health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN TERTIARY AND QUATERNARY HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
NEMLC RECOMMEDATIONS FOR MEDICINE AMENDMENTS (2025-2029) REVIEW CYCLE

Rituximab – Indolent lymphomas

Version	Last updated	Detail
V2.0	October 2026	**Review-update** – Cost changes, and evaluation of any evidence changes.
V1.0	June 2022	Initial published NEMLC Review

PRICE INDICATOR

BACKGROUND AND RATIONALE FOR REVIEW UPDATE

In June 2022, the Rituximab for indolent lymphomas review was tabled at NEMLC. The recommendation was:

- To conditionally not include rituximab on the Essential Medicines List (EML) for indolent lymphomas as the price at the time was found to be unaffordable.
- To consider in future if a price reduction of between 66% and 80% (as informed by economic analysis) was achieved.

Since this review in 2022, there have been 3 oncology tender cycles (HP04-2022ONC; HP04-2024ONC; HP04-2026ONC), with a downward trend in rituximab prices across successive tender cycles.

As part of the Oncology Evidence Working Group scope of work, a re-evaluation of rituximab for indolent lymphomas was identified as a priority.

This update to the previous review will cover the following areas:

- Evaluation of any updated data
- Price changes since previous review
- Evidence to Decision Making Framework consideration.

EXECUTIVE SUMMARY

- Rituximab for indolent lymphomas was reviewed in 2022, however not recommended as the price at the time was considered unaffordable.
- An economic analysis at the time informed that rituximab would be considered affordable at a price reduction of between 66% and 80% of the price at time of evaluation in 2022.
- Since the 2022 review, 3 tender cycles have consistently shown a decrease in the price of rituximab.
- A review update was thus undertaken:
  - No new evidence on efficacy or safety has been identified since review in 2022.
  - The price of rituximab has decreased significantly since 2022, with a 64% price reduction for rituximab 100mg vial, and 47% price reduction for rituximab 500mg vial. Although this rituximab price decrease does not meet all the willingness to pay thresholds it does meet the upper limit of thresholds and is approaching the medium value threshold.
  - Evidence to Decision Framework was included.
- Based on the significant price decrease now meeting the upper limit of previous thresholds set; together with the strong evidence of benefit, it is recommended for inclusion on the EML for this indication.

Key Recommendations

Type of ERC recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	☐	☐	☐	X

High level summary of conclusions	It is recommended that rituximab be included on the Essential Medicine List (EML) for CD20 positive indolent B-cell non-Hodgkin lymphomas to be used with chemotherapy. Rituximab plus CHOP/CVP provides significant benefit in terms of overall survival, overall response and disease control. This evidence was accepted during previous review of this agent for indolent lymphomas in 2022. Due to availability of newer agents to manage indolent lymphomas, no new clinical trials have been undertaken comparing chemotherapy alone versus chemotherapy plus rituximab; additionally, no applicable systematic reviews or meta-analyses were identified when updating historic search from (2021 to September 2026). The price of rituximab has decreased significantly since 2022, with a 64% price reduction for rituximab 100mg vial, and 47% price reduction for rituximab 500mg vial. Although this rituximab price decrease does not meet all the willingness to pay thresholds it does meet the upper limit of thresholds and is approaching the medium value threshold.

NEMLC Ratification	**Date**	**Comments/Recommendation**

EML Status	EML	Non-EML – contingent on stated reference price threshold in Rand Value	Non-EML
	X	☐	☐

Therapeutic Interchange Considerations (if applicable) *	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick box
						X

Trigger for review	n/a
Notes for Contracting	*It is recommended that negotiations be undertaken to each a similar mg/ml price for both strengths (historically the 100mg vial been more affordable)*

RESEARCH QUESTION:

Research question and PICO from 2022 review:
Should rituximab be used in addition to chemotherapy (e.g. CHOP/CVP) in the management of newly diagnosed and relapsed patients with indolent B cell non-hodgkins lymphoma?

PICO: Eligibility criteria for review

Population:	CD20 positive Indolent B cell non-hodgkins lymphoma. Newly diagnosed and relapsed
Intervention:	Rituximab + chemotherapy
Comparators:	Chemotherapy alone: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone)
Outcomes:	Response rate, progression free survival, overall survival; adverse effects
Study designs:	Randomised controlled trials (RCTs), meta-analyses, systematic reviews

METHODS

Methods approach for this review update comprised 3 areas:

1. Evidence: Assessment of any new applicable evidence has been published since time of last review.
2. Costing Update: Review of updated Price in relation to previously set willingness to pay threshold, including adjustment for inflation.
3. Evidence to Decision Framework (EtDF): Addition of updated EtDF.

Evidence: Evaluation of new evidence

- Apply search strategy: 2021 to current date:
  - *MESH terms search: (((rituximab[MeSH Terms]) AND (indolent lymphomas[MeSH Terms]))) NOT (bendamustine[MeSH Terms]) (Filters applied: Meta-Analysis, Randomized Controlled Trial, Systematic Review)*
- Apply necessary quality appraisal to new and original evidence.
- GRADE tables if applicable.

Costing Update

- Documentation of rituximab price since 2022.
- Cost-effectiveness model from 2022 updated with current prices and compared to thresholds explored in that analysis (adjusted for inflation).

Evidence to Decision Framework (EtDF)

EtDF included as part of review update.

RESULTS

Evidence: Evaluation of new evidence

1. Result of the search

The previous search strategy was applied in PubMed, and a similar Cochrane search was run.
No applicable studies comparing rituximab plus chemotherapy to chemotherapy alone (meta-analyses, systematic reviews, randomised controlled trials).

2. Previous evidence included:

Author, year	Study type	Title
Schulz et.al. 2007[1]	Cochrane Systematic Review	Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma.
Marcus et. al. 2008[2]	Randomised Phase III study	Phase III Study of R-CVP Compared with Cyclophosphamide, Vincristine, and Prednisone Alone in Patients with Previously Untreated Advanced Follicular Lymphoma

3. Methodological quality of previously included studies

Appraisal of the previously included studies was undertaken (as not included in previous review).

