National Essential Medicine List

Tertiary Medication Review Process

Basic Cost Effectiveness Analysis: Rituximab For Adult Patients With Indolent B Cell Non-Hodgkin Lymphoma

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EXECUTIVE SUMMARY

Medicine: rituximab
Indication: C82, C83.0, C83.1
Patient population: B-cell indolent non-Hodgkin Lymphoma (iNHL)
Level of Care: Tertiary and Quaternary Hospital Level
Prescriber level: Specialist (oncologist)
Current Standard of Care/ Comparator(s): cyclophosphamide, vincristine, and prednisone (CVP) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).
Methods: Decision tree model from a public health sector perspective over a four-year time horizon.
Findings: The intervention, rituximab is more effective and more costly than the comparator with an incremental cost and benefit of R 54 656 and 0.306 QALYs respectively. The base case analysis resulted in an incremental cost-effectiveness ratio of R 178 402. At the current contract price, the addition of rituximab to either CVP or CHOP is deemed to be not cost-effective, compared with either CVP or CHOP alone. The analysis is most sensitive to the price of rituximab.
Recommendations: It is recommended that rituximab not be added onto the EML at the current contract price but be considered for inclusion if a future cost reduction of 66% - 80% of the contract price is achieved.

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Kim MacQuilkan: Better Health Programme South Africa, Right to Care

INTRODUCTION

This document is an annexure to the medicine review of rituximab for indolent B Cell Non-Hodgkin Lymphoma. The review showed that rituximab plus chemotherapy compared to chemotherapy alone provides benefits in terms of overall survival and progression free survival, without increased risk of severe adverse events. However, the addition of rituximab to the current standard of care (cyclophosphamide, vincristine, and prednisone – CVP/cyclophosphamide, doxorubicin, vincristine, and prednisone - CHOP) will increase the budget impact and thus a cost-effectiveness analysis was conducted.

This economic evaluation compares the cost-effectiveness of induction treatment of rituximab plus CVP (R-CVP) or rituximab plus CHOP (R-CHOP) to CVP or CHOP alone in adult patients with indolent B cell non-Hodgkin's lymphoma.

METHODOLOGY

A cost-effectiveness analysis was conducted to investigate the value for money of amending the EML recommendation of CVP or CHOP alone to rituximab plus CVP or CHOP (R-CVP or R-CHOP) for the induction treatment of patients with indolent B-Cell non-Hodgkin Lymphoma.

Perspective

The setting for this study is the South African public health sector and the evaluation takes the perspective of the payer (government). Only direct costs to the government are considered. Indirect costs, such as loss of productivity and worker absenteeism, are not included.

The economic model

The model focussed on CVP as a comparator due to the availability of direct data estimates (discussed further under model parameters). A decision tree model was created in Microsoft Excel ®, to compare rituximab with CVP (R-CVP) with CVP alone (Figure 1). At the start of the first year in the model, patients could get treatment of R-CVP or CVP alone. At the end of years 1, 2, 3 and 4 the patient could survive or die. Adverse events were not included as the literature did not show any differences between groups that would result in additional costs or reduced health benefits. This was confirmed by experts on the Tertiary and Quaternary Hospital Level Expert Review Committee. The decision tree does not account for disease progression due to time and resource constraints. This would have required constructing a Markov model and the collection of necessary data such as proportion of patients moving between different Markov states, and resource use for each state. The model was run over a four-year time horizon following treatment to align with the data that was available. Only initial treatment costs were included and a discounting of 5% per annum was applied to QALYs.

