



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN):	Vildagliptin 50mg tablet
Indication:	Used for the treatment of type 2 diabetes mellitus (T2DM) as monotherapy ; in dual combination with metformin, sulfonylurea, or thiazolidinedione (TDZ) when diet exercise, and a single anti-diabetic agent do not result in adequate glycemic control.
Date/s of deliberation:	14 January 2015 04 March 2015 05 June 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>It was noted that vildagliptin is less effective compared to other hypoglycemic agents in lowering glycated hemoglobin (HbA1c), fasting blood sugar (FBS) and achievement of HbA1c less than 7%. Likewise, in terms of efficacy, it was found that the drug is as good as metformin.</p> <p>In terms of safety, it was discussed that the evaluation showed significantly lower incidence of any adverse events (headache, diarrhea and constipation), weight gain, hypoglycemia and severe adverse event vildagliptin. The Council also evaluated the safety data submitted by the company to determine if the proposed drug has significant advantage over metformin and it was seen that vildagliptin was at least as safe as or non-inferior to the comparator in terms of long-term safety.</p>
Cost data:	It was noted that vildagliptin is more expensive with an average monthly treatment cost of P 1,351 compared to Php 650 for metformin.
Review of appeal:	The Council recognized the revised evidence tables and cost-comparison tables submitted in the appeal for reconsideration. With regard to the evidence table, the overall results confirmed the previous findings of the ERG that Vildagliptin has minimal efficacy advantage in terms of HbA1C and other glucose control parameters but safer in terms of hypoglycemia

over other oral hypoglycemic drugs.

It was noted that the estimates in the cost comparison tables were different from the evaluation of the ERG because of the following:

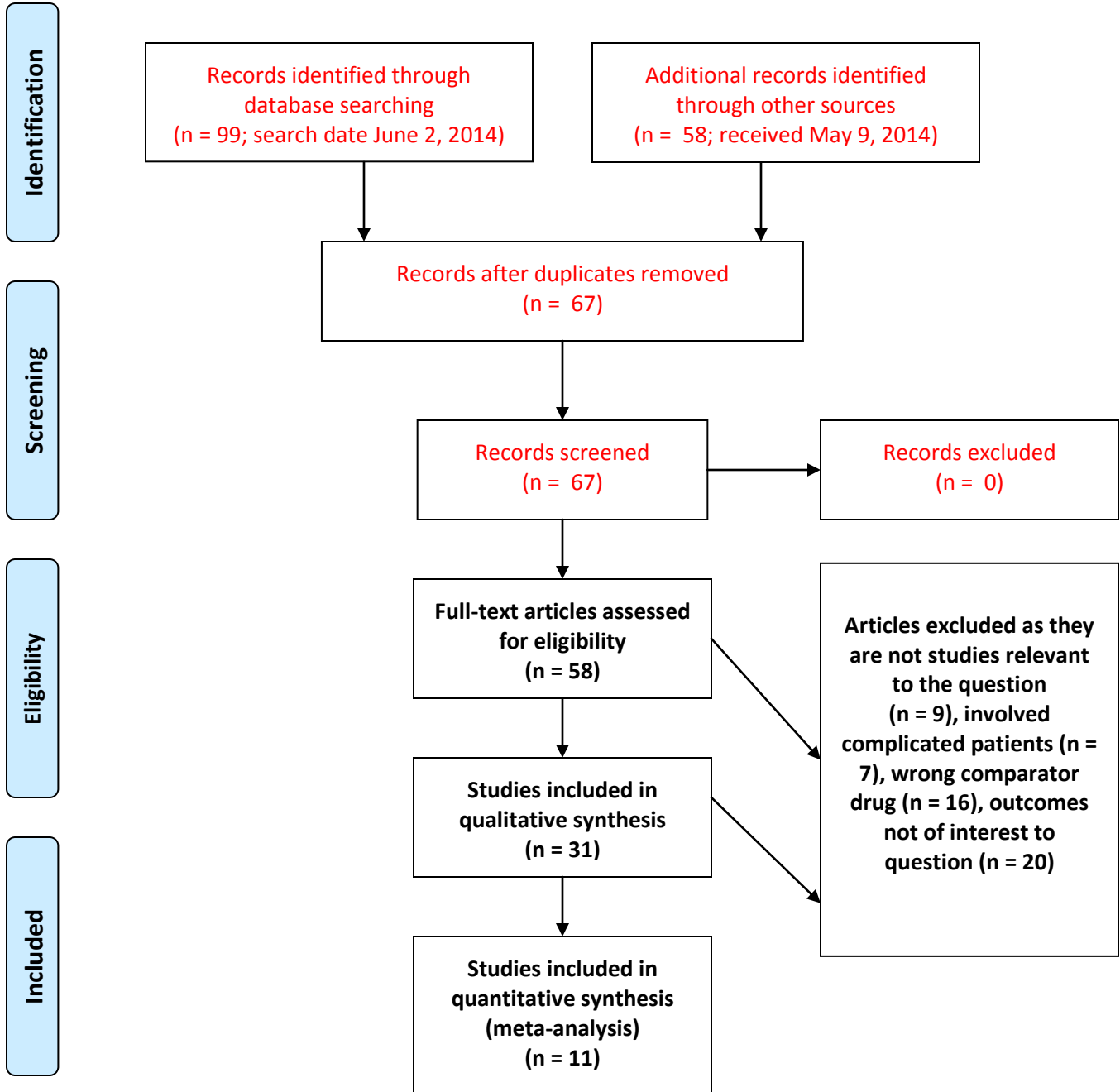
- The cost-effectiveness table from the manufacturer used MIMS price for both drugs. The ERG used the Drug Price Reference Index for the control drug (metformin) and the submitted price offer for the new drug being evaluated.
- The manufacturer also assumed that the treatment of hypoglycemia/other side effect is P 300 per episode, while the ERG did not factor this cost as the intervention may just be a simple glass of juice or lifestyle modification. The incidence of severe hypoglycemia/other side effect is not significantly different from other oral hypoglycemic.