- Schulz et.al.: Two reviewers (NS, JR) assessed this systematic review, using the AMSTAR-2 tool.[3] The overall quality of the review was found to be Moderate. *See annexure 1.*
- Marcus et.al. RCT: Risk of Bias as assessed by ROB2 tool[4], as assessed as low risk of bias, *see annexure 2.*

4. Effectiveness and/or safety: PREVIOUS EVIDENCE

Comparison: R-CHOP vs CHOP

- Outcome: Overall survival

The Shulz et.al. pooled analysis included 7 studies for this outcome and showed that R-CHOP improves overall survival compared to CHOP alone, OR 0.65 (95% CI 0.54 to 0.78), I2= 0%. Absolute value: 65 fewer deaths per 1000 (95% CI 40 to 88 fewer). See figure 3

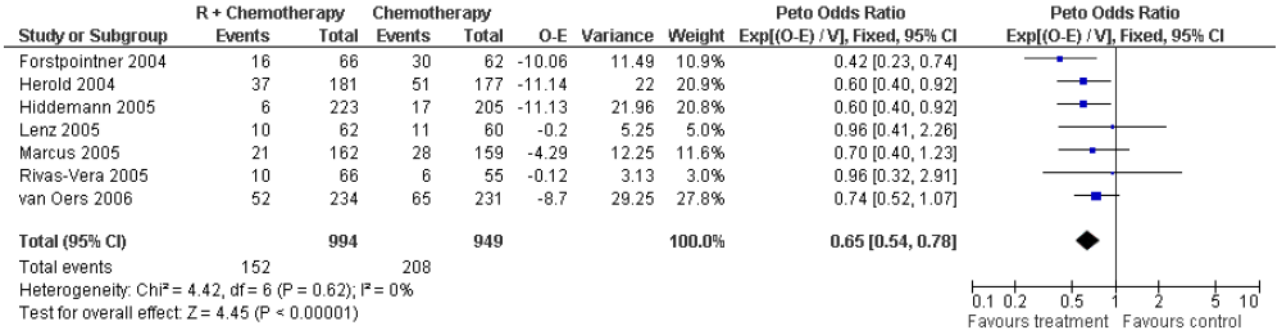


Figure 3: Forest plot: Overall survival

- Outcome: Failure Free Survival (Disease Control)

Failure Free Survival (disease control) described different endpoints for treatment outcome, including event-free survival, time to treatment failure, progression-free survival, and time to progression. Schulz et.al. pooled analysis included 7 studies for this outcome and showed that R-CHOP improved disease control compared to CHOP alone, OR 0.62 (95% CI 0.55 to 0.71), I2 = 0%. Absolute value: 119 fewer events per 1000 (95% CI 148 fewer to 46 fewer) See figure 4.

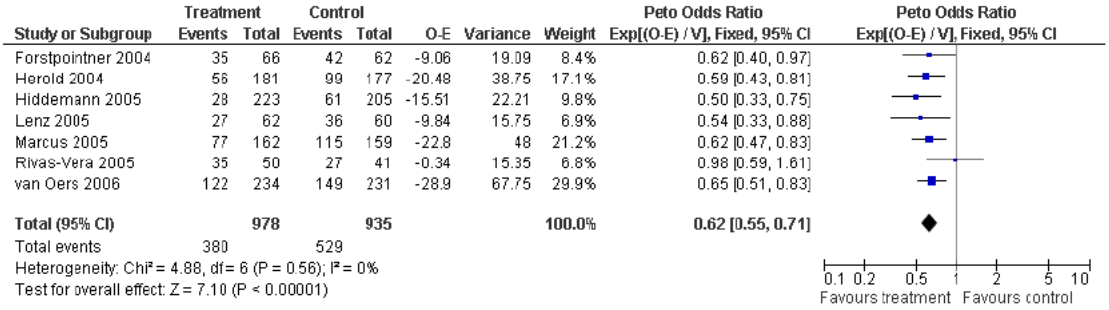


Figure 4: Forest plot: Disease Control, Failure Free Survival

- Outcome: Overall response
  - Schulz et.al. pooled analysis included 7 studies for this outcome and showed that R-CHOP improved overall response compared to CHOP alone, OR 1.21 (95% CI 1.16 to 1.27), I2 = 81%. Absolute values: 37 more per 1000 (95% CI 29 more to 46 more). See figure 5.

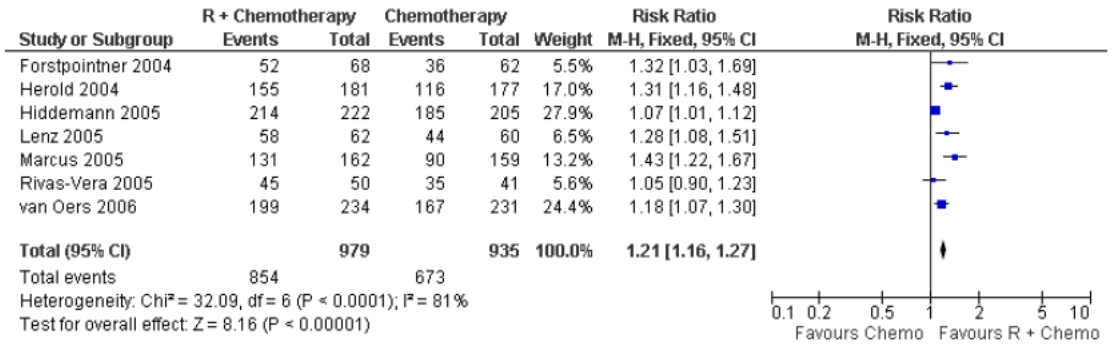


Figure 5: Forest plot: Overall response

- ## Outcome: Adverse events

  Schulz et.al. pooled analysis included 4 studies for evaluation of toxicity. Toxicity was mild to moderate in both groups, with the most often reported grade 3 or 4 adverse events being haematotoxicity, fever and infection. For fever, the RR for developing fever or leukocytopenia was statistically significantly higher in patients treated with R-chemo than in patients treated with chemotherapy alone (RR = 3.79; 95% CI 1.47 to 9.78 and RR = 1.31; 95% CI = 1.11 to 1.55, respectively. There was no evidence of a difference between treatment groups with respect to the risk of infection, thrombocytopaenia and granulocytopenia. See figure 6.

