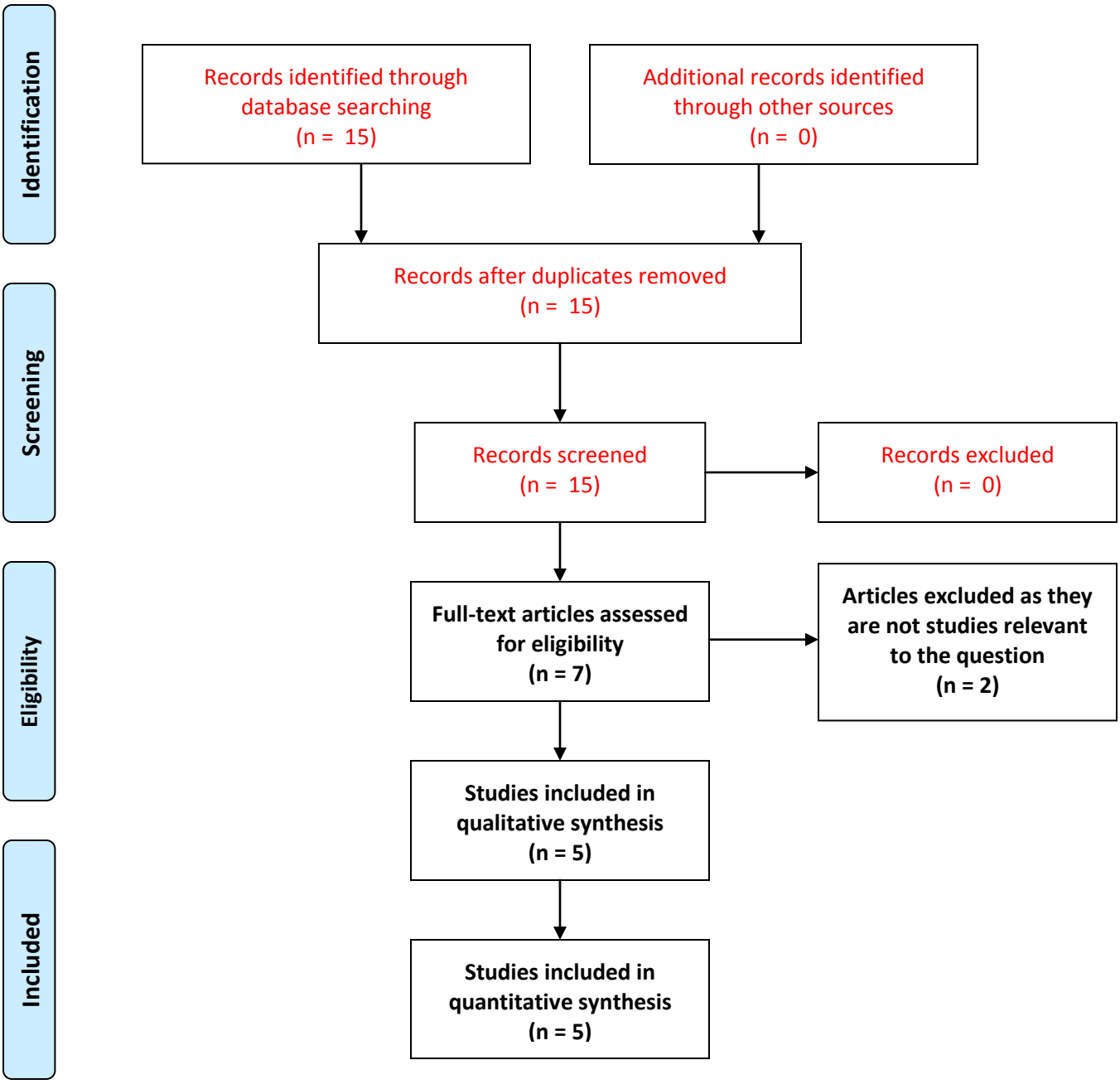
Name of medicine (INN):	**Bortezomib 3.5mg/vial powder for injection (I.V)**
Indication:	Indicated for the treatment of patients with multiple myeloma and mantle cell lymphoma who have received at least 1 prior therapy.
Date of deliberation:	24 July 2015 26 November 2015
Recommendation:	**DISAPPROVAL**
Clinical evidence:	Based on the evaluation of the available evidence, it was noted that complete/non-complete response was higher in the bortezomib group with OR=2.98 after induction and this was statistically significant (p<0.01). A similar finding was also seen among patients who underwent transplant OR=2.74 (p<0.01). Compared with thalidomide, bortezomib had similar overall survival HR = 0.80 (95% CI; 0.56 and 1.14) and event-free survival HR = 0.73 (95% CI; 0.54 and 1.0). On the other hand, compared with mephalan, bortezomib had better overall survival HR = 0.65 (95% CI; 0.51 and 0.84) and better event-free survival HR = 0.48 (95%CI; 0.37 and 0.63) In terms of safety, it was seen that bortezomib is as safe as control with cardiotoxicity as the outcome OR=1.15 (95% CI; 0.82 and 1.62). Compared with thalidomide, bortezomib has lesser adverse event RR = 0.53 (95% CI; 0.38 and 0.73) but compared with melphalan, bortezomib has more adverse event RR = 1.28 (95% CI; 1.06 and 1.54). *(See Attachment for the full ERG evaluation)*
Cost data:	A bortezomib-based regimen is more expensive costing around Php 75,180, compared to a thalidomide or melphalan-based regimen, which will cost Php 18,156 and Php 2,171, respectively. *(See Attachment).*
Remarks:	The ERG evaluated the documents submitted by the proponent to

