Committee

Executive Summary

Date: November 2025

Medicine(s) (INN): Dactinomycin

Medicine(s) (ATC): L01DA01

Indication/s (ICD10 code/s): Rhabdomyosarcoma (C49.9)

Patient population/s: Patients diagnosed with rhabdomyosarcoma.

Prevalence of condition/s: Rhabdomyosarcoma is the most common soft-tissue sarcoma in children and adolescents, but rare after the age of 45years. Soft tissue sarcomas account for only 1% of all adult malignancies and rhabdomyosarcoma comprise merely 3.3% of all soft tissue sarcomas arising in adulthood.[1] Rhabdomyosarcoma comprises approximately 6% of childhood malignancies in South Africa.[2] Global incidence rate is approximately 4.5 patients per million individuals aged less than 20 years.[3]

Level of Care: Tertiary and Quaternary

Prescriber Level: Specialist (Oncologist)

Current Standard(s) of Care: Dactinomycin is historic standard of care

Background:

Rhabdomyosarcoma is a tumour arising from striated muscle and accounts for half of all soft tissue sarcomas.[2] The use of dactinomycin has been seen to be an important part of management of rhabdomyosarcomas since the 1970s.[4]

Dactinomycin was previously not registered with the South African Health Products Regulatory Authority (SAHPRA) and was therefore only accessible through a Section 21 authorization, which permits the use of unregistered medicines under specific circumstances. Due to its unregistered status at the time, it could not be included on the National Essential Medicines List. However, in 2022, dactinomycin achieved formal registration with SAHPRA, marking a significant step toward broader and more consistent access within the country.

Thus, since dactinomycin is the historic standard of care, it is proposed that this be included on the Essential Medicines List.

Methods: A search was conducted for clinical practice guidelines for rhabdomyosarcoma, as well as papers documenting use prior to 2007 to demonstrate historic use.

Summary of Evidence:

The recently published European standard of clinical practice recommendations for children and adolescents with rhabdomyosarcoma (a joint EpSSG, CWS and ERN, PaedCan project)[5] provides comprehensive, up-to-date, evidence-based, multidisciplinary recommendations for the diagnosis and management of rhabdomyosarcoma. Dactinomycin is part of all standard-of-care regimens for all age groups for the systemic treatment of rhabdomyosarcoma, see table below. Additionally, the NCCN (National Comprehensive Cancer Network) Clinical Practice Guideline in Oncology – Soft Tissue Sarcoma[6], outlines the management of rhabdomyosarcoma for adults – with recommendations in table below:

Clinical Practice Guideline (CPG) recommendations:

Guideline	Recommendations		AGREE II assessment
European standard clinical practice recommendations for children and adolescents with Rhabdomyosarcoma – a joint EpSSG, CWS and ERN PaedCam project[5]	*II A*	*A multimodal treatment strategy including chemotherapy for all is advised in all patients.*	*5/7 (Guideline is of high quality in terms of scope and clarity. Some improvements could be made in transparency of methodology, patient involvement, and implementation tools)*
	II IA	*Dependent on risk group assignment different chemotherapy regimens will be given:* • *Subgroup A: 4 courses (4 weeks each) of VA separated by a 3-week rest.* • *Subgroup B: 4 courses (3 weekly) of IVA followed by a 5 courses of VA* • *Subgroup C: 5 courses of IVA and 4 courses of VA +/- ifosamide when combined with radiotherapy. Where no radiotherapy is planned, patients should receive 9 IVA courses.*	
	I A	*Subgroup D/E/F: 9 courses of IVA plus maintenance (24 weeks)*	
	III A	*Subgroup G/H: 4 courses of IVA + doxorubicin and 5 courses of IVA plus maintenance (48 weeks).*	
NCCN Clinical Practice Guideline in Oncology – Soft Tissue Sarcoma[6]	*2A*	*<u>Preferred regimens: Non-pleomorphic rhabdomyosarcoma</u>* • *Vincristine, dactinomycin, cyclophosphamide (VAC)* • *Vincristine, dactinomycin, ifosfamide (VAI-Europe)*	*4/5 (Guideline is of moderate quality; the specific evidence strength around rhabdomyosarcoma in adults is lower (with data extrapolated from children. This guideline was strong in terms of clarity and scope, but weaker in terms of rigour and applicability)*

V: vincristine; A: dactinomycin; I: ifosfamide

Subgroup A: Low risk; Subgroup B/C: Standard risk; Subgroup D/E/F: High risk; Subgroups G/H: Very high risk

Level of evidence		Grades of recommendations	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analysis of well-conducted randomized trials without heterogeneity.	**A**	Strong evidence for efficacy with a substantial clinical benefit, strongly recommend.
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses or such trials or tails with demonstrated heterogeneity.	**B**	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.
III	Prospective cohort studies.	**C**	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse event, costs), optional.