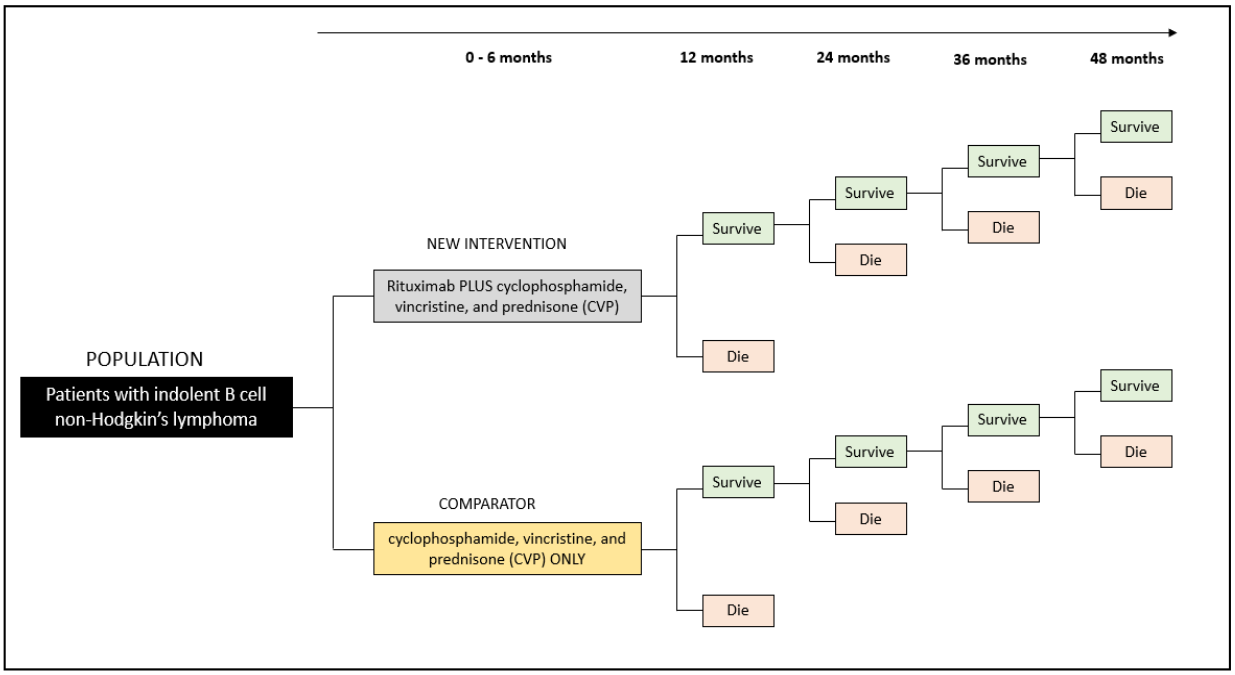

Figure 1. Decision tree model comparing rituximab plus cyclophosphamide, vincristine, and prednisone (CVP) to CVP alone

Costs

The costs of treatment were obtained from the National Department of Health Master Health Products List[1] (Table 1). Only the prices of medications were included since resource use for administering of R-CVP is not expected to vary significantly from CVP alone. Other resource costs such as health worker and

facility costs were also excluded as the number of cycles for chemotherapy administration was assumed to be the same for both interventions. The model assumed 6 cycles of treatment as cycles may vary between 4 and 8 cycles, this will be explored in the sensitivity analysis. The costs assume minimal wastage based on expert opinion of current practice however this is also included in the sensitivity analysis.

Table 1. Treatment costs per individual for six cycles

Description	Drug	Value (per patient)	Reference
Rituximab PLUS CVP (R-CVP)	Rituximab (IV)	R 54 656	1
	Cyclophosphamide (IV)	R 1 341	
	Vincristine (IV)	R 1 466	
	Prednisone (oral)	R 39	
	TOTAL	**R 57 502**	
CVP only	Cyclophosphamide (IV)	R 1 341	
	Vincristine (IV)	R 1 466	
	Prednisone (oral)	R 39	
	TOTAL	**R 2 846**	

Outcomes and health utilities

Data to populate the model were obtained from the literature and mainly informed by the Marcus *et al*. (2008) Phase III study[2] (Table 2). This study was selected due to the longer trial length (4 years) and availability of survival estimates at the end of years 1 to 4. Due to the nature of the condition where patients have a longer median survival, the length of follow-up was an important factor. A systematic review conducted by Schulz et. 2009[3] only had data for two years follow-up and did not provide a breakdown at end of each year. It also included comparators other than CVP or CHOP. The Marcus et al. (2008) study focussed only on patients with follicular lymphoma however, as this is the most prevalent type of iNHL, it was assumed to be appropriate for the purposes of this analysis.

