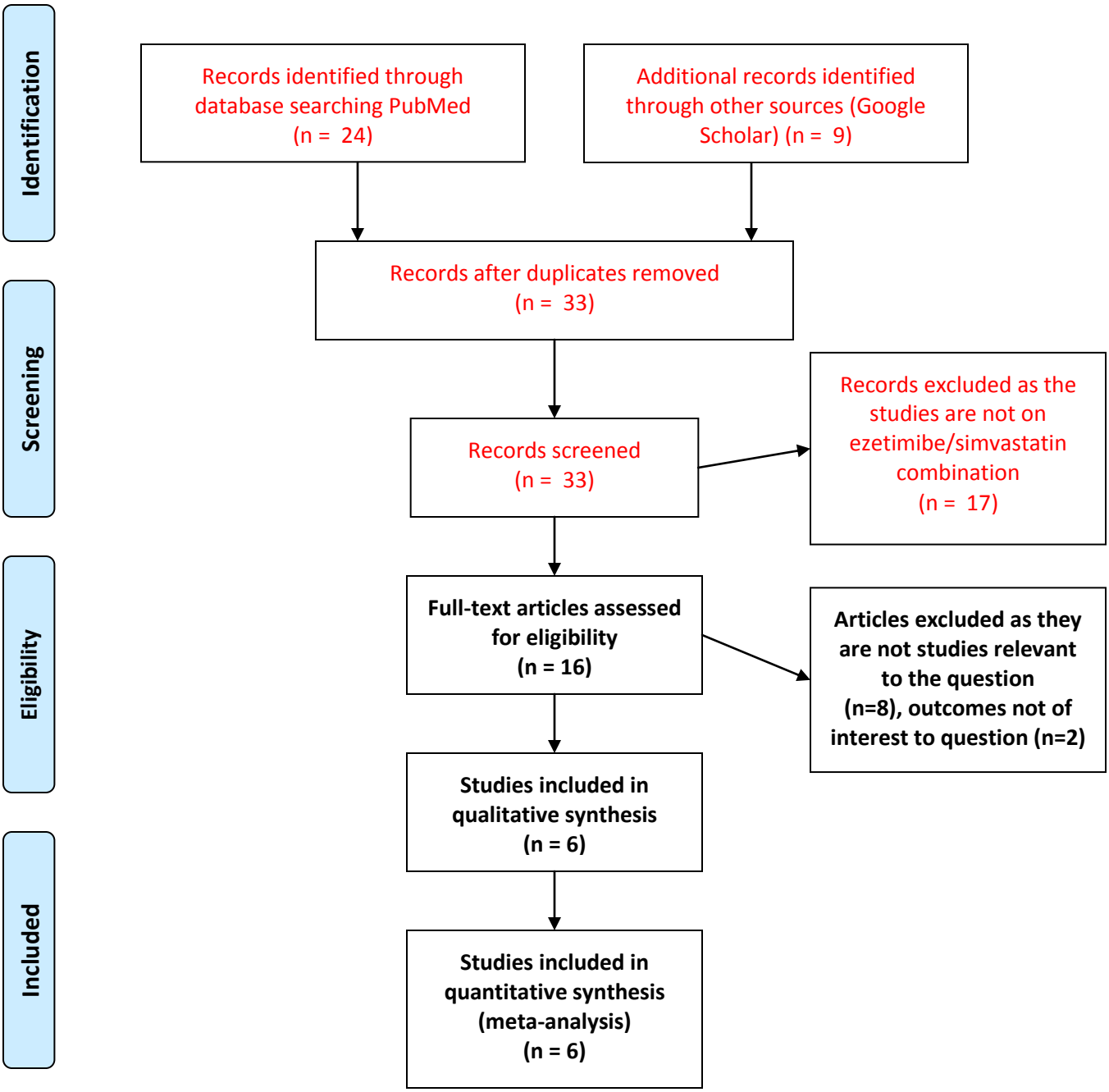
Name of medicine (INN):	**Ezetimibe 10 mg tablet**
Indication:	Primary hypercholesterolemia; homozygous familial hypercholesterolemia ; homozygous sitosterolemia ; co- administration with fenofibrate.
Date of deliberation:	01 July 2015 26 November 2015
Recommendation:	**DISAPPROVAL**
Clinical evidence:	The Council noted in the ERG evaluation that the only available evidence on the use of ezetimibe is in terms of LDL-C lowering wherein ezetimibe/simvastatin has greater percent decrease from baseline compared with simvastatin alone (52.5% vs. 38.0%). In terms of achieving the target LDL-C <100mg/dl, the combination of ezetimibe/simvastatin has greater effect with 75.3% compared with only 51.9% among patients taking simvastatin. When compared with atorvastatin, the ezetimibe/simvastatin combination was also found to be better in reducing LDL-C (53.4% vs. 45.3%). It was likewise observed that there were no available studies which measured clinical outcomes such as cardiovascular events and most of the studies included analyzed the data across pooled doses. There is one study (Pearson et al.) that presented data for subgroup of doses, which showed the following results: - Change in LDL-C, ezetimib/simvastatin (10/40) decreased by 53.3% and for simvastatin (80) the decrease was 46.6%. - Achieving LDL-C <100mg/dl and CRP <1mg/dl, ezetimib/simvastatin (10/40) was 36.1% and for simvastatin (80) was 21.5%. These comparisons however were not subjected to statistical testing. As for the safety of the drug, it was reported that the incidence of rhabdomyolysis was lower in the ezetimibe/simvastatin combination compared to statin alone (0.09% vs. 0.20%). This result, however, was not statistically significant. The same is true for Musculoskeletal and connective tissue adverse event, wherein there was also no significant