IV	Retrospective cohort studies or case-control studies.	**D**	Moderate evidence against efficacy or for adverse outcome, generally not recommended.
V	Studies without control group, case reports, expert opinion	**E**	Strong evidence against efficacy or for adverse outcome, never recommended.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥ 1 randomised phase 3 trial or high-quality, robust meta-analyses, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50% bur < 85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

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: X / NO: Listed for the following indications: • **Rhabdomyosarcoma primary site** • Malignant neoplasms of kidney, except renal pelvis • Malignant trophoblastic neoplasms of placenta • Ewing sarcoma of bone and articular cartilage of unspecified sites.
2	The medicine is currently registered by South African Health Products Regulatory Authority (SAHPRA).	YES: X / NO: Registered with SAHPRA in 2022
3	A documented rapid literature review identified no new safety concerns or new evidence of lack of efficacy.	YES: X / NO: *See above: Summary of Evidence*
4	The anticipated costs and usage are not likely to result in a substantial impact on the budget.	YES: X / NO: *Comment:* *SEP: R2611.46 (dactinomycin 0.5mg injection) – July 2025.*
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.) *Information after 2007 would need to be subject to standard review processes for a new inclusion.*	YES: X / NO: *See above: Summary of Evidence*
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: X / NO: *See above: CPG recommendations*
AND		
3	It is currently use in practice for this indication.	YES: X / NO: *Comment:*

Modified Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: X / Moderate / Small / None	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large / Moderate / Small: X / None	
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High: X / Moderate / Low / Very low *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Evidence graded as IIA for the majority of subgroups -* Strong evidence for efficacy with a substantial clinical benefit, strongly recommend – in children (adult recommendations extrapolated from children).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: X / Favours control / Intervention = Control *or* Uncertain	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes / No: X	*Multi-agent chemotherapy protocols, with dactinomycin being an essential component.*

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	*Current Standard of Care*
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	*Item is already procured for this indication – Tendering may allow for better prices.*
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	Dactinomycin already used for this indication

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 dactinomycin be included on the Essential Medicine List for use in regimens to manage rhabdomyosarcoma.

Rationale: Dactinomycin has historically been used as part of frontline treatment regimens for the management of rhabdomyosarcoma since the 1970s and is part of regimens in established treatment guidelines.

Level of Evidence: IA – IIIA - Strong evidence for efficacy with a substantial clinical benefit, strongly recommend.
Review indicator: Changes in evidence of safety/availability of newer agents for management of this condition.

NEMLC RECOMMENDATION:
NEMLC ratified recommendation 27 November 2025.

Monitoring and evaluation considerations:
n/a

Research priorities:
n/a

References

[1] Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A. Comparing adult and pediatric rhabdomysarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: an analysis of 2600 patients. J Clin Oncol. 2009, 27 (20):3391-3397.

[2] Jacobson J, Jamieson J, Mushunje S, Harrison D. Management and outcomes of children with rhabdomyosarcoma in a low-to-middle-income country: A first report from Chris Hani Baragwanath Academic Hospital, South Africa. Journal of Pediatric Surgery Open. 2024 (6), 100139.

[3] Skapek SX, Ferrari A, Gupta A, Lupo PJ, Butler E, Shipley J, et.al. Rhabdomyosarcoma. Nat Rev Dis Primers. 2020, 5(1):1-48.

[4] Frei E. The Clinical Use of Actinomycin. Cancer Chemotherapy Reports. 1974, 58:49 – 54. https://babel.hathitrust.org/cgi/pt?id=mdp.39015004432756&seq=55

[5] Merks JHM, Brack E, Ebinger M, Minard-Colin V, Defachelles AS, Hladun R, et.al. European standard clinical practice recommendations for children and adolescents with Rhabdomyosarcoma a joint EpSSG, CWS and ERN PaedCan project. EJC Paediatric Oncology. 2025 (100229).

[6] Von Mehren M, Kane JM, Armstrong SA, Balach T, Bishop AJ, Buehler D, et.al. NCCN Clinical Practice Guidelines in Oncology – Soft Tissue Sarcoma, version 1.2025. May 2025. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf