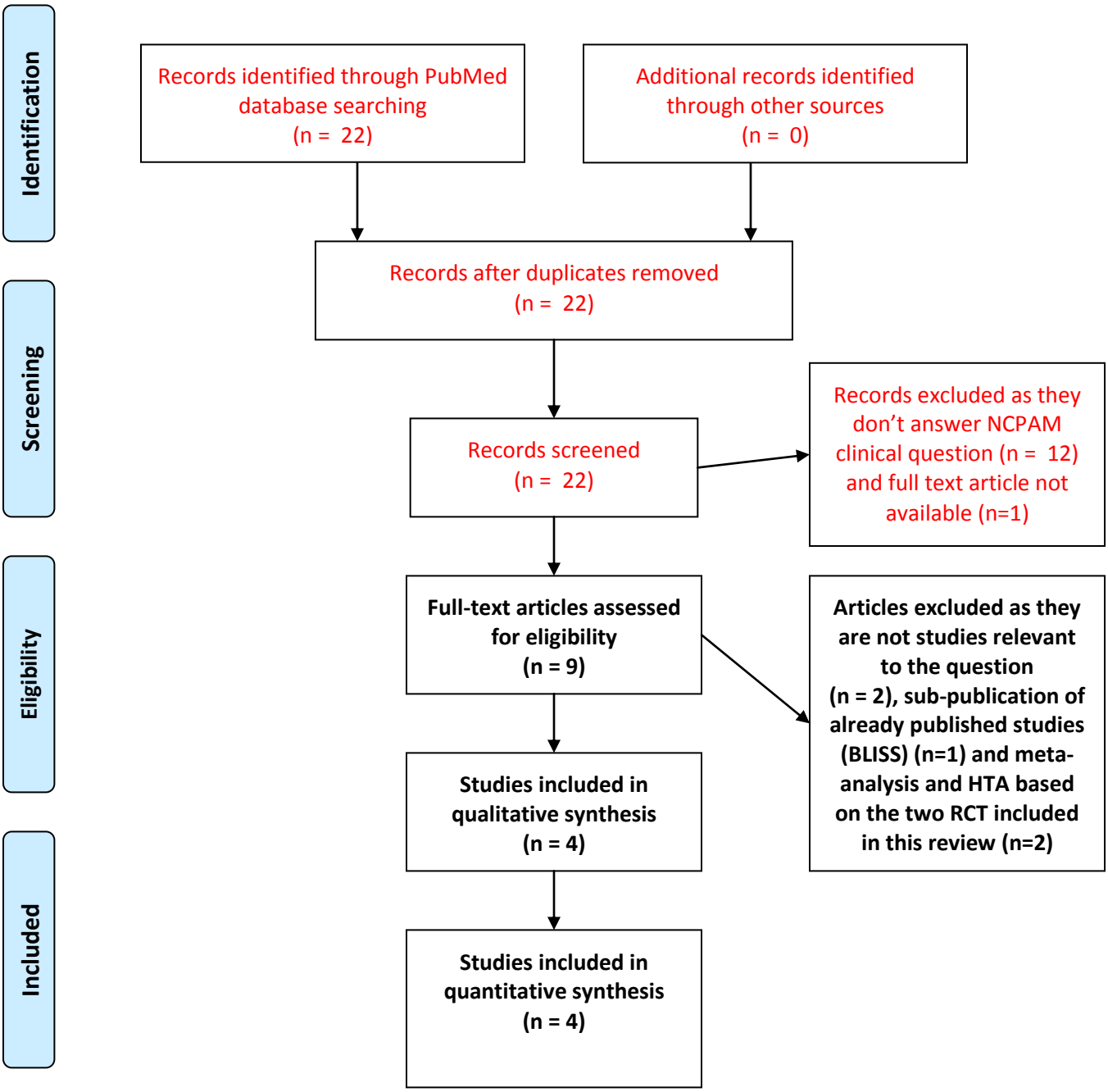
Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN):	**Belimumab 80 mg/mL powder for solution for IV infusion**
Indication:	For reducing disease activity in adult patients with active autoantibody positive Systemic Lupus Erythematosus (SLE) who are receiving standard therapy.
Date of deliberation:	01 July 2015
Recommendation:	**DISAPPROVAL**
Clinical evidence:	The Council noted that the evidence found for the clinical effectiveness of belimumab are only from short-term studies. The ERG report showed that after 52 weeks of treatment with belimumab given 1 mg/kg, the patients had better: (1) response rate (OR=1.55, 95% CI: 1.10 and 2.19), (2) reduction of severe flares (OR=0.76, 95% CI: 0.52 and 1.09) and (3) disease index (OR=1.51, 95% CI: 1.07 and 2.14). Similar significant findings were also seen when the drug was given at 10 mg/kg. After 76 weeks of treatment, however, the effect was only significant for belimumab 1 mg/kg in terms of (1) reduction of severe flares (18.5% vs. 26.5%) and (2) >4 points reduction in disease index (42.1% vs. 33.8%). It was likewise observed that belimumab did not have any significant difference in all measured outcomes and there was also no significant effect on the quality of life (QOL). As regards its safety, the ERG report showed that belimumab and standard of care (SOC) did not significantly differ in terms of incidence of serious adverse event, i.e., 19.5% and 18.0% for belimumab 1 mg/kg and 10 mg/kg, respectively compared to 16.6% for the SOC. *(See Attachment for the full ERG evaluation)*
Cost data:	The Council acknowledged the cost of treatment presented in the report of the Evidence Review Group *(See Attachment)* and noted that the yearly treatment cost with the drug amounts to Php 127,500 and Php 424,995 with the 120 mg and 400 mg vial preparations, respectively. On