	difference between ezetimibe/statin combination and simvastatin (16.4% vs. 15.4%). Overall, the adverse event was similar between the combination and high dose statin (60% vs. 60%). *(See Attachment for the full ERG evaluation)*
Cost data:	Based on the cost data submitted by the proponent, there is a high price disparity between ezetimibe and simvastatin (Php 35.78 for ezetimibe versus Php 1.50/ Php 1.80/ Php 5.80 for simvastatin 10/20/40 mg). The very high cost of the drug combination was also pointed out with a total direct cost per month of about Php 1,118.40 to Php 1,247.40 compared to the cost of simvastatin which would only amount to Php 90 to Php 348 monthly. *(See Attachment).*
Remarks:	The ERG evaluated the documents submitted by the proponent to support their appeal and it was noted that ezetimibe/simvastatin is more effective (but only blood cholesterol levels) and equally safe (musculoskeletal-related clinical outcomes) than a comparable or high dose simvastatin. There is also a recently published randomized controlled trial that showed small reduction in mortality when ezetimibe is added to simvastatin. Given these data, the Council took into consideration that clinical outcome is of paramount importance, thus there is insufficient evidence and justification to include ezetimibe/simvastatin fixed dose combination on top of the current statin formulation. Also, since 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 ezetimibe in the PNF.**

PRISMA Table

PubMed search strategy was search of "ezetimibe" limited to "meta-analysis" last December 2014. The yield was 24 artcles. Additional records were reviewed from the search conducted by PNF Secretariat.



1. Among patients with dyslipidemia of whatever cause (Primary Hypercholesterolemia, Homozygous Familial Hypercholesterolemia) how effective is Ezetimibe 10 mg tablet in combination with any statin (simvastatin, atorvastatin) compared to a higher dose of the same statin for; a) Lowering LDL (mean difference), b) Achievement of LDL targets (less than 100 mg/dL) and c) Relative risk of MACE (major adverse coronary events) or all cardiovascular events including stroke

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Ezetimibe/simvastatin No. of events *	Ezetimibe/simvastatin Total # of patients	Simvastatin No. of events *	Simvastatin Total # of patients		
	Feldman et al. Clin Ther 2006	Systematic review	Post-hoc analysis of 3 RCTs (3,083 patients, 20-87 y/o with elevated lipid profile)	Ezetimibe/simvastatin vs. simvastatin (both interventions pooled across doses)	% reduction from baseline (LDL-C)	53%	1,236	38%	1,234	High	P<0.01
					% reduction from baseline (non-HDL-C)	48%		35%			
					% reduction from baseline (apo B)	42%		30%			
					% reduction from baseline (trigycerides)	26%		19%			
	Pearson et al. Am J Cardiol 2007	Pooled analysis of 3 RCT	3 RCTs (2,541 patients with elevated lipid profile)	Ezetimibe/simvastatin (10/40) vs. simvastatin (80)	% reduction from baseline (LDL-C)	55.3%		46.4%		High	Figure 1 (comparisons not subjected to statistical testing)
					% reduction from baseline CRP	35.0%		18.4%			Figure 3
					Achievement <100mg/dl LDL-C and <1mg/dl CRP	36.1%		21.5%			Table 3
				Ezetimibe/simvastatin (10/40) vs. simvastatin	% reduction from baseline (LDL-C)	57.4%		52.9%			Figure 2

