National Essential Medicine List
Tertiary Medication Review Process
Component: Oncology - Bortezomib

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: November 2020
Medicine (INN): Bortezomib
Medicine (ATC): L01XX32
Indication (ICD10 code): Multiple Myeloma
Patient population: Transplant eligible multiple myeloma
Prevalence of condition: Multiple myeloma accounts for approximately 1% of all cancers. [1]
Level of Care: Tertiary
Prescriber Level: Specialist Oncologist/ Clinical Haematologist
Current standard of Care: Thalidomide plus corticosteroids
Efficacy estimates: (preferably NNT): Complete response (CR) rate was significantly higher with VTD than with TD (35% vs 14%, P 0.001), NNT: 5. The median progression-free survival (PFS) was significantly longer with VTD (56.2 vs 28.2 months, P 0.01).[2]

2. **Name of author(s)/motivator(s):** Esnath Maramba

3. **Author affiliation and conflict of interest details:** Employed by Council for Medical Schemes. Assessed as potentially significant, all decisions made by committee as a collective and not the lead reviewer.

4. **Introduction/ Background**

Multiple myeloma (MM) is a malignant clonal bone marrow plasma cell tumor with excessive monoclonal protein production leading to bone destruction and marrow failure.

MM remains an incurable disease and to prolong progression-free survival (PFS) and overall survival (OS), one goal of frontline treatment is to maximize depth of tumor reduction which is often pursued with autologous stem cell transplant (ASCT), a standard of care for eligible patients. Induction therapy before transplantation can influence post-transplant results. Therefore, best frontline treatment for transplant-eligible patients should be based on best available evidence to guide therapy.

5. **Purpose/Objective i.e. PICO question**

-P *(patient/population):* transplant eligible multiple myeloma patients
-I *(intervention):* Addition of bortezomib to induction regimen
-C *(comparator):* Non bortezomib induction regimen
-O *(outcome):* Overall survival, progression free survival, response rate

6. **Methods:**
    a. **Data sources:** Pubmed
    b. **Search strategy:** (((bortezomib[MeSH Terms])) AND (multiple myeloma[MeSH Terms]))
        - Bortezomib induction therapy for transplant eligible multiple myeloma: 77 results from PUBMED.
        - Included RCTs, meta-analyses for transplant eligible MM.

    c. **Excluded studies:**
        - Excluded studies for transplant ineligible multiple myeloma
        - Excluded studies not looking at induction therapy
        - Excluded studies of bortezomib verses new agent e.g. monoclonal antibodies

d. Evidence synthesis

Author, date	*Type of study*	N	Population	Comparators	Primary outcome	Effect sizes	Comments
Scott et.al. 2016[3]	Cochrane Review (16 RCTs)	5626	Patients diagnosed with MM *Age cut off of 65 years for transplant eligible*	Bortezomib (monotherapy or in combination with cyclophosphamide, melphalan; corticosteroids, immuno-modulatory agents) VERSUS No Bortezomib (no therapy or non-bortezomib therapy)	Overall survival Progression-free survival	Bortezomib versus no bortezomib with the same background therapy in each arm. • OS (n=1586 ; Peto OR 0.77, 95% CI 0.65 to 0.92, p < 0.00001) • PFS (n=1855 ; Peto OR 0.65, 95% CI 0.57 to 0.74, p<0.00001) Bortezomib versus no bortezomib with different background therapy in each arm or compared to other agent(s). • OS (n=2532; Peto OR 0.76, 95% CI 0.67 to 0.88, p<0.00001) • PFS (n=2489 patients; Peto OR 0.67, 95% CI 0.61 to 0.75, p<0.00001)	• Greater risk of thrombocytopenia, neutropenia, GIT toxicities and peripheral neuropathy in bortezomib. • Statistical heterogeneity of studies.
Nooka et al, 2013.	Meta-analysis (4 trials) GIMEMA-MMY-3006, HOVON-65/GMMG-HD4, PETHEMA/GEM, and IFM2005-01 trials)	2169	Transplant-eligible patients	Bortezomib-containing induction regimen (BCIR) **vs** Non bortezomib-containing induction regimen	Overall survival Progression-free survival	All studies demonstrated PFS. Pooled PFS favored BCIR (HR, 0.71; 95% CI, 0.60-0.83; P = 0.001). 1 study demonstrated OS. Pooled OS favored BCIR (HR, 0.79; 95% CI, 0.66-0.95; P < 0.014)	BCIR – higher odds of developing selected grade ≥3 toxicities (peripheral neuropathy and varicella-zoster virus reactivation)
Rosiñol et al, 2013	PETHEMA/GEM study Included in meta-analysis above	386	≤ 65 years old Newly diagnosed and untreated symptomatic MM	–bortezomib plus thalidomide plus dexamethasone (VTD) VS	Overall survival Progression-free survival	OS at 4 years (no significant differences among groups) • 74% with VTD • 65% with TD	