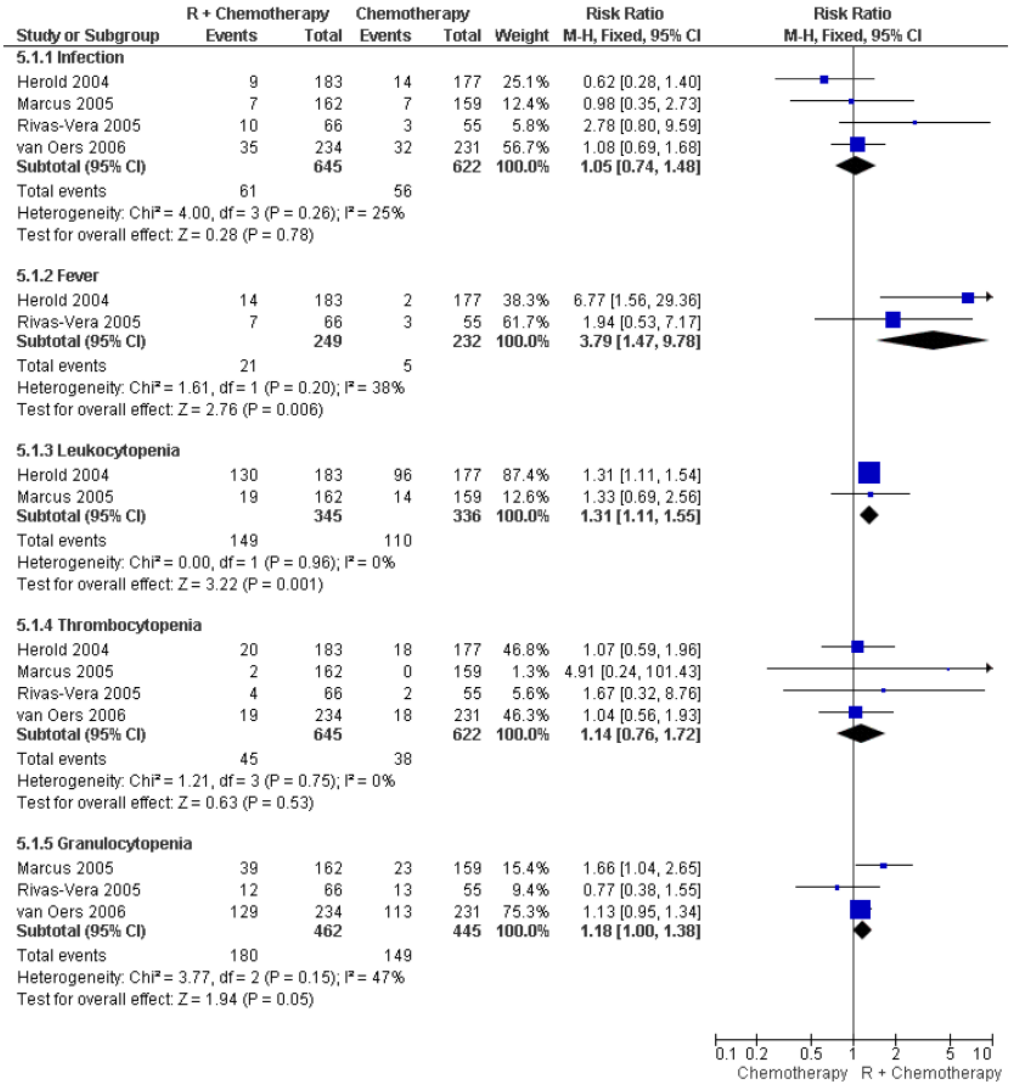


Figure 6: Forest plot: Adverse events

Comparison: R-CVP vs CVP

- Outcome: Overall survival

  Marcus 2008 et.al., a phase 3 randomised trial showed 4-year overall survival to be 83% versus 77% for R-CVP and CVP alone respectively, p = 0.029. See figure 7 below:

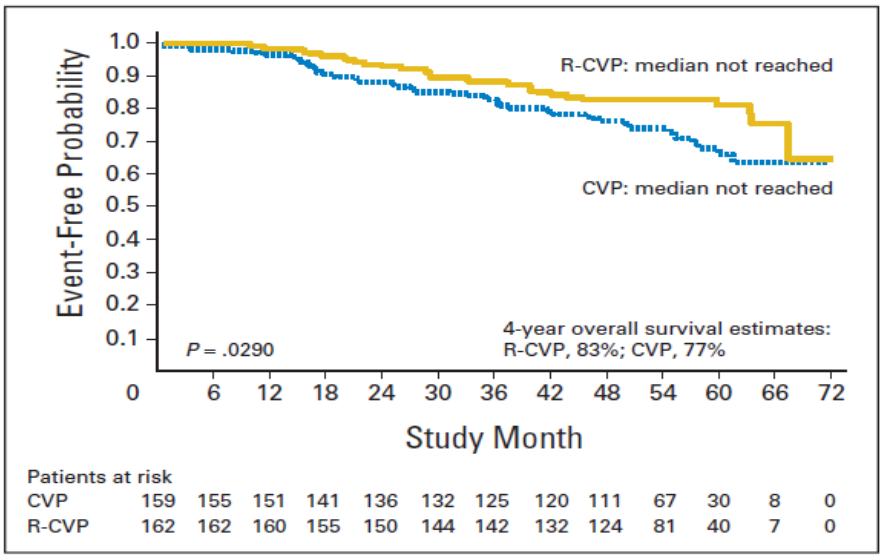


Figure 7: Overall survival in patients assigned to CVP alone versus CVP plus rituximab

- Outcome: Time to Treatment Failure (TTF)

  Marcus et.al. 2008 measured time to treatment failure (*as the time between random assignment and any of the following events: progressive disease, relapse after response, institution of new antilymphoma treatment, stable disease after cycle 4 (SD4), or death resulting from any cause*) as a primary end point. TTF was found to be significantly prolonged in patients receiving R-CVP compared to CVP alone, [CVP = median 7 months (6 to 9 months) vs R-CVP = median 27 months (25 to 37 months); p < 0.0001].

- Outcome: Overall response

  Marcus 2008 et.al., showed the overall response rate to be 57% for CVP alone versus 81% for R-CHOP; p < 0.0001).

- Outcome: Overall response

  The incidence of adverse events was similar in the R-CVP and CVP groups, however there was a higher incidence of grade 3 and 4 neutropenia during treatment with R-CVP (24%) compared with CVP (14%), this however did not translate into a higher rate of infections.

Costing Update

Cost of Rituximab

The price of rituximab 100mg and 500mg vials has decreased over the last 3 tender cycles, since 2022 from R1987.40 to R715.00 for the 100mg vial and from R7 618.76 to R4 029.43 for the 500mg vial. An important note is that there has been a bigger decrease in the 100mg vial than the 500mg vial which results in 5 vials of the 100mg vial being more affordable than 1 vial of the 500mg which should be explored for future contracts. See table 1 below:

Table 1: Rituximab Tender Prices

	HP04-2020ONC/01	HP04-2022ONC		HP04-2024ONC	HP04-2026ONC
	Jun-22	**Jun-23**	**Jun-24**	**Jun-25**	**Sep-26**
Rituximab; 100mg/10ml; injection; 10 ml	R1,987.40	R993.70	R993.70	R805.00	R715.00
	Roche Products (Pty) Ltd	*Roche Products (Pty) Ltd*		*Dr Reddy's Laboratories (Pty) Ltd*	*Dr Reddy's Laboratories (Pty) Ltd*
		% decrease since June 2022		**% decrease since June 2022**	**% decrease since June 2022**
		50%		59%	64%