				(80)	% reduction from baseline CRP Achievement <100mg/dl LDL-C and <1mg/dl CRP	29.7% 25.5%		30.9% 25.6%			Figure 6 Table 4
	Guyton et al. Diab Vasc Dis Res 2011	Meta-analysis	27 RCTs (21,794 patients with elevated LDL-C)	Ezetimie/simvastatin vs. statin (both interventions pooled across doses)	% reduction from baseline (LDL-C) with DM % reduction from baseline (LDL-C) with non-DM	-51.6% -47.7%	1,543 4,534	-38.0% -36.6%	1,736 4,344	High	SMD = -13.7 (95%CI; -14.6 and -12.7) SMD = -11.1% (95%CI; -11.7 and -10.5)
	Morrone et al. Atherosclero 2012	Meta-analysis	27 RCTs (11,714 in ezetimib/simvastatin and 10,517 in simvastatin with elevated lipid profile)	Ezetimie/simvastatin vs. statin (both interventions pooled across doses)	Attainment of target LDL-C <100mg/dl	75.3%	11,423	51.9%	10,247	High	OR = 4.22 (95%CI; 3.94 and 4.52)

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

2. Among patients with dyslipidemia of whatever cause (Primary Hypercholesterolemia, Homozygous Familial Hypercholesterolemia) how safe is Ezetimibe 10 mg tablet in combination with any statin (simvastatin, atorvastatin) compared to a higher dose of the same statin for; a) All adverse events, b) Rhabdomyolysis and c) Development of Diabetes mellitus

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Ezetimibe/simvastatin		Simvastatin			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
	Davidson et al. Am J Cardiol 2006	Systematic review	17 controlled studies	Ezetimibe/simvastatin vs. simvastatin (both interventions pooled across doses)	Any musculoskeletal and connective tissue adverse event (core factorial pool)	203 (16.4%)	1,236	190 (15.4%)	1,234	Moderate	Manufacturer sponsored review of manufacturer sponsored studies. Core factorial pool included robust RCTs, overall pool included all RCTs on ezetimibe/simvastatin vs all other statins and the long term pool are RCTs with extended treatment.
					Any musculoskeletal and connective tissue adverse event (overall pool)	585 (12.8%)	4,558	325 (12.7%)	2,563		
					Any musculoskeletal and connective tissue adverse event (Long-term pool)	299 (19.6%)	1,525	143 (16.1%)	889		
	Feldman et al. Clin Ther2006	Systematic review	Post-hoc analysis of 3 RCTs (3,083 patients, 20-87 y/o with elevated lipid profile)	Ezetimibe/simvastatin vs. simvastatin (both interventions pooled across doses)	All clinical adverse event	142 (60%)	1,236	739 (60%)	1,234	High	P<0.01

	Kashani et al. Am J Cardiol	Meta-analysis	18 RCTs (14,471 patients)	Ezetimie/simvastatin vs. statin (both interventions pooled across doses)	Rhabdomyolysis	7 (0.09%)	7,921	10 (0.20%)	6,057	High	NS
				Ezetimibe/simvastatin vs. simvastatin (both interventions pooled across doses)	Rhabdomyolysis	6 (0.1%)	4,145	7 (0.2%)	3,393		NS
				Ezetimibe/simvastatin vs. atorvastatin (both interventions pooled across doses)	Rhabdomyolysis	1 (0.1%)	981	1 (0.1%)	831		NS