Specific utility data for quality of life was sourced from the Tufts CEA registry[4] and assumed to be the same for patients who survive for both the intervention and comparator. It was assumed that 6 months prior to end of life the patient would be in a palliative care health state.

Table 2. Model parameters

Percentages	**Value**	**Reference**
Percentage of patients on R-CVP who are alive at 12 months	0,988	**2**
Percentage of patients on CVP who are alive at 12 months	0,950	
Percentage of patients on R-CVP who are alive at 24 months	0,926	
Percentage of patients on CVP who are alive at 24 months	0,855	
Percentage of patients on R-CVP who are alive at 36 months	0,877	
Percentage of patients on CVP who are alive at 36 months	0,786	
Percentage of patients on R-CVP who are alive at 48 months	0,765	
Percentage of patients on CVP who are alive at 48 months	0,698	
Utilities	**Value**	**Reference**
Quality of Life of a patient who survives at year 1	0,805	**5**
Quality of Life of a patient who survives at year 2	0,805	
Quality of Life of a patient who survives at year 3	0,805	
Quality of Life of a patient who survives at year 4	0,805	
Quality of Life of a patient with advanced disease - palliative care	0,380	**6**

RESULTS

Base Case analysis

Table 3 shows the base case cost-effectiveness analysis. The total cost of Rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) was estimated to R 57 502 per patient for 6 cycles of therapy. The cost of CVP alone was R2 846. The weighted QALYs were 2.449 for R-CVP and 2.143 for the CVP alone. The incremental cost-effectiveness ratio (ICER) was estimated at R207 594.12.

Table 3. Base case cost-effectiveness analysis

Regimen	Total Cost	Total QALYS	Incremental costs	Incremental benefit	ICER (cost per QALY)
CVP	R2 846	2.143	R0	0	R 0
R-CVP	R 57 502	2.499	R 54 656	0.306	R 178 402

Figure 2 presents the comparison of the ICERs for R-CVP and CVP on the cost-effectiveness plane. R-CVP is more effective but more costly thus does not dominate CVP.

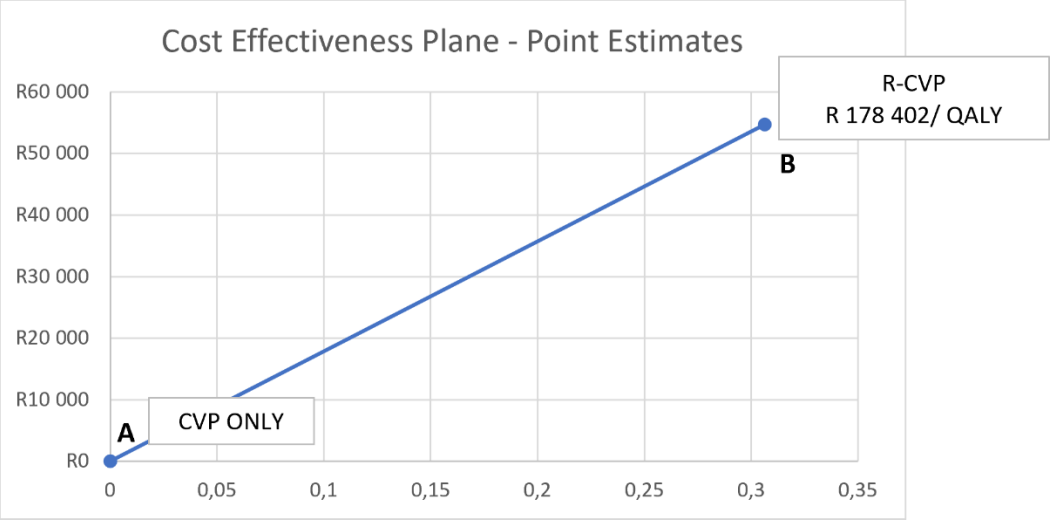

Figure 2. Comparison of incremental cost-effectiveness ratio for rituximab plus CVP to CVP alone

The cost-effectiveness of R-CVP must be further evaluated taking into consideration a willingness to pay (WTP) threshold. In the absence of a set threshold in South Africa, the ICER will be compared to a range of WTP thresholds (see Table 4 below) as determined from other similar NEMLC decisions taken in the past and adjusted for inflation. At current price of rituximab, R-CVP is deemed to be not cost-effective at any of the WTP thresholds.