	support their appeal and it was noted that most of the submitted articles did not offer additional evidence to the previous review. The Council concurred to this and given that the product has prohibitive cost and the proponent did not give a lower price offer, the initial recommendation to disapprove its inclusion still remains. **The Secretary of Health has officially disapproved the proposal to include bortezomib in the PNF.**

PRISMA Table



1. How effective is Bortezomib 3.5mg powder for injection in treating multiple myeloma and mantle cell lymphoma?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Bortezomib		Control			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
	Nooka et al. Cancer. 2013	Meta-analysis	2,169 multiple myeloma patients who participated in 3 RCTs	Bortezomib vs non-bortezomib induction regimen	Complete/non-complete response after induction	23%	1,148	10%	1,021	High	OR 2.98 (p <0.01)
					Complete/non-complete response after transplant	45%	1,148	25%	1,021		OR 2.74 (p <0.01)
					Overall response rate after induction	83%	1,148	65%	1,021		OR 2.68 (p <0.01)
					Overall response rate after transplant	87%	889	79%	894		OR 1.91 (p <0.01)
	Xiao et al. PLoS One. 2014	Meta-analysis	2,679 multiple myeloma patients who participated in 3 RCTs	Bortezomib vs. control	All cardiotoxicity	78	1337	69	1342	High	1.15 (95% CI; 0.82 and 1.62)
					High grade cardiotoxicity	18	1098	16	1103		1.13 (95% CI; 0.57 and 2.23)
	Kumar et al. Am J Hematol. 2011	Systematic review (2,798 patients with SLE)	6 RCTs	Indirect comparison of bortezomib and thalidomide	Overall survival	Raw data not in the text		Raw data not in the text			HR = 0.80 (95% CI; 0.56 and 1.14) no significant difference
					Event-free Survival						HR = 0.73 (95% CI; 0.54 and 1.0) no significant difference
					Very Good Partial Response						RR = 0.59 (95% CI; 0.28 and 1.23) no significant difference

					Partial Response Treatment related mortality Deep vein thrombosis Grade III/IV adverse event						RR = 0.85 (95% CI; 0.59 and 1.21) no significant difference RR = 0.38 (95% CI; 0.09 and 1.63 no significant difference RR = 0.27 (95% CI; 0.06 and 1.23) no significant difference RR = 0.53 (95% CI; 0.38 and 0.73) no significant difference
	Kumar et al. Am J Hematol. 2011	Systematic review of 6 RCTs (2,798 patients with SLE)	Cited one RCT	bortezomib vs. melphalan	Overall survival Event-free Survival Very Good Partial Response Treatment related mortality Deep vein thrombosis Grade III/IV adverse event	Raw data not in the text		Raw data not in the text			HR = 0.65 (95% CI; 0.51 and 0.84) bortezomib is better HR = 0.48 (95%CI; 0.37 and 0.63) bortezomib is better RR = 2.12 (95%CI; 1.12 and 4.01) bortezomib is better RR = 0.42 (95% CI; 0.11 and 1.63) RR 0.66 (95% CI; 0.19 and 2.32) RR = 1.28 (95% CI; 1.06 and 1.54)
	Prince et al. Eur J	Systematic review	One bortezomib study and 15	Indirect comparison of bortezomib vs	Favorable response Favorable response	53% 41%	333	32% 22%	1007		

	Haematol. 2007		thalidomide studies	thalidomide	by European Group Blood and Marrow Transplantation						

EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE

QUALITY ASSESSMENT							SUMMARY OF FINDINGS					Importance
							No. of patients		Effect		Over-all Quality	
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute MD		
Outcome: Overall response rate after induction												
1	Meta-analysis	None	None	None	None		Bortezomib	Non-bortezomib	2.68 (p <0.01)		High	Critical
Outcome: Overall response rate after transplant												
1	Meta-analysis	None	None	None	None		Bortezomib	Non-bortezomib	1.91 (p <0.01)		High	Critical
Outcome: Overall survival												
1	Meta-analysis	None	None	None	None		Bortezomib	Thalidomide	0.80 (95% CI; 0.56 and 1.14)		High	Critical
Outcome: Overall survival												
1	Meta-analysis	None	None	None	None		Bortezomib	Mephalan	0.65 (95% CI; 0.51 and 0.84)		High	Critical
Outcome: Grade III/IV Adverse event												
1	Meta-analysis	None	None	None	None		Bortezomib	Thalidomide	0.53 (95% CI; 0.38 and 0.73)		High	Critical
Outcome: Grade III/IV Adverse event												
1	Meta-analysis	None	None	None	None		Bortezomib	Mephalan	1.28 (95% CI; 1.06 and 1.54)		High	Critical

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

PARAMETER (Indicate information for intended recipient)* ***INTENDED RECIPIENT:***	**NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION**	**CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF**	**REFERENCES**
COST PER DOSAGE UNIT (in PhP) a. Proposed list price to the government b. Current prevailing market price	a. Bortezomib (Velcade) inj 3.5mg/vial (P 75,180) b. Php 98,674	Thalidomide 50 mg tab ($17) Mephalan 2 mg tab in 25s (P542.81)	Bortezomib is price from company Mephalan is MIMS price Thalidomide is internet price
NUMBER OF DOSAGE UNITS PER UNIT COURSE	1 injection plus dexamethasone	24 tablets of Thalidomide 4 tabs every month for 6 months plus dexamethasone 100 tabs of mephalan 2 mg for 6 months plus dexamethasone	
TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)	Php 75,180	P 18,156 (Thalidomide) P 2,171.24 (Mephalan)	44.5 exchange rate: $ to Peso
ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP) a. Implementation costs: (cost of drug administration, monitoring, additional diagnostic services, additional equipment, travel, caregiver, etc.)			

TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs	Php 75,180	P 18,156 (Thalidomide) P 2,171.24 (Mephalan)	
ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE			
QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)			
DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)			

Note:
Reference: NICE. Bortezomib and Thalidomide for the first line treatment of Multiple Myeloma. **NICE technology appraisal guidance 228 July 2011** guidance.nice.org.uk/ta228

Incremental Cost-effectiveness Ratio

A. Bortezomib + Melphalan + prednisone vs. melphalan + prednisone will incur 19,000 pounds per QALY gained (equivalent to Php 1,307,701.58)

B. Bortezomib + Melphalan + prednisone vs. melphalan + prednisone + thalidomide will incur 320,000 pounds per QALY gained (equivalent to Php 22,024,447.68)

C. Oral melphalan + prednisone + Thalidomide vs. injectable melphalan and prednisone will incur 9170 pounds per QALY gained (equivalent to Php 631,000.00)

D. Cyclophosphamide + thalidomide + dexamethasone vs. melphalan + prednisone will incur 33200 pounds per QALY gained (equivalent to Php 2,285,036.45)

Conclusion of the Guideline:

The Committee concluded that thalidomide in combination with an alkylating agent and a corticosteroid is a cost-effective option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. The Committee did not accept the manufacturer of bortezomib's assertion that the bortezomib regimen (VMP) was cost effective compared with the thalidomide regimen (MPT). However, the Committee did consider that bortezomib regimens could be cost effective for people who are unable to tolerate or have a contraindication to thalidomide.

Reviewer's Recommendation:

The data above further support that based on the current evidence and cost considerations, we cannot justify inclusion of bortezomib in the PNDF.

REVIEWERS' RECOMMMENDATIONS

Literature Search

- We searched PubMed database last February 2015 using the terms "bortezomib" AND "meta-analysis". This yielded 15 articles. We reviewed the 15 articles and considered 11 for full text retrieval. Only 7 articles are available as full text. We reviewed the full text articles and included 5 in this review.