*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		
Outcome: Attainment of target LDL-C												
1	Meta-analysis of 27 RCTs	None	None	None	None		Ezetimibe/ simvastatin (pooled dose)	Statin (pooled dose)	OR = 4.22 (95%CI; 3.94 and 4.52)		High	Critical
Outcome: Percent reduction in LDL-C (DM patients)												
1	Meta-analysis of 27 RCTs	None	None	None	None		Ezetimibe/ simvastatin (pooled dose)	Statin (pooled dose)		SMD = -13.7 (95%CI; -14.6 and -12.7)	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	Ezetimibe[1] Php 35.78 per 10 mg tablet	Simvastatin[2] 10 mg tab- Php 1.50 20 mg tab- Php 1.80 40 mg tab- Php 5.80	[1]company submission [2]DPRI
NUMBER OF DOSAGE UNITS PER UNIT COURSE	30 tabs for monthly treatment	60 tabs for monthly treatment	
TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)	10 mg tab= Php 1,073.40 10 mg Ezetimibe/10 mg Simvastatin= Php 1,118.40 10 mg Ezetimibe/20 mg Simvastatin= Php 1,127.40 10 mg Ezetimibe/40 mg Simvastatin= Php 1,247.40	10 mg tab- Php 90 20 mg tab- Php 108 40 mg tab- Php 348	
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	10 mg tab= Php 1,073.40 *as add-on to simvastatin: 10/10= Php 1,118.40 10/20= Php 1,127.40 10/40= Php 1,247.40	10 mg tab- Php 90 20 mg tab- Php 108 40 mg tab- Php 348	
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, December 19, 2014 using the term "ezetimibe" and yiileded 1,987 articles. We limit the search to "meta-analysis" and yielded 24 articles. We reviewed the abstracts of the articles and considered 16 for full text retrieval.
- We reviewed the 16 full text articles and included 6 in this quantitative review. We also reviewed 9 articles retrieved via Google Scholar. The summary of the search is shown in the PRISMA table.
- The studies included in the quantitative analysis are:
  - Morrone D(1), Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, Shah AK, Tershakovec AM. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis. 2012 Aug;223(2):251-61. doi: 10.1016/j.atherosclerosis.2012.02.016. Epub 2012 Feb 16.
  - Guyton JR(1), Betteridge DJ, Farnier M, Leiter LA, Lin J, Shah A, Johnson-Levonas AO, Brudi P. Achievement of recommended lipid and lipoprotein levels with combined ezetimibe/statin therapy versus statin alone in patients with and without diabetes. Diab Vasc Dis Res. 2011 Apr;8(2):160-72. doi: 10.1177/1479164111406457.
  - Kashani A(1), Sallam T, Bheemreddy S, Mann DL, Wang Y, Foody JM. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. Am J Cardiol. 2008 Jun 1;101(11):1606-13. doi: 10.1016/j.amjcard.2008.01.041. Epub 2008 Apr 9.
  - Pearson T(1), Ballantyne C, Sisk C, Shah A, Veltri E, Maccubbin D. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol. 2007 Jun 15;99(12):1706-1713. Epub 2007 May 2.
  - Feldman T(1), Davidson M, Shah A, Maccubbin D, Meehan A, Zakson M, Tribble D, Veltri E, Mitchel Y. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe coadministered with simvastatin in older versus younger patients with primary hypercholesterolemia: a post Hoc analysis of subpopulations from three pooled clinical trials. Clin Ther. 2006 Jun;28(6):849-59.
  - Davidson MH(1), Maccubbin D, Stepanavage M, Strony J, Musliner T. Striated muscle safety of ezetimibe/simvastatin (Vytorin). Am J Cardiol. 2006 Jan 15;97(2):223-8. Epub 2005 Nov 21.

Effectiveness/Efficacy

- There were no studies that measured cardiovascular events or mortality in the reviewed articles. We considered change in lipid profile, primarily LDL cholesterol. We also considered musculoskeletal and rhabdomyolysis as safety parameters.
- Most of the studies included analyzed the data across pooled doses. In terms of the drug's effect on LDL-C, the ezetimibe/simvastatin had greater percent decrease from baseline compared with simvastatin alone (52.5% vs. 38.0%). The percent decrease is even greater among patients with DM. In terms of achievement of target LDL-C, the combination ezetimibe/simvastatin also has greater effect with 75.3% compared to only 51.9% among patients taking simvastatin. When compared to atorvastatin, the eztimibe/simvastatin combination was also found to be better in reducing LDL-C (53.4% vs. 45.3%).
- There is one study (Pearson et al.) that presented data for subgroup of doses. In terms of change in LDL-C, ezetimib/simvastatin (10/40) decreased by 53.3% and for simvastatin (80) the decrease was 46.6%. In terms of achieving LDL-C <100mg/dl and CRP <1mg/dl,

ezetimib/simvastatin (10/40) was 36.1% and for simvastatin (80) was 21.5%. These comparisons however were not subjected to statistical testing. But overall, eztimib/simvastatin is better than double dose simvastatin.