Table 4: Willingness to pay thresholds

Description	Value	ICER < WTP threshold
WTP Threshold sourced from draft HTA methodology and utilised for bortezomib for multiple myeloma 2021[6]	R40 000	No
WTP Threshold sourced from previous NEMLC decision for Gemcitabine plus Capecitabine for pancreatic cancer[7]	R75 000	No
WTP Threshold sourced from previous NEMLC decision for rituximab for diffuse B-Cell lymphoma[8]	R90 000	No

Sensitivity analysis

Multiple univariate sensitivity analyses were conducted to test the impact on the ICER when changing certain assumptions and parameters (Appendix A). The most variation was observed when medication costs of rituximab were altered. For benefits, the variation of survival estimates at the end of Year 2 resulted in the largest difference in ICERs (Figure 3). A two-way sensitivity analysis was then undertaken to explore this further (Appendix B).

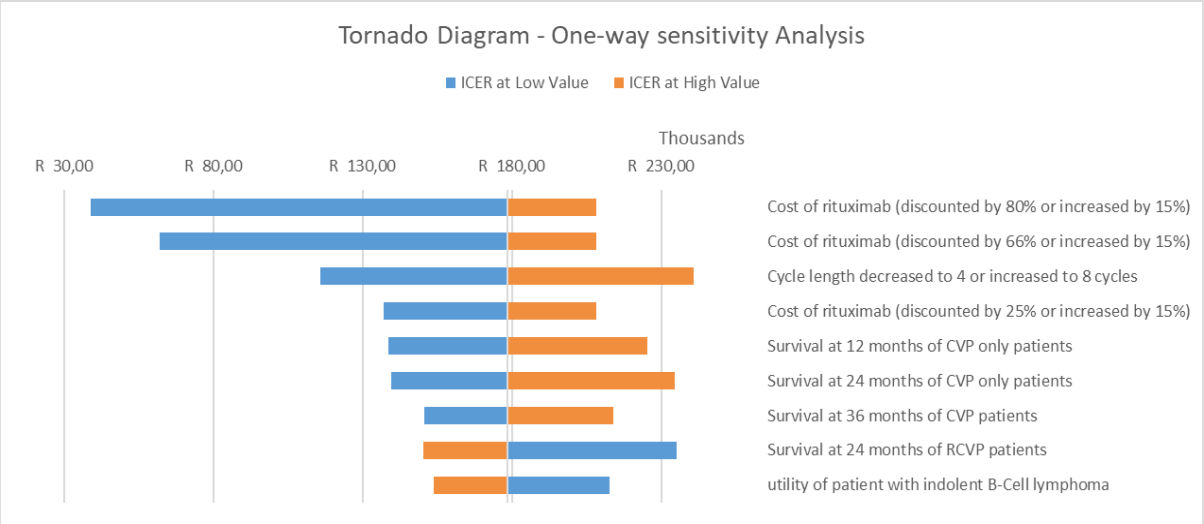

Figure 3. Tornado diagram for one-way sensitivity analysis

Cost-effectiveness threshold Analysis

The adjusted ICERs derived from the sensitivity analyses were compared to the above mentioned WTP thresholds (Appendix C). Figure 4 below presents the results of the ICERs if the cost of rituximab is reduced and demonstrates at what percentage discount rituximab may be deemed cost-effective at different WTP thresholds.