	HP04-2020ONC/01	HP04-2022ONC		HP04-2024ONC	HP04-2026ONC
	Jun-22	**Jun-23**	**Jun-24**	**Jun-25**	**Sep-26**
Rituximab; 500mg/50ml; injection; 50 ml	R7,618.76	R7,618.75	R7,618.75	R5,333.00	R4,029.43
	Roche Products (Pty) Ltd	*Roche Products (Pty) Ltd*		*Dr Reddy's Laboratories (Pty) Ltd*	*Dr Reddy's Laboratories (Pty) Ltd*
		% decrease since June 2022		**% decrease since June 2022**	**% decrease since June 2022**
		0%		30%	47%

<u>Cost-Effectiveness Analysis - Update</u>

The costs of rituximab plus CVP (intervention) and CVP alone for six cycles were updated accordingly. See Table 2 below. All other parameters remained the same as no new evidence was considered appropriate for inclusion based on the updated search. The overall cost per 6 cycles of R-CVP reduced by R23 964.99 from June 2022 (R57 502 to R33 537.01). *The sensitivity analysis on 4 and 8 cycles was not updated.*

Table 2: Updated costs for model R-CVP versus CVP

Rituximab PLUS CVP (R-CVP)	Rituximab (IV)	R 30 609.00
	Cyclophosphamide (IV)	R 2 366.28
	Vincristine (IV)	R 531.30
	Prednisone (oral)	R 30.43
	TOTAL	**R 33 537.01**
CVP only	Cyclophosphamide (IV)	R 2 366.28
	Vincristine (IV)	R 531.30
	Prednisone (oral)	R 30.43
	TOTAL	**R 2 928.01**

Table 3 shows the updated base case cost-effectiveness analysis. The updated incremental cost-effectiveness ratio (ICER) was estimated at R99 910.89 (compared to R178 402 in 2022).

Table 3. Base case cost-effectiveness analysis

Regimen	Total Cost	Total QALYS	Incremental costs	Incremental benefit	ICER (cost per QALY)
CVP	R2 928.01	2.143	R0	0	R 0
R-CVP	R 33 537.01	2.499	R 30 609	0.306	R 99 910.89

The recommendation in 2022, suggested considering the agent if there was price reduction of 66-80%. This recommendation was informed by comparisons against a number of different potential willingness to pay thresholds (see full CEA report for details). The threshold values from 2022 were adjusted for inflation to enable an updated comparison – See table 4 below.

Table 4: Updated Willingness to Pay Thresholds Comparison

Description of different WTP thresholds*	2022 Value	ICER < WTP threshold in 2022	2026 Value adjusted for inflation**	ICER < WTP threshold in 2026
WTP Threshold sourced from draft HTA methodology and utilised for bortezomib for multiple myeloma 2021	R40 000	No	R47 920	No
WTP Threshold sourced from previous NEMLC decision for Gemcitabine plus Capecitabine for pancreatic cancer	R75 000	No	R89 850	No
WTP Threshold sourced from previous NEMLC decision for rituximab for diffuse B-Cell lymphoma & Upper Woods *et al* estimate	R90 000	No	R110 140	Yes

**See CEA report for more details. **Inflation estimates derived from estimate between CPI and SEPA.*

In 2022, the ICER did not meet any of the WTP thresholds. Although the price of rituximab does not currently meet all the WTP thresholds it does now meet the upper limit of thresholds and is approaching the medium value threshold.

Budget Impact Analysis - Update

The estimated budget impact was updated based on the price changes however number of patients (150) remained the same as the 2022 estimate. The total estimated cost per annum is R5 030 551.35 for R-CVP (reduced by R3 594 749.65 from R8 625 301 in 2022) and R439 201.35 for CVP alone (increased by R12 279.35 from R426 922 in 2022). The updated incremental cost is estimated to be R4 591 450 per annum (reduced by R3 607 029 from R8 198 379 in 2022 – See Table 5.

Table 5: Budget impact of rituximab plus CVP versus CVP alone per annum

Estimated 150 per year in the state sector - At full contract price				
Regimen - 6 cycles	**Cost per patient**	**No**	**TOTAL**	**Incremental**
R-CVP	R 33 537	150	R5 030 551	R4 591 450
CVP only	R 2 928	150	R 439 201	

Evidence to Decision Framework (EtDF)

Assessment

Problem Priority **Why is this medicine being evaluated?**
Rituximab has been added to chemotherapy for the management of indolent lymphophomas globally for several years, and an accepted standard. Cost changes for rituximab have enabled the reconsideration of this agent in the South African public setting for this indication.

Desirable Effects **How substantial are the desirable anticipated effects (i.e., benefits)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Trivial ○ Small ○ Moderate **X <u>Large</u>** ○ Varies (if so, why?) ○ Don't know	The evidence shows significant effects with rituximab plus chemotherapy in terms of overall survival, disease control and overall response, compared to chemotherapy alone.	*The ERC judged that the benefits to be large.*
Undesirable Effects **How substantial are the undesirable anticipated effects (i.e., harms and toxicity)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Large ○ Moderate **X <u>Small</u>** ○ Trivial ○ Varies (if so, why?) ○ Don't know	Increased neutropenia and fever in R-CVP and R-CHOP respectively but did not translate to increased infections.	*The ERC judged that magnitude of the undesirable effects to be small.*
Certainty of evidence[1] **What is the overall certainty of the evidence of effects (across all critical outcomes)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Very low ○ Low ○ Moderate **X <u>High</u>** ○ No included studies	Although there were limited RCTs in the included meta-analysis, as well as in subsequent searches; the direction of effect is consistent and there is high certainty of the evidence	*The ERC considered the certainty of the evidence to be high overall.*
Values **Is there important uncertainty in how people with conditions, caregivers, healthcare providers or decision-makers value the main outcomes?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Important uncertainty ○ Possibly important uncertainty ○ Probably no important uncertainty **X <u>No important uncertainty</u>**	There is broad acceptance of rituximab as a core component to treatment of all CD20 positive indolent NHL in all guideline.	• *The ERC judged that there were no varying values among the affected population/ healthcare providers/ others.*

[1] **CERTAINTY OF EVIDENCE**
High certainty: confident in the evidence / We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: mostly confident, but further research may change the effect / We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: some confidence, further research likely to change the effect / Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: findings indicate uncertain effect / We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect

Balance of effects
Does the balance of effects favour the medicine being considered an essential medicine? Do the desirable effects outweigh the undesirable effects?

Judgement	Research evidence	Additional considerations (by committee)
X Yes (*Favours the intervention*) ○ *Probably Yes (Probably favours the intervention)* ○ Probably No (*Probably favours the comparison*) ○ No (*Favours the comparison*) ○ Varies (if so, why?) ○ Don't know	Desirable effects judgement: Large Undesirable effects judgement: small	• *The ERC judged that the balance of health effects favours rituximab plus chemotherapy over chemotherapy alone.*

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations (by committee)
○ Large costs **X Moderate costs** ○ Negligible costs or savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	*See Cost discussion in "price change section"* *AND* *Historic cost economic analysis* Price of medicines Medicine / Tender price ZAR) * Rituximab 100mg / R715.00 Rituximab 500mg / R4029.43	• *The ERC judged that the costs of rituximab have decreased since 2022 and currently are in the upper limit of thresholds previously identified.*

Equity*
What would be the impact on health equity?