- Reduction in other lipid profile was also greater in ezetimibe/simvastatin combination vs. simvastatin alone (42% vs. 30% for Apo B; 26% vs. 19% for triglycerides)

Safety

- In terms of safety, the incidence of rhabdomyolysis was also lower in the ezetimibe/simvastatin combination compared to statin alone (0.09% vs. 0.20%). However this was not statistically significant. The incidence of rhabdomyolysis was also similar when the comparator was atorvastatin.
- In terms of musculoskeletal and connective tissue adverse event there was also no significant difference between ezetimibe/statin combination and simvastatin (16.4% vs. 15.4%)
- Overall adverse event was also similar between the combination and high dose statin (60% vs. 60%)

Summary of Review

- In summary, we found the combination of ezetimibe/simvastatin to be more efficacious than simvastatin or atorvastatin alone and with equal safety profile. Efficacy is based only on surrogate outcomes like blood cholesterol levels.

Cost Data (Cost-comparison table)

- In terms of cost, ezetimibe/simvastatin is a lot more expensive than high dose simvastatin (P 2,744 vs 348 for monthly treatment)

Overall Recommendation

- Overall, we found ezetimibe/simvastatin to be more effective (but only blood cholesterol levels) and equally safe (musculoskeletal-related clinical outcomes) than a comparable or high dose simvastatin. We found no available evidence for clinical outcomes like mortality or myocardial infarction.
- If clinical outcome is of paramount importance, there is not enough evidence and justification to include ezetimibe/simvastatin fixed dose combination on top of the current statin formulation in the formulary.
    - However, if surrogate outcomes like cholesterol lowering is acceptable, then ezetimib/simvastatin may be included but with conformance to DPRI.

References

1. WHO. Global cardiovascular infobase: WHO collaborating center on surveillance of cardiovascular diseases. Geneva: World Health Organization; 2002.

2. Dans A, Morales D, Velandria F, Abola T, Roxas Jr. A, Punalan F, Sy R, Paz Pacheco E. National Nutrition and Health Survey (NNHes): Atherosclerosis-related diseases and reisk factors. Phil J Int Med. 2005;43:103-15.

3. Morrone D(1), Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, Shah AK, Tershakovec AM. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis. 2012 Aug;223(2):251-61. doi: 10.1016/j.atherosclerosis.2012.02.016. Epub 2012 Feb 16.

4. Guyton JR(1), Betteridge DJ, Farnier M, Leiter LA, Lin J, Shah A, Johnson-Levonas AO, Brudi P. Achievement of recommended lipid and lipoprotein levels with combined ezetimibe/statin therapy versus statin alone in patients with and without diabetes. Diab Vasc Dis Res. 2011 Apr;8(2):160-72. doi: 10.1177/1479164111406457.

5. Kashani A(1), Sallam T, Bheemreddy S, Mann DL, Wang Y, Foody JM. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. Am J Cardiol. 2008 Jun 1;101(11):1606-13. doi: 10.1016/j.amjcard.2008.01.041. Epub 2008 Apr 9.

6. Pearson T(1), Ballantyne C, Sisk C, Shah A, Veltri E, Maccubbin D. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol. 2007 Jun 15;99(12):1706-1713. Epub 2007 May 2.

7. Feldman T(1), Davidson M, Shah A, Maccubbin D, Meehan A, Zakson M, Tribble D, Veltri E, Mitchel Y. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe coadministered with simvastatin in older versus younger patients with primary hypercholesterolemia: a post Hoc analysis of subpopulations from three pooled clinical trials. Clin Ther. 2006 Jun;28(6):849-59.

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Response to appeal on the reviewers' recommendation on Ezetimibe

We reviewed the recently published article submitted to support the appeal (Cannon et al, 2015). We included this evidence in the evidence table. We are revising our recommendation to:
"Overall, we found ezetimib/simvastatin to be more effective (but only blood cholesterol levels) and equally safe (musculoskeletal-related clinical outcomes) than a comparable or high dose simvastatin. There is also a recently published randomized controlled trial that showed small reduction in mortality when ezetimibe is added to simvastatin. Ezetimib/simvastatin may be included in the PNF but with conformance to DPRI or reasonable pricing."

Because cost is significant issue for PNDF, it is recommended that the manufacturer decrease the cost of ezetimibe comparable to the comparator drugs for it to be reconsidered for inclusion in the PNF.