				–thalidomide plus dexamethasone (TD) VS –alternating chemotherapy regimens containing vincristine, BCNU, melphalan, cyclophosphamide, prednisone, doxorubicin, dexamethasone, and bortezomib (VBMCP/VBAD/B)	Response rate	• 70% with VBMCP/VBAD/B PFS (p = 0.01) [at least 21 months increase] • 56.2 months with VTD • 35.3 months with TD • 28.2 months with VBMCP/VBAD/B CR to 6 cycles of induction therapy (complete myeloma cell clearance) • 35% with VTD (p = 0.0001 vs. TD) • 14% with TD • 21% with VBMCP/VBAD/B (p = 0.01 vs. VTD) CR to induction therapy and autologous HSCT • 46% with VTD (p = 0.004 vs. TD) • 24% with TD • 38% with VBMCP/VBAD/B (not significant vs. VTD)	
Durie et.al 2017[4]	RCT	525 adults	Newly diagnosed MM without a specific intent for immediate autologous stem cell transplantation	Lenolidomide PLUS dexamethasone (6 cycles) Versus Bortezomib PLUS lenolidomide	<u>Primary outcome</u>: PFS <u>Secondary outcome:</u> OS and Overall (partial or	**PFS - prolonged by 13 months** 43 months vs. 30 months (HR for progression or death 0.71, 95% CI 0.56-0.91) **OS - prolonged by 11 months** 75 months vs. 64 months (hazard ratio [HR] for death 0.71, 95% CI 0.52-0.96)	≥ grade 3 any adverse events in 82% vs. 75% (no p value reported) ≥ grade 3 neurological adverse events in 33% vs. 11% (p < 0.0001, NNH 4)

				PLUS dexamethasone (8 cycles)	better) response	Overall (partial or better) response 82% vs. 72% (p = 0.02, NNT 10).	
Long term follow up							
Joseph et.al 2020[5]	Cohort Study	1000	Median age 61 years, 54.6% male	Follow up study for patients who received lenalidomide plus bortezomib plus dexamethasone (RVD)	Overall response	977 patients (97.7%), response assessment after RVD induction • overall response in 97.1% • stringent complete response (CR) plus CR in 35.9% • very good partial response or better in 67.6% • stable disease in 1.5% • progressive disease in 1.1% 742 patients (74.2%) who received RVD plus autologous stem cell transplantation, response assessment at 100 days after transplantation • overall response in 98.5% • stringent complete response (CR) plus CR in 71% • very good partial response or better in 89.9% • stable disease in 0.3% • progressive disease in 1.2%	

e. **Evidence quality:** Some of the studies from the Cochrane review showed moderate statistical heterogeneity for PFS estimates. Some studies that have been included have bortezomib added to lenalidomide which is not the current standard of care in our setting; this may potentially overstate the benefits compared to thalidomide.

7. Alternative agents: No other proteasome inhibitors available in South Africa

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group. List specific exclusion from the group:	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	

RESOURCE USE	**How large are the resource requirements?** More intensive: X Less intensive: Uncertain:	Cost of medicines/ cycle: **Medicine** / **Cost (ZAR)** Bortezomib / R14 868 **Cost per course (6 cycles):** Bortezomib/thalidomide/prednisone: R 124,908.00
EQUITY	**Would there be an impact on health inequity?** Yes: No: Uncertain: X	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: X No: Uncertain:	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	**X**

Recommendation

- Bortezomib should be included as induction therapy for transplant eligible multiple myeloma patients (≤ 65 years of age).
- The subcutaneous route and dosing is recommended due to the decrease risk of peripheral neuropathy compared to IV administration.

Rationale: Favourable PFS and CR outcomes

Level of Evidence: Randomised Controlled Trials and Meta-analyses

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations	PTCs to monitor usage
Research priorities	Registries – patient outcomes

References:

[1] National Cancer Registry. 2016. https://www.nicd.ac.za/centres/national-cancer-registry/

[2] Rosiñol, L., Oriol, A., Teruel, A. I., Hernández, D., López-Jiménez, J., de la Rubia, J., Granell, M., Besalduch, J., Palomera, L., González, Y., Etxebeste, M. A., Díaz-Mediavilla, J., Hernández, M. T., de Arriba, F., Gutiérrez, N. C., Martín-Ramos, M. L., Cibeira, M. T., Mateos, M. V., Martínez, J., Alegre, A., … Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma (PETHEMA/GEM) group (2012). Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood, 120(8), 1589–1596. https://doi.org/10.1182/blood-2012-02-408922

[3] Scott, K., Hayden, P. J., Will, A., Wheatley, K., & Coyne, I. (2016). Bortezomib for the treatment of multiple myeloma. The Cochrane database of systematic reviews, 4, CD010816.

[4]Durie, B., Hoering, A., Abidi, M. H., Rajkumar, S. V., Epstein, J., Kahanic, S. P., Thakuri, M., Reu, F., Reynolds, C. M., Sexton, R., Orlowski, R. Z., Barlogie, B., & Dispenzieri, A. (2017). Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet (London, England), 389(10068), 519–527.

[5] Joseph, N. S., Kaufman, J. L., Dhodapkar, M. V., Hofmeister, C. C., Almaula, D. K., Heffner, L. T., Gupta, V. A., Boise, L. H., Lonial, S., & Nooka, A. K. (2020). Long-Term Follow-Up Results of Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy and Risk-Adapted Maintenance Approach in Newly Diagnosed Multiple Myeloma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 38(17), 1928–1937. https://doi.org/10.1200/JCO.19.02515