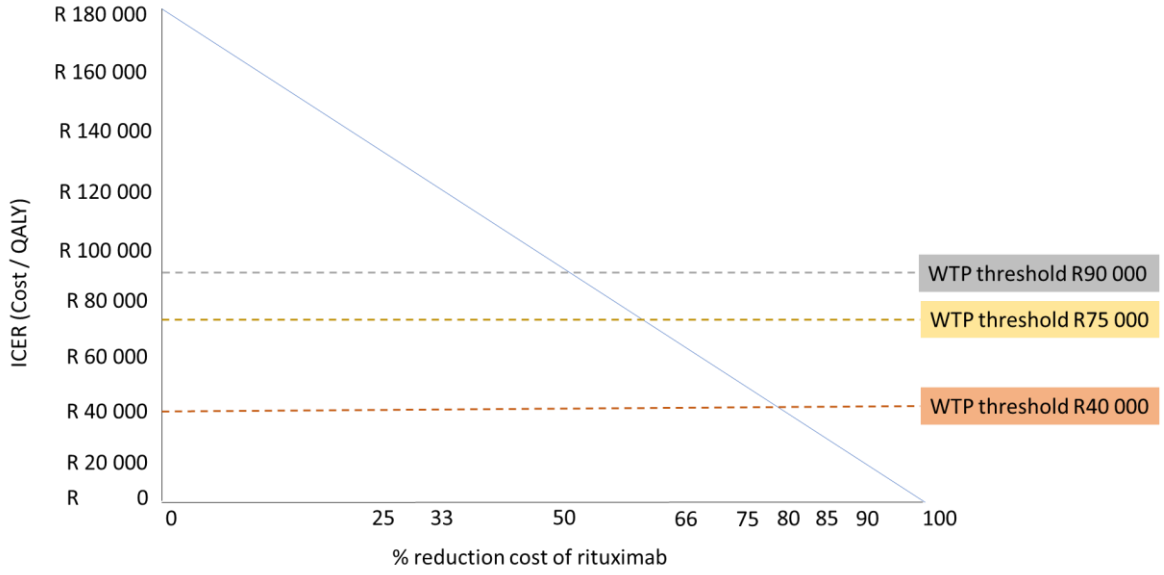

Figure 4. WTP threshold analysis diagram – reduction in price of rituximab

A reduction of 66% in contract price of rituximab results in an ICER of R61 969/QALY and R-CVP may be deemed cost-effective at the higher two WTP thresholds (R90 000 and R75 000) but not the lowest one (R40 000). A reduction of 80% in cost of rituximab satisfies all WTP thresholds (ICER of R38 777/QALY). In the two-way sensitivity analysis, a 4-cycle regimen with a 66% reduction in cost of rituximab produces an estimate below the three WTP thresholds (ICER of R39 249/QALY). An 8-cycle regimen at an 85% reduction in rituximab price results in an ICER of R38 777/QALY (below all 3 WTP thresholds).

BUDGET IMPACT ANALYSIS

Budget impact calculated on the base case assumptions and an estimated 150 patients in the public sector, results in a total cost per annum of R9 966 796 and R426 922 for R-CVP and CVP alone, respectively. The incremental cost is estimated to be R9 539 874 per annum (Table 5).

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

Estimated 150 per year in the state sector - At full contract price				
Regimen - 6 cycles	**Cost per patient**	**No**	**TOTAL**	**Incremental**
R-CVP	R57 502	150	R8 625 301	R8 198 379
CVP only	R2 846	150	R 426 922	

The potential discounted costs of rituximab that were explored in the sensitivity and WTP threshold analyses were applied and tabulated in Table 6.

Table 6 – Budget impact with discounted prices of rituximab

Regimen	R-CVP	CVP	Incremental Cost
Discount Achieved	*Total / patient*	*Total / patient*	
66%	R3 274 694	R426 922	R2 847 772
75%	R2 618 824		R2 191 902
80%	R2 208 905		R1 781 983
85%	R1 798 986		R1 372 064

CONCLUSION

The new intervention of rituximab plus CVP is not likely to be cost-effective at the current contract prices of rituximab. We have attempted to provide guidance using cost-effectiveness thresholds based on previous NEMLC decisions HTA methodology, to aid in decision making when adopting cost-effective options. This is done for illustrative purposes, to show how decisions can be made once a threshold value is adopted. The model was based on some conservative assumptions including relatively short time horizon of four years in the context of iNHL, discounting of 5% of health benefits as well as the exclusion of multiple different disease states or varying quality of life utilities. Thus, although only 80% discount on rituximab satisfied all WTP thresholds in the base-case analysis, a reduction of at least 66% in the contract price of rituximab could potentially be deemed cost-effective.