	the other hand, treatment with prednisone tablet would only cost around Php 9,125 per year. Given this, the FEC discussed that even though belimumab was seen to be more effective based on short term studies, this does not sufficiently justify the very high cost of the drug.
Remarks:	The Secretary of Health has officially disapproved the proposal to include belimumab in the PNF. There was no appeal received within the set deadline, thus the recommendation of the Council still remains.

PRISMA Table



1) What is the clinical benefit of Belimumab in reducing disease activity of patients with systemic lupus erythematosus (SLE)?
2) What is the cost-effectiveness of Belimumab 80mg/mL vs other immunosuppressive agents (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) in the management of systemic lupus erythematosus (SLE)?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Belimumab		Placebo			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
1	Navarra et al. Lancet 2011 (BLISS-52)	RCT	867 SLE patients	Belimumab 1 mg/kg plus standard care vs. placebo plus standard care (standard care is long-term steroid based treatment)	SRI response rate	148 (51%)	288	125 (44%)	287		OR=1.55 (95% CI;1.10 and 2.19)
					Reduction >4 pts SELENA-SLEDA	153 (53%)	288	132 (46%)	287		OR=1.51 995%CI; 1.07 and 2.14)
					Patients with severe flare	51 (18%)	288	66 (23%)	287		OR=0.76 (95%CI; 0.52 and 1.09)
					Serious adverse events	47 (16%)	288	36 (13%)	287		
				Belimumab 10 mg/kg plus standard care vs. placebo plus standard care (standard care is long-term steroid based treatment)	SRI response rate	167 (58%)	290	125 (44%)	287		OR=1.83 (95%CI; 1.30 and 2.59)
					Reduction >4 pts SELENA-SLEDA	169 (58%)	290	132 (46%)	287		OR=1.71 (95%CI; 1.21 and 2.41)
					Patients with severe flare	40 (14%)	290	66 (23%)	287		OR=0.57 (95%CI; 0.39 and 0.85)
					Serious adverse events	41 (14%)	290	36 (13%)			
2	Furie et al. Arth Rheuma (BLISS-76)	RCT	819 SLE patients	Belimumab 1 mg/kg plus standard care vs.	SRI response rate	106 (39.1%)	271	89 (32.4%)	275		NS

				placebo plus standard care (standard care is long-term steroid based treatment)	Reduction >4 pts SELENA-SLEDA	114 (42.1%)	271	93 (33.8%)	275		p<0.05
					Patients with severe flare	50 (18.5%)	271	73 (26.5%)	275		p<0.05
					Serious adverse events	63 (23.2%)	271	54 (19.6%)	275		NS
				Belimumab 10 mg/kg plus standard care vs. placebo plus standard care (standard care is long-term steroid based treatment)	SRI response rate	105 (38.5%)	273	89 (32.4%)	275		NS
					Reduction >4 pts SELENA-SLEDA	113 (41.4%)	273	93 (33.8%)	275		NS
					Patients with severe flare	56 (20.5%)	273	73 (26.5%)	275		NS
					Serious adverse events	61 (22.3%)	273	54 (19.6%)	275		NS
3	Wallace et al. Lupus 2013	Pooled analysis of phase 2 and 3 studies	1,458 SLE patients	Belimumab 1 mg/kg plus standard care vs. placebo plus standard care	Serious adverse events	19.5%	673	16.6%	675		NS
				Belimumab 10 mg/kg plus standard care vs. placebo plus standard care	Serious adverse events	18.0%	674	16.6%	675		NS
4	Strand et al. Ann Rheum Dis 2014	Pooled analysis of BLISS-52 and 76	SLE patients from 2 RCTs (865 in BLISS 52 and 819 in BLISS 76)	Belimumab 1 mg/kg plus standard care vs. placebo plus standard care	Mean change from baseline EQ-5D VAS	10.88	SD 0.85	8.99	SD 0.89		NS
				Belimumab 1 mg/kg plus	Mean change from baseline EQ-5D VAS	9.10	SD 0.95	8.99	SD 0.89		NS