Judgement	Research evidence	Additional considerations (by committee)
○ Reduced ○ Probably reduced ○ Probably no impact **X Probably increased** ○ Increased ○ Varies ○ Don't know	Comment on **PROGRESS-Plus** elements: **P**lace of residence, **R**ace/ethnicity/culture/language, **O**ccupation, **G**ender/sex, **R**eligion, **E**ducation, **S**ocioeconomic status, **S**ocial capital, personal characteristics associated with discrimination (age, disability), features of relationships, and time-dependent relationships (instances where person may be temporarily disadvantaged) • No research evidence searched for equity particularly. • Ad hoc reporting indicates that some provinces and facilities are already using rituximab in indolent lymphomas, and thus incorporating on the National EML will allow for equitable access across provinces and facilities. • Increased procurement volumes may enable more favourable pricing (economies of scale).	• *The ERC considered the listing as EML would probably allow for increased equity.*

<table>
<tr><th colspan="3">Acceptability*
Is the option acceptable to recommend as an essential medicine to key stakeholders?</th></tr>
<tr><th>Judgement</th><th>Research evidence</th><th>Additional considerations (by committee)</th></tr>
<tr><td>○ No
○ Probably no
○ Probably yes
X <u>Yes</u>
○ Varies (if so, why?)
○ Don't know</td><td>• Rituximab is a globally accepted component of treatment for CD20 positive B-cell malignancies.</td><td>• The ERC judged that there was no reason to suspect differences in acceptability from that presented in the evidence.</td></tr>
<tr><th colspan="3">Feasibility*
Is the option feasible to implement?</th></tr>
<tr><th>Judgement</th><th>Research evidence</th><th>Additional considerations (by committee)</th></tr>
<tr><td>○ No
○ Probably no
X <u>Probably yes</u>
○ Yes
○ Varies (if so, why?)
○ Don't know</td><td>• No research evidence identified, however since some oncology centres are already using this intervention, it is considered feasible to implement nationally.

Therapeutic equivalence to be checked internally by EDP Technical Oversight Committee, ERC and NEMLC in collaboration with stakeholders.<table><tr><td>Alternative Medicine/s (INN)</td><td></td></tr><tr><td>Is the alternative SAHPRA registered?</td><td></td></tr><tr><td>Formulation/s</td><td></td></tr><tr><td>Equipotent Dose/ Dose range</td><td></td></tr><tr><td>N/A</td><td>X</td></tr></table></td><td>• The ERC judged that there was no reason to suspect feasibility concerns, and that both patients and healthcare professionals would consider this a feasible intervention.</td></tr>
</table>

SUMMARY OF JUDGEMENTS

Indicate the relevant judgements below per domain in **bold**

	Judgement						
Desirable effects	Trivial	Small	Moderate	**Large**		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	**High**			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
Balance of effects	Favors the comparison	Probably favors the comparison		Probably favors the intervention	**Favors the intervention**	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION[2]

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	X

[2] **STRENGTH OF THE RECOMMENDATION:**

Strong recommendation

Strong recommendations are those recommendations for which the guideline development group is confident that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Strong recommendations can be adopted as practice (most patients should receive the recommended medicine) or policy (adapted as policy) in most situations. For patients, most people would want the recommended medicine and only a small proportion would not.

Conditional recommendation

The guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small. Therefore, discussion (or substantial debate) may be required before a conditional recommendation can be adopted as practice or policy. For patients, the majority of people would want the recommended medicine, but many would not.

CONCLUSIONS

Rituximab plus CHOP/CVP provides significant benefit in terms of overall survival, overall response and disease control. This evidence was accepted during previous review of this agent for indolent lymphomas in 2022. Due to availability of newer agents to manage indolent lymphomas, no new clinical trials have been undertaken comparing chemotherapy alone versus chemotherapy plus rituximab; additionally, no applicable systematic reviews or meta-analyses were identified when updating historic search from (2021 to September 2026).

The price of rituximab has decreased significantly since 2022, with a 64% price reduction for rituximab 100mg vial, and 47% price reduction for rituximab 500mg vial. Although this rituximab price decrease does not meet all the willingness to pay thresholds it does meet the upper limit of thresholds and is approaching the medium value threshold.

Recommendation

It is recommended that rituximab be included for CD positive B-cell indolent non-Hodgkin Lymphomas to be used with chemotherapy.

REVIEW TEAM

Review contributors as detailed below:

Name & Affiliation	Declaration of Interests	Write up and referencing	Clinical Expertise & interpretation	Quality assurance
Prof J Malherbe [1]	X		X	
Prof E Verburgh [2]	X		X	
Dr Y Wang [3]	X			X
Ms K MacQuilkan [4]	X	X		
Ms N Seedat [5]	X			X
Dr J Riddin [6]	X	X		X

1. Associate Professor: Department Internal Medicine Clinical Haematologist and Head: Division of Clinical Haematology Faculty: Health Science, University of Free State.
2. Clinical haematologist and associate professor in Clinical Haematology at the University of Cape Town.
3. Clinical Pharmacist, Frere Hospital, East London.
4. National Department of Health, Essential Drugs Programme – Oversight.
5. Essential Drugs Programme – Oversight; Technical Support Specialist – Genesis Analytics.
6. National Department of Health, Essential Drugs Programme – Oversight.

ACKNOWLEDGEMENTS

The members of the Oncology Evidence Working Group, Expert Review Committee (ERC) and National Essential Medicines List Committee.

REFERENCES

[1] Schulz H, Bohlius J et al. Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Cochrane Database of Systematic Reviews 2007, Issue 4

[2] Marcus R, Imrie K et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. Journal of Clinical Oncology 2007;26:4579-4586.

[3] Shea BJ, R. B. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 20(358), J4008.

[4] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898.

Appendix 1: AMSTAR 2 assessment Schultz et.al.