APPENDIX A. ONE-WAY AND TWO-WAY SENSITIVITY ANALYSES

ONE-WAY Sensitivity Analysis (extreme values)

Parameter	*Lower Value*	LV ICER	Difference	*Point Estimate*	ICER	*Upper Value*	UV ICER	Difference
CVP survival 12 months	0,911	R 138 723,30	R 39 678,98	0,950	R 178 402,28	0,978	R 225 177,81	-R 46 775,53
R-CVP survival 12 months	0,966	R 216 571,82	-R 38 169,54	0,988	R 178 402,28	0,998	R 164 014,07	R 14 388,21
CVP survival 24 months	0,797	R 139 433,87	R 38 968,41	0,855	R 178 402,28	0,905	R 234 466,57	-R 56 064,29
R-CVP survival 24 months	0,881	R 234 986,13	-R 56 583,85	0,926	R 178 402,28	0,961	R 150 220,43	R 28 181,85
CVP survival 36 months	0,719	R 150 638,99	R 27 763,29	0,786	R 178 402,28	0,846	R 213 782,75	-R 35 380,47
R-CVP survival 36 months	0,822	R 216 366,31	-R 37 964,03	0,877	R 178 402,28	0,922	R 155 502,00	R 22 900,28
CVP survival 48 months	0,625	R 165 588,96	R 12 813,32	0,698	R 178 402,28	0,767	R 192 327,08	-R 13 924,80
R-CVP survival 48 months	0,697	R 196 054,35	-R 17 652,07	0,765	R 178 402,28	0,827	R 164 909,09	R 13 493,19
Utility Year 1 – 4, survival	0,684	R 212 552,86	-R 34 150,58	0,805	R 178 402,28	0,926	R 153 706,47	R 24 695,81
Utility advanced disease	0,323	R 176 519,06	R 1 883,22	0,380	R 178 402,28	0,437	R 180 326,12	-R 1 923,84
Discounting (both lower values)	0%	R 154 218,71	R 24 183,57	5%	R 178 402,28	3%	R 168 492,12	R 9 910,16

Assumption	LV Survival estimate	LV Death estimate	Adjusted ICER LV	Difference	ICER	UV Survival estimate	UV Death estimate	Adjusted ICER UV	Difference
No difference in survival at 12 months between regimens (R-CVP year 1 value)	0,965880875	0,03	R253 241,28	-R74 839,00	R 178 402,28	0,998492038	0,0015	R244 970,32	-R66 568,04

ONE-WAY Sensitivity Analysis (changes to treatment costs)

Assumption	Adjusted value of R	Adjusted RVP value	Adjusted ICER	*Point Estimate RCVP*	ICER	Difference	Point estimate R only
Number of cycles reduced to 4	R36 437,24	R38 334,67	R115 838,15	R 57 502,01	R 178 402,28	R62 564,13	R 53 707,15
Number of cycles increased to 8	R72 874,48	R76 669,34	R240 966,41	R 57 502,01	R 178 402,28	-R62 564,13	R 53 707,15
6 cycles but wastage	R57 636,96	R60 776,36	R189 090,09	R 57 502,01	R 178 402,28	-R10 687,81	R 53 707,15

Price discounts for rituximab	Adjusted value of R	Adjusted RVP value	Adjusted ICER	*Point Estimate RCVP*	ICER	Difference	Point estimate R only
Cost R-CVP with 25% discount	R40 991,90	R44 786,76	R136 898,41	R 57 502,01	R 178 402,28	R41 503,87	R 54 655,86
Cost R-CVP with 33% discount	R36 072,87	R39 867,73	R120 842,21	R 57 502,01	R 178 402,28	R57 560,07	R 54 655,86
Cost R-CVP with 50% discount	R27 327,93	R31 122,79	R92 297,84	R 57 502,01	R 178 402,28	R86 104,44	R 54 655,86
Cost R-CVP with 66% discount	R18 036,43	R21 831,29	R61 969,45	R 57 502,01	R 178 402,28	R116 432,82	R 54 655,86
Cost R-CVP with 75% discount	R13 663,97	R17 458,83	R47 697,27	R 57 502,01	R 178 402,28	R130 705,01	R 54 655,86
Cost R-CVP with 80% discount	R10 931,17	R14 726,03	R38 777,16	R 57 502,01	R 178 402,28	R139 625,12	R 54 655,86
Cost R-CVP with 85% discount	R8 198,38	R11 993,24	R29 857,04	R 57 502,01	R 178 402,28	R148 545,24	R 54 655,86
Cost R-CVP with 90% discount	R5 465,59	R9 260,45	R20 936,93	R 57 502,01	R 178 402,28	R157 465,35	R 54 655,86