1. Among patients with dyslipidemia of whatever cause (Primary Hypercholesterolemia, Homozygous Familial Hypercholesterolemia) how effective is Ezetimibe 10 mg tablet in combination with any statin (simvastatin, atorvastatin) compared to a higher dose of the same statin for; a) Lowering LDL (mean difference), b) Achievement of LDL targets (less than 100 mg/dL) and c) Relative risk of MACE (major adverse coronary events) or all cardiovascular events including stroke

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Ezetimibe/simvastatin No. of events *	Ezetimibe/simvastatin Total # of patients	Simvastatin No. of events *	Simvastatin Total # of patients		
	Cannon et al, 2015	RCT	18,144 patients with coronary syndrome	Ezetimib/simvastatin vs. simvastatin	Death from cardiovascular causes or stroke (primary endpoint)	32.7%	2,572	34.7%	2,742	High	RR=0.94; 95%CI; 0.89 and 0.99 (small reduction)
	Feldman et al. Clin Ther 2006	Systematic review	Post-hoc analysis of 3 RCTs (3,083 patients, 20-87 y/o with elevated lipid profile)	Ezetimibe/simvastatin vs. simvastatin (both interventions pooled across doses)	% reduction from baseline (LDL-C) % reduction from baseline (non-HDL-C) % reduction from baseline (apo B) % reduction from baseline (trigycerides)	53% 48% 42% 26%	1,236	38% 35% 30% 19%	1,234	High	P<0.01
	Pearson et al. Am J Cardiol 2007	Pooled analysis of 3 RCT	3 RCTs (2,541 patients with elevated lipid profile)	Ezetimibe/simvastatin (10/40) vs. simvastatin (80) Ezetimibe/simv	% reduction from baseline (LDL-C) % reduction from baseline CRP Achievement <100mg/dl LDL-C and <1mg/dl CRP % reduction from	55.3% 35.0% 36.1% 57.4%		46.4% 18.4% 21.5% 52.9%		High	Figure 1 (comparisons not subjected to statistical testing) Figure 3 Table 3 Figure 2

				astatin (10/40) vs. simvastatin (80)	baseline (LDL-C) % reduction from baseline CRP Achievement <100mg/dl LDL-C and <1mg/dl CRP	 29.7% 25.5%		 30.9% 25.6%			 Figure 6 Table 4
	Guyton et al. Diab Vasc Dis Res 2011	Meta-analysis	27 RCTs (21,794 patients with elevated LDL-C)	Ezetimie/simvastatin vs. statin (both interventions pooled across doses)	% reduction from baseline (LDL-C) with DM % reduction from baseline (LDL-C) with non-DM	-51.6% -47.7%	1,543 4,534	-38.0% -36.6%	1,736 4,344	High	SMD = -13.7 (95%CI; -14.6 and -12.7) SMD = -11.1% (95%CI; -11.7 and -10.5)
	Morrone et al. Atherosclero 2012	Meta-analysis	27 RCTs (11,714 in ezetimib/simvastatin and 10,517 in simvastatin with elevated lipid profile)	Ezetimie/simvastatin vs. statin (both interventions pooled across doses)	Attainment of target LDL-C <100mg/dl	75.3%	11,423	51.9%	10,247	High	OR = 4.22 (95%CI; 3.94 and 4.52)

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

2. Among patients with dyslipidemia of whatever cause (Primary Hypercholesterolemia, Homozygous Familial Hypercholesterolemia) how safe is Ezetimibe 10 mg tablet in combination with any statin (simvastatin, atorvastatin) compared to a higher dose of the same statin for; a) All adverse events, b) Rhabdomyolysis and c) Development of Diabetes mellitus

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				Ezetimibe/simvastatin vs. simvastatin (both interventions pooled across doses)	Rhabdomyolysis	6 (0.1%)	4,145	7 (0.2%)	3,393		NS
				Ezetimibe/simvastatin vs. atorvastatin (both interventions pooled across doses)	Rhabdomyolysis	1 (0.1%)	981	1 (0.1%)	831		NS

*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		
Outcome: Attainment of target LDL-C												
1	Meta-analysis of 27 RCTs	None	None	None	None		Ezetimibe/ simvastatin (pooled dose)	Statin (pooled dose)	OR = 4.22 (95%CI; 3.94 and 4.52)		High	Critical
Outcome: Percent reduction in LDL-C (DM patients)												
1	Meta-analysis of 27 RCTs	None	None	None	None		Ezetimibe/ simvastatin (pooled dose)	Statin (pooled dose)		SMD = -13.7 (95%CI; -14.6 and -12.7)	High	Critical