AMSTAR 2 Judgements

		Reviewer 1 (NS)		Reviewer 2 (JR)	
No.	**Criteria**	**Comments**	**Y/ PY/ N#**	**Comments**	**Y/ PY/ N#**
1	Research questions and inclusion criteria for the review included the components of PICO	The review question and eligibility criteria clearly specify all PICO elements. Population: adults (>18 years) with histologically proven indolent lymphoma or mantle cell lymphoma. Intervention: chemotherapy plus rituximab (R-chemo). Comparator: identical chemotherapy alone. Outcomes: overall survival, disease control (TTF/EFS/PFS/TTP), overall and complete response, and toxicity.	**Y**	The review clearly specified the population (adults >18 years with histologically proven indolent lymphoma or mantle cell lymphoma), intervention (rituximab plus chemotherapy), comparator (identical chemotherapy alone), and relevant outcomes including OS, disease control, response and toxicity. The eligibility criteria were explicitly stated.	Y
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	A Cochrane protocol was published in 2002 (Kober et al., 2002; CD003805) before publication of the completed systematic review. The protocol prespecified the review question, eligibility criteria, search strategy, risk-of-bias/quality assessment and planned methods of quantitative synthesis and investigation of heterogeneity. The completed review followed these prespecified methods, and no significant unexplained deviations from the protocol were identified.	**Y**	Protocol was published with prespecified review question, eligibility criteria, search strategy, risk of bias, and planned methods.	Y
3	Review authors explained selection of the study designs for inclusion in the review	The authors restricted inclusion to randomised controlled trials. This study design was appropriate to the intervention-effectiveness question comparing rituximab plus chemotherapy with identical chemotherapy alone. The background contextualised the review question using evidence from randomised trials, and the selected study design aligned directly with the objective of evaluating comparative treatment effects.	**Y**	Restricted to RCTs, which was appropriate for research question being addressed.	Y
4*	Review authors used a comprehensive literature search strategy	The review used a comprehensive literature search strategy. CENTRAL, MEDLINE, EMBASE, LILACS and databases of ongoing trials were searched. Conference proceedings were hand-searched, investigators, pharmaceutical companies and relevant haemato-oncology study groups were contacted, and reference lists were checked. No language restrictions were applied. Searches were updated through December 2005, and detailed database search strategies were reported in the appendices.	**Y**	Searches included CENTRAL/Cochrane, MEDLINE, EMBASE, LILACS and databases of ongoing trials. They also searched conference proceedings (ASH, ASCO and ESMO), checked references, contacted investigators and pharmaceutical companies, contacted relevant trial/study groups, included unpublished data, and imposed no language restrictions. The search was updated through December 2005, close to publication.	Y
5	Review authors perform study selection in duplicate	Two reviewers (H. Schulz and N. Skoetz) independently screened titles and abstracts and undertook full-text assessment when required. Disagreements were resolved by consensus with involvement of a third reviewer (A. Engert), satisfying duplicate study selection.	**Y**	Two reviewers independently screened titles/abstracts and full texts. Disagreements were resolved by consensus with a third reviewer.	Y
6	Review authors perform data extraction in duplicate	The review states that the same reviewers who independently screened the studies also independently performed data extraction and quality assessment. Authors of included studies were contacted for unreported data. This satisfies duplicate data extraction.	**Y**	The same two reviewers independently extracted data and assessed study quality, with disagreements resolved through consensus/third-reviewer involvement.	Y

7*	Review authors provided a list of excluded studies and justify the exclusions	The review provides a dedicated 'Characteristics of excluded studies' table listing excluded studies by study ID together with a specific reason for exclusion (e.g., non-randomised design, rituximab monotherapy or maintenance/consolidation therapy, non-identical chemotherapy, inappropriate outcomes). References to excluded studies are also provided.	**Y**	The review provides a Characteristics of excluded studies table with reasons for exclusion.	Y
8	Review authors described the included studies in adequate detail	The review described the included studies in adequate detail, including study design, participant characteristics and disease status, interventions and comparators, outcomes, and follow-up/observation periods. The characteristics of included studies tables provide sufficient detail to understand the populations, treatment comparisons and study characteristics relevant to the review question.	**Y**	Detailed characteristics are provided for the seven included trials, including participants, lymphoma subtype, treatment status, chemotherapy regimen, rituximab dose, outcomes, follow-up, withdrawals, ITT analysis, allocation concealment and funding. Treatment regimens and doses are also described.	Y
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	The review authors used a structured assessment of methodological quality/risk of bias in the included RCTs, including assessment of randomisation, allocation concealment, masking/blinding, withdrawals and dropouts, and intention-to-treat analysis. Methodological information was sought from study investigators where reporting was incomplete, and study quality was subsequently considered in sensitivity analyses. The approach was appropriate to the RCTs included in the review.	**Y**	The authors assessed important domains including randomisation, allocation concealment, masking/blinding, withdrawals/dropouts and ITT analysis, and contacted investigators for missing information.	Y
10	Review authors reported on the sources of funding for the studies included in the review.	Funding was explicitly sought and reported within the characteristics of included studies. Funding entries include Deutsche Krebshilfe, pharmaceutical funding, combined Deutsche Krebshilfe/pharmaceutical funding, 'not applicable', and a blank entry where information was apparently unavailable.	**Y**	Funding is reported in the characteristics of included studies, including pharmaceutical funding where applicable, and individual study funding is presented.	Y
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	The review authors used appropriate statistical methods for meta-analysis. Dichotomous outcomes were pooled using risk ratios with Mantel–Haenszel methods, while time-to-event outcomes were analysed using hazard ratios. A fixed-effect model was used for meta-analysis. Statistical heterogeneity was assessed, and potential sources of heterogeneity were investigated through prespecified subgroup and sensitivity analyses according to clinical and methodological characteristics. The statistical combination and investigation of heterogeneity were therefore considered appropriate for the included RCTs.	**Y**	The statistical methods were generally appropriate for the effect measures—HRs for time-to-event outcomes and Mantel-Haenszel RRs for binary outcomes.	Y
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	The review authors assessed the potential impact of risk of bias on the meta-analysis through sensitivity analyses based on methodological characteristics of the included studies, including allocation concealment and attrition bias. These analyses examined whether the pooled findings were influenced by study quality and methodological limitations.	**Y**	The authors conducted sensitivity analyses according to study quality, allocation concealment and attrition, and specifically examined whether study quality altered the pooled estimates. They reported no important difference in the overall survival result according to study quality.	Y
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	The review authors accounted for the methodological quality and risk of bias of the included studies when interpreting the findings. Sensitivity analyses examined whether results differed according to methodological characteristics, including allocation concealment and attrition bias,	**Y**	The review acknowledges limitations related to study quality and the less reliable evidence in some subgroups. It specifically notes that the MCL survival finding was less reliable because of heterogeneity and performs sensitivity analyses according to study quality. The	Y