APPENDIX B – THRESHOLD ANALYSIS

Description	Adjusted ICER	WTP Threshold		
One-way analysis		**< R40000**	**< R75000**	**<R90000**
Cost of R-CVP with 25% discount of Rituximab	R136 898,41	No	No	No
Cost of R-CVP with 33% discount of Rituximab	R120 842,21	No	No	No
Cost of R-CVP with 50% discount of Rituximab	R92 297,84	No	No	No
Cost of R-CVP with 66% discount of Rituximab	R61 969,45	No	Yes	Yes
Cost of R-CVP with 75% discount of Rituximab	R47 697,27	No	Yes	Yes
Cost of R-CVP with 80% discount of Rituximab	R38 777,16	Yes		
Cost of R-CVP with 85% discount of Rituximab	R29 857,04	Yes		
Cost of R-CVP with 90% discount of Rituximab	R20 936,93	Yes		

Two-way analysis	***First factor - 4 cycles***				***First factor - 8 cycles***			
Second factor	**Adjusted ICER**	**< R40000**	**< R75000**	**<R90000**	**Adjusted ICER**	**< R40000**	**< R75000**	**<R90000**
50% discount on Rituximab	R59 467,43	No	Yes	Yes	R122 031,55	No	No	Yes
66% discount on Rituximab	R39 248,50	Yes			R81 593,70	No	No	Yes
75% discount on Rituximab	R29 733,71	Yes			R62 564,13	No	Yes	Yes
80% discount on Rituximab	R23 786,97	Yes			R50 670,64	No	Yes	Yes
85% discount on Rituximab	R17 840,23	Yes			R38 777,16	Yes		
CVP only	***First factor - % patients alive at end of year 2 <u>Lower Value</u>***				***First factor - % patients alive at end of year 2 <u>Upper Value</u>***			
Second factor	**Adjusted ICER**	**< R40000**	**< R75000**	**<R90000**	**Adjusted ICER**	**< R40000**	**< R75000**	**<R90000**
50% discount on Rituximab	R72 137,22	No	Yes	Yes	R121 303,15	No		
66% discount on Rituximab	R48 433,47	No	Yes	Yes	R81 443,83	No	Yes	
75% discount on Rituximab	R37 278,76	Yes			R62 686,51	No	Yes	
80% discount on Rituximab	R30 307,06	Yes			R50 963,18	No	Yes	
85% discount on Rituximab	R23 335,37	Yes			R39 239,85	Yes		
R-CVP	***First factor - % patients alive at end of year 2 <u>Lower Value</u>***				***First factor - % patients alive at end of year 2 <u>Upper Value</u>***			
Second factor	**Adjusted ICER**	**< R40000**	**< R75000**	**<R90000**	**Adjusted ICER**	**< R40000**	**< R75000**	**<R90000**
50% discount on Rituximab	R121 571,95	No			R77 717,74	No	Yes	
66% discount on Rituximab	R81 624,31	No			R52 180,26	No	Yes	
75% discount on Rituximab	R62 825,42	No	R40 162,63		R57 201,22	No	Yes	
80% discount on Rituximab	R51 076,11	No	R32 651,61		R46 048,60	No	Yes	
85% discount on Rituximab	R39 326,80	Yes			R25 140,59	Yes		

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[8] Adjusted for inflation, this was ICER per LY gained but is similar to the upper range of a threshold derived from Woods et al. 2016 https://pubmed.ncbi.nlm.nih.gov/27987642/