  - Xiao Y(1), Yin J(1), Wei J(1), Shang Z(1). Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: a systematic review and meta-analysis. PLoS One. 2014 Jan 29;9(1):e87671. doi: 10.1371/journal.pone.0087671. eCollection 2014.
  - Nooka AK(1), Kaufman JL, Behera M, Langston A, Waller EK, Flowers CR, Gleason C, Boise LH, Lonial S. Bortezomib-containing induction regimens in transplant-eligible myeloma patients: a meta-analysis of phase 3 randomized clinical trials. Cancer. 2013 Dec 1;119(23):4119-28. doi: 10.1002/cncr.28325. Epub 2013 Sep 4.
  - Kumar A(1), Hozo I, Wheatley K, Djulbegovic B. Thalidomide versus bortezomib based regimens as first-line therapy for patients with multiple myeloma: a systematic review. Am J Hematol. 2011 Jan;86(1):18-24. doi: 10.1002/ajh.21904.
  - Prince HM(1), Adena M, Smith DK, Hertel J. Efficacy of single-agent bortezomib vs. single-agent thalidomide in patients with relapsed or refractory multiple myeloma: a systematic comparison. Eur J Haematol. 2007 Aug;79(2):93-9. Epub 2007 Jun 28.

Results of the Review

Effectiveness

- Overall response rate after induction or transplant was higher with bortezomib-based regimen. After induction the complete/non-complete response was higher in the bortezomib group with OR=2.98 and this was statistically significant ($p<0.01$). A similar finding was also seen among those with transplant OR=2.74 ($p<0.01$).
- In an indirect comparison with thalidomide, bortezomib had similar overall survival HR= 0.80 (95% CI; 0.56 and 1.14) and event-free survival HR = 0.73 (95% CI; 0.54 and 1.0).
- When compared with mephalan, bortezomib had better overall survival HR = 0.65 (95% CI; 0.51 and 0.84) and better event-free survival HR = 0.48 (95%CI; 0.37 and 0.63).

Safety

- In terms of safety, bortezomib is just as safe as control with cardiotoxicity is the outcome OR=1.15 (95% CI; 0.82 and 1.62).
- Compared with thalidomide, bortezomib has lesser adverse event RR = 0.53 (95% CI; 0.38 and 0.73) but compared with mephalan, bortezomib has more adverse event RR = 1.28 (95% CI; 1.06 and 1.54).

Cost data

- In terms of cost, a bortezomib-based regimen will cost Php 75,180 but a thalidomide-based regimen will cost P18,156 and a mephalan-based regimen cost 2,171.

Overall Recommendation

- Overall, it was found that bortezomib-based regimen is as effective and safe as thalidomide-based regimen but is two times more expensive. Thus there is not enough evidence and justification to include bortezomib in the PNDF. Thalidomide may be a more cost-effective alternative to mephalan (PNDF drug).

References

1. Heller S(1), Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. J Diabetes. 2013 Dec;5(4):482-91. doi: 10.1111/1753-0407.12060. Epub 2013 May 7.
2. Singh SR(1), Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ. 2009 Feb 17;180(4):385-97. doi: 10.1503/cmaj.081041.
3. Raskin et al. Use of Insulin Aspart, a Fast-Acting Insulin Analog, as the Mealtime Insulin in the Management of Patients With Type 1 Diabetes. *Diabetes Caer, 2000* 23:583–588
4. Pettitt et al. Efficacy, safety and lack of immunogenicity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. Diabet. Med. 2007. 24, 1129–1135
5. Rys P(1), Pankiewicz O, Łach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: a systematic review. Diabetes Metab. 2011 Jun;37(3):190-200. doi: 10.1016/j.diabet.2010.12.003. Epub 2011 Feb 17.
6. Herrmann BL(1), Kasser C, Keuthage W, Huptas M, Dette H, Klute A. Comparison of insulin aspart vs. regular human insulin with or without insulin detemir concerning adipozytokines and metabolic effects in patients with type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2013 Apr;121(4):210-3. doi: 10.1055/s-0033-1334905. Epub 2013 Mar 19.

Response to appeal on the reviewers' recommendation on Bortezomib

We reviewed the articles submitted to support the appeal on bortezomib. We found out that most of the submitted articles did not offer additional evidence to our previous review. Thus we maintain the original findings of the ERG.

"Overall, we found bortezomib-based regimen to be as effective and safe as thalidomide-based regimen but is more than two times more expensive. Thus there is not enough evidence and justification to include bortezomib in the PNDF. Thalidomide may be a more cost-effective alternative to mephalan (PNF drug)."

Because cost is significant issue for PNF, it is recommended that the manufacturer decrease the cost of bortezomib comparable to current drugs in the PNF for multiple myeloma.