		and the robustness of the findings in relation to study quality was considered in the interpretation and discussion of the results.		authors also acknowledge limitations associated with the available trial evidence	
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	The review authors assessed statistical heterogeneity and investigated potential sources through subgroup and sensitivity analyses based on clinical and methodological characteristics, including lymphoma subtype, previous treatment, disease stage, treatment duration and study quality. Where substantial heterogeneity was observed, plausible explanations were discussed; for example, differences in prior treatment status were identified as a likely contributor to heterogeneity in the mantle-cell lymphoma analyses.	**Y**	Heterogeneity was actively investigated using subgroup and sensitivity analyses based on lymphoma subtype, previous treatment, stage, study duration, study quality, data source and individual large studies.	Y
15*	For quantitative synthesis, review authors carried out adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	The authors prespecified an appropriate assessment of publication bias using funnel plots and Egger's linear regression test for meta-analyses containing at least four trials. The review also sought unpublished evidence and examined published versus unpublished sources. However, the results of the funnel-plot/Egger assessments were not clearly reported, and the likely impact of publication bias or small-study effects on the review findings was not discussed.	**N**	The authors generated funnel plots when ≥4 studies were available and performed Egger's linear regression test, using P<0.1 as the threshold. They also included unpublished data and compared published versus unpublished sources in sensitivity analyses. Only 7 studies included thus funnel plot would have limited interpretability.	Y
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	The review authors reported potential conflicts of interest, including relationships of individual authors with Hoffmann-La Roche through sponsored research, presentations, advisory activities and honoraria. Sources of financial and institutional support for conducting the review were also explicitly reported.	**Y**	The review had no pharmaceutical or grant support. Potential conflicts of several authors were documented.	Y
OVERALL QUALITY ASSESSMENT:		**MODERATE**			
Rationale and conclusion:		The review demonstrates strong methodological quality across AMSTAR 2 domains. It was conducted according to a prespecified Cochrane protocol and used a comprehensive search strategy, duplicate study selection and data extraction, a justified list of excluded studies, adequate descriptions of included studies, assessment of methodological quality/risk of bias, and appropriate statistical methods for meta-analysis. Risk of bias and heterogeneity were explored through sensitivity and subgroup analyses and considered when interpreting the findings, while funding sources and potential conflicts of interest were also reported. For Domain 15, a critical AMSTAR 2 domain, the authors reported methods for assessment of publication bias, however, did not discuss application. It was noted that only 7 studies were included (limited funnel plot interpretability), however no discussion on this limitation. Overall confidence in the results of the review is rated **MODERATE** through consensus.			

[#] *Y= Yes, PY = Partial yes, N = No*

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

** Overall confidence categories are applied according to AMSTAR 2: High, Moderate, Low and Critically low.

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that *were* included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the *question* of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

Appendix 2: Risk of Bias assessment Marcus et.al.

ROB 2 Domain	Judgement (JR)
Domain 1: Bias arising from the randomisation process	Low risk
Domain 2: Bias due to deviations from intended interventions	Low risk
Domain 3: Bias due to missing outcome data	Low risk
Domain 4: Bias in measurement of the outcome	Low risk *(however, some potential concern on one outcome - complete response assessment as not clear whether response assessors were blinded)*
Domain 5: Bias in selection of the reported result	Low risk
Overall	**Low risk of bias**

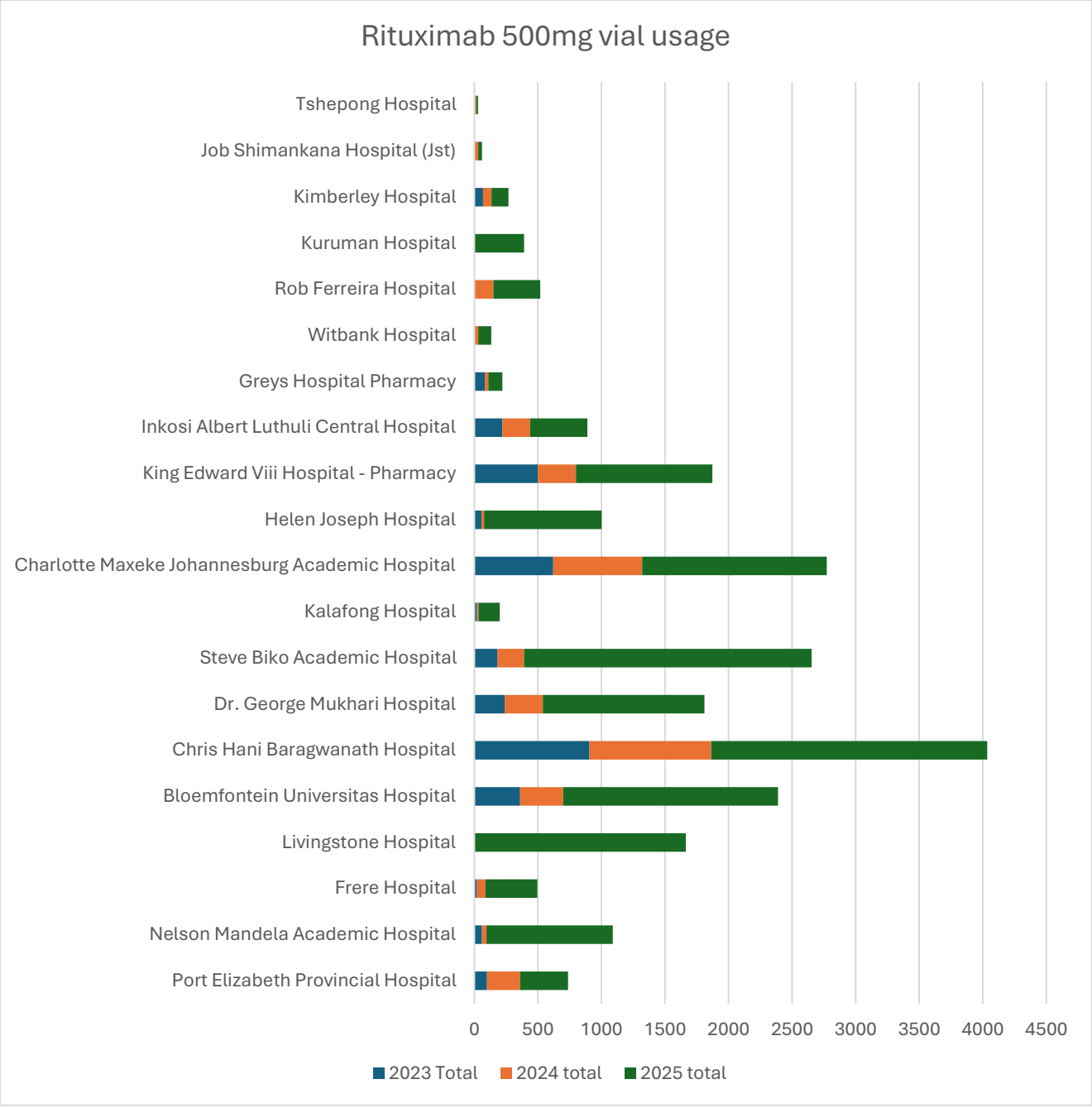
Appendix 3: Rituximab Utilisation

Appendix 1 reflects the provincial and hospital rituximab utilization for the years of 2023, 2024, and 2025. Note, WC is not reflected/reported consistently in this data.