				standard care vs. placebo plus standard care							

*group means with standard deviations may be reported if the data are continuous

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		
No available meta-analysis for this drug												

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	Belimumab[1] 120 mg vial for infusion Php 8,500 400 mg vial for infusion Php 28,333	Prednisone[2] 20mg tab (P 5.00)	[1]company submission [2]DPRI
NUMBER OF DOSAGE UNITS PER UNIT COURSE	15 injections in one year	1,825 tablets (5 tabs per day for 365 days)	
TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)	**Php 127,500** (120 mg vial) **Php 424,995** (400 mg vial)	**Php 9,125**	
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 127,500** (120 mg vial) **Php 424,995** (400 mg vial)	**Php 9,125**	
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)			

REVIEWERS' RECOMMMENDATIONS

Literature Search

- We searched PubMed database last February 2015 using the term "belimumab" limited to "randomized controlled trials" OR "meta-analysis" Or "systematic reviews". The yield was 22 articles. We reviewed the 22 articles and considered 10 for full text retrieval and possible inclusion.
- Nine full text articles were available for review. Of the 9, four are included in this review.
  - Strand V(1), Levy RA, Cervera R, Petri MA, Birch H, Freimuth WW, Zhong ZJ, Clarke AE; BLISS-52 and -76 Study Groups. Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibody-positive systemic lupus erythematosus from the randomised controlled BLISS trials. Ann Rheum Dis. 2014 May;73(5):838-44. doi: 10.1136/annrheumdis-2012-202865. Epub 2013 Mar 22.
  - Wallace DJ(1), Navarra S, Petri MA, Gallacher A, Thomas M, Furie R, Levy RA, van Vollenhoven RF, Cooper S, Zhong ZJ, Freimuth W, Cervera R; BLISS-52 and -76, and LBSL02 Study Groups. Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. Lupus. 2013 Feb;22(2):144-54. doi: 10.1177/0961203312469259. Epub 2012 Dec 4.
  - Furie R(1), Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, Sanchez-Guerrero J, Schwarting A, Merrill JT, Chatham WW, Stohl W, Ginzler EM, Hough DR, Zhong ZJ, Freimuth W, van Vollenhoven RF; BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011 Dec;63(12):3918-30. doi: 10.1002/art.30613.
  - Navarra SV(1), Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EK, Thomas M, Kim HY, León MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA; BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Feb 26;377(9767):721-31. doi: 10.1016/S0140-6736(10)61354-2.

Effectiveness/Efficacy

- Two RCTs compared belimumab with standard of care and measured outcomes after 52 weeks and after 76 weeks. Standard care involved steroid based treatment.
- After 52 weeks of treatment, belimumab 1mg/kg had better response rate (OR=1.55 (95% CI;1.10 and 2.19), reduction of severe flares (OR=0.76 (95%CI; 0.52 and 1.09) and disease index (OR=1.51 995%CI; 1.07 and 2.14). Similar significant findings were also seen when belimumab was given at 10 mg/kg.
- However, after 76 weeks of treatment, the effect was only significant for belimumab 1 mg/kg in terms of reduction of severe flares (18.5% vs. 26.5%) and >4 points reduction in disease index (42.1% vs. 33.8%). Belimumab 10 mg/kg did not have any significant difference in all measured outcomes.
- There was also no significant effect on the quality of life.

Safety

- In terms of serious adverse event, the incidence was not significantly different between belimumab and standard care (19.5% vs 16.6% for belimumab 1 mg/kg vs. standard care and 18.0% vs. 16.6% for belimumab 10 mg/kg vs. standard care).

Summary of Review

- Overall, we found favorable effect of belimumab after 52 weeks of treatment, but the benefit is not present after 76 weeks.