This is collective rituximab utilization for all indications. Currently rituximab is approved for:

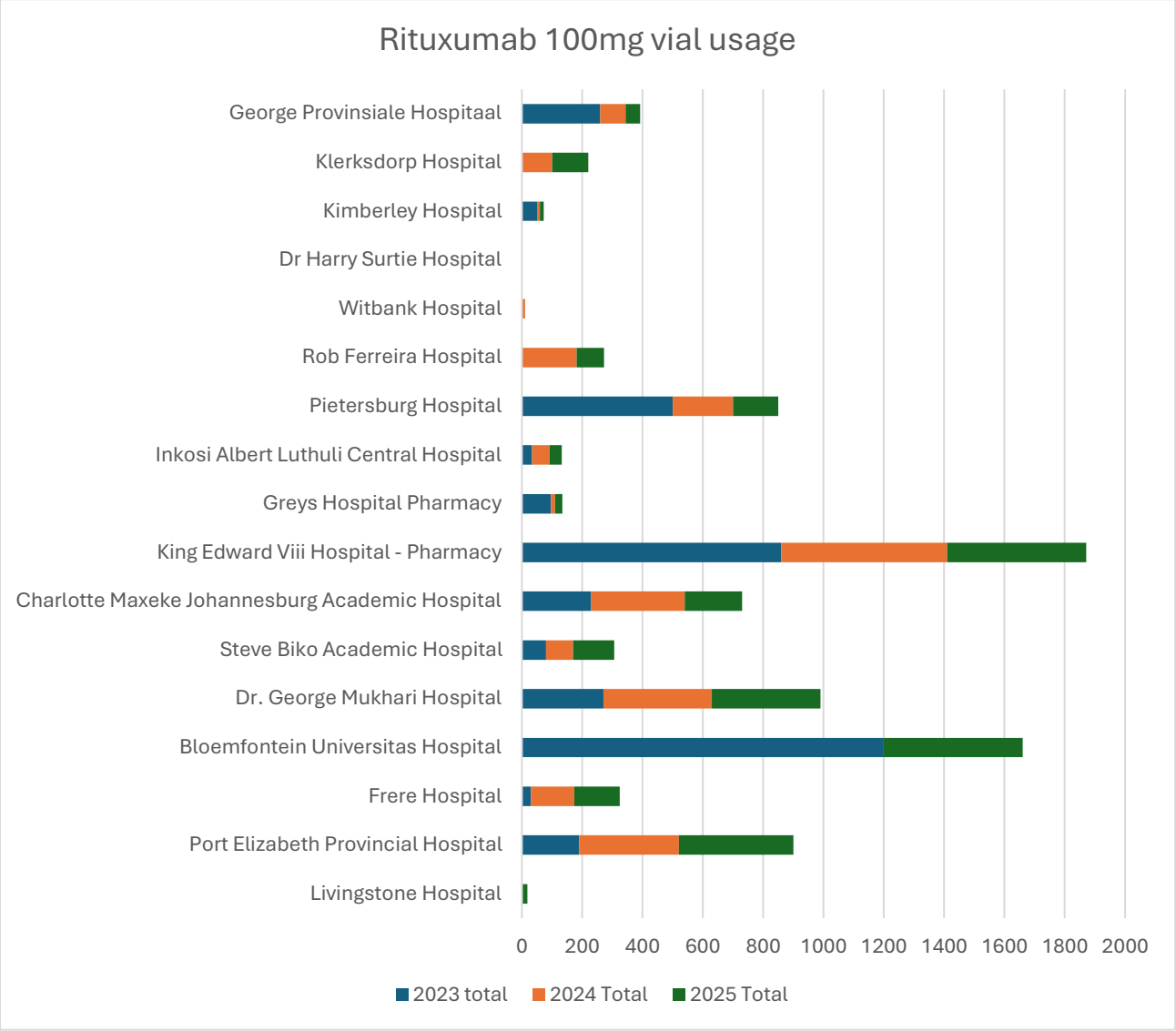
- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma: first line.
- Rheumatoid Arthritis patient's refractory to synthetic DMARDs.
- Refractory lupus nephritis. (special access)

Rituximab 500mg vial utilisation				
Province	**Facility Description**	**2023 Total**	**2024 total**	**2025 total**
EC	Port Elizabeth Provincial Hospital	100	260	378
EC	Nelson Mandela Academic Hospital	60	35	995
EC	Frere Hospital	20	66	410
EC	Livingstone Hospital	0	2	1662
FS	Bloemfontein Universitas Hospital	360	340	1690
GP	Chris Hani Baragwanath Hospital	905	960	2171
GP	Dr. George Mukhari Hospital	240	300	1270
GP	Steve Biko Academic Hospital	182	209	2262
GP	Kalafong Hospital	20	13	167
GP	Charlotte Maxeke Johannesburg Academic Hospital	620	700	1452
GP	Helen Joseph Hospital	56	20	926
KZN	King Edward VIII Hospital - Pharmacy	500	300	1072
KZN	Inkosi Albert Luthuli Central Hospital	220	220	450
KZN	Greys Hospital Pharmacy	83	26	111
MP	Witbank Hospital	0	30	102
MP	Rob Ferreira Hospital	0	149	369
NC	Kuruman Hospital	0	0	392
NC	Kimberley Hospital	68	66	134
NW	Job Shimankana Hospital (Jst)	0	30	30
NW	Tshepong Hospital	0	14	14



Rituximab 100mg vial usage				
Province	**Facility Description**	**2023 total**	**2024 Total**	**2025 Total**
EC	Livingstone Hospital	0	1	17
EC	Port Elizabeth Provincial Hospital	190	330	380
EC	Frere Hospital	30	144	150
FS	Bloemfontein Universitas Hospital	1200	0	460
GP	Dr. George Mukhari Hospital	270	360	360
GP	Steve Biko Academic Hospital	80	90	136
GP	Charlotte Maxeke Johannesburg Academic Hospital	230	310	190
KZN	King Edward VIII Hospital - Pharmacy	860	550	461
KZN	Greys Hospital Pharmacy	96	14	24
KZN	Inkosi Albert Luthuli Central Hospital	34	58	40
LP	Pietersburg Hospital	500	200	150

MP	Rob Ferreira Hospital	0	181	91
MP	Witbank Hospital	0	10	0
NC	Dr Harry Surtie Hospital	0	0	2
NC	Kimberley Hospital	52	8	12
NW	Klerksdorp Hospital	0	100	120
WC	George Provincial Hospital	260	84	48



Appendix 2 (Initial NEMLC medicine review – June 2022

Rituximab - Indolent Lymphomas_Tertiary_

Appendix 3 (2022 economic analysis report)

CEA for rituximab in iNHL_v5.pdf