Cost Data (Cost-comparison table)

- Belimumab is significantly more expensive than a steroid based or standard treatment (P 127,500 vs. P 9,125).

Overall Recommendation

- In summary we found the effectiveness of belimumab to be short-term and the cost is 12 times higher than steroid-based treatment. Thus, there is not enough evidence and justification to include belimumab in the formulary.

References

1. Osio-Salido E(1), Manapat-Reyes H. Epidemiology of systemic lupus erythematosus in Asia. Lupus. 2010 Oct;19(12):1365-73. doi: 10.1177/0961203310374305.

2. Specchia ML(1), de Waure C(1), Gualano MR(2), Doria A(3), Turchetti G(4), Pippo L(5), Di Nardo F(1), Capizzi S(1), Cadeddu C(1), Kheiraoui F(1), Iaccarino L(3), Pierotti F(4), Palla I(4), Veneziano MA(1), Gliubizzi D(1), Sferrazza A(1),

3. Nicolotti N(1), Porcasi R(5), La Torre G(6), Di Pietro ML(1), Ricciardi W(1). Health technology assessment of belimumab: a new monoclonal antibody for the treatment of systemic lupus erythematosus. Biomed Res Int. 2014;2014:704207. doi: 10.1155/2014/704207. Epub 2014 Aug 17.

4. Borba HH(1), Wiens A, de Souza TT, Correr CJ, Pontarolo R. Efficacy and safety of biologic therapies for systemic lupus erythematosus treatment: systematic review and meta-analysis. BioDrugs. 2014 Apr;28(2):211-28. doi: 10.1007/s40259-013-0074-x.

5. Kandala NB(1), Connock M, Grove A, Sutcliffe P, Mohiuddin S, Hartley L, Court R, Cummins E, Gordon C, Clarke A. Belimumab: a technological advance for systemic lupus erythematosus patients? Report of a systematic review and meta-analysis. BMJ Open. 2013 Jul 19;3(7). pii: e002852. doi: 10.1136/bmjopen-2013-002852. Print 2013.

6. Strand V(1), Levy RA, Cervera R, Petri MA, Birch H, Freimuth WW, Zhong ZJ, Clarke AE; BLISS-52 and -76 Study Groups. Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibody-positive systemic lupus erythematosus from the randomised controlled BLISS trials. Ann Rheum Dis. 2014 May;73(5):838-44. doi: 10.1136/annrheumdis-2012-202865. Epub 2013 Mar 22.

7. Dooley MA(1), Houssiau F, Aranow C, D'Cruz DP, Askanase A, Roth DA, Zhong ZJ, Cooper S, Freimuth WW, Ginzler EM; BLISS-52 and -76 Study Groups. Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. Lupus. 2013 Jan;22(1):63-72. doi: 10.1177/0961203312465781.

8. Wallace DJ(1), Navarra S, Petri MA, Gallacher A, Thomas M, Furie R, Levy RA, van Vollenhoven RF, Cooper S, Zhong ZJ, Freimuth W, Cervera R; BLISS-52 and -76, and LBSL02 Study Groups. Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. Lupus. 2013 Feb;22(2):144-54. doi: 10.1177/0961203312469259. Epub 2012 Dec 4.

9. Manzi S(1), Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, Ginzler EM, D'Cruz DP, Doria A, Cooper S, Zhong ZJ, Hough D, Freimuth W, Petri MA; BLISS-52 and BLISS-76 Study Groups. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012 Nov;71(11):1833-8. doi: 10.1136/annrheumdis-2011-200831. Epub 2012 May 1.

10. Furie R(1), Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, Sanchez-Guerrero J, Schwarting A, Merrill JT, Chatham WW, Stohl W, Ginzler EM, Hough DR, Zhong ZJ, Freimuth W, van Vollenhoven RF; BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011 Dec;63(12):3918-30. doi: 10.1002/art.30613.

11. Navarra SV(1), Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EK, Thomas M, Kim HY, León MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA; BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Feb 26;377(9767):721-31. doi: 10.1016/S0140-6736(10)61354-2. Epub 2011 Feb 4.

12. Furie RA(1), Petri MA, Wallace DJ, Ginzler EM, Merrill JT, Stohl W, Chatham WW, Strand V, Weinstein A, Chevrier MR, Zhong ZJ, Freimuth WW. Novel evidence-based systemic lupus erythematosus responder index. Arthritis Rheum. 2009 Sep 15;61(9):1143-51. doi: 10.1002/art.24698.