Remarks:

After considering the documents submitted for reconsideration, the Secretary of Health, upon the recommendation of the Formulary Executive Council (FEC), has officially disapproved the said request.

PRISMA Table

PubMed search strategy was MESH search of vildagliptin limited to randomized controlled trials and studies on human subjects. The yield was 99 articles. Additional records were reviewed from the search conducted by PNDF Secretariat.



Among patients with Type 2 diabetes mellitus how effective is vildagliptin as monotherapy or as add on to monotherapy of metformin compared to other anti-diabetic agents (sulfonylureas, pioglitazone) for

- lowering blood sugar (mean difference of FBS, HbA_{1c}) [mean difference]
- achievement of target glycosylated hemoglobin(HbA_{1c}) level of $\leq 7\%$

EVIDENCE TABLE 1 (EFFECTIVENESS MEASURES)

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Vidagliptin with or without Metformin		Other Oral Hypoglycemics			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
1	Schweizer et al, Diabet Med, 2007	RCT	DM Type 2	Vildagliptin vs Metformin	Reduction in HbA _{1c}	1.0%	SD 0.1	1.4%	SD 0.1	High	
					Reduction in FBS	0.9 mmol/L	SD 0.1	1.9 mmol/L	SD 0.2		
					HbA _{1c} <7%	179	511	112	249		
2	Filozof and Gautier, Diabet Med, 2010	RCT	DM Type 2	Vildagliptin/metformin vs gliclazide/metformin	Reduction in HbA _{1c}	0.81%	SD 0.06	0.85%	SD 0.06	High	
					HbA _{1c} <7%	176	513	158	494		
3	Hyun and Tae, Diabetes Metab, 2011	RCT	DM Type 2	Vildagliptin/metformin vs glimepiride/metformin	Reduction in HbA _{1c}	0.94%	SD 1.15	1.0%	SD 1.32	High	
					HbA _{1c} <7%	25	51	28	51		
					Reduction in FBS	1.54 mmol/L	SD 2.41	2.16 mmol/L	SD 2.51		
4	Rosenstock et al, Diab Obes Metab, 2007	RCT	DM Type 2	Vildagliptin vs Pioglitazone (2 arms of 4 arm	Reduction in HbA _{1c}	1.1%	SD 0.1	1.4%	SD 0.1	High	

				RCT)	HbA _{1c} <7%	58	136	57	133		
					Reduction in FBS	1.9 mmol/L	SD 0.2	1.3 mmol/L	SD 0.2		
5	Bolli et al, Diab Obes Metab, 2008	RCT	DM Type 2	Vildagliptin vs Pioglitazone	Reduction in HbA _{1c}	0.9%	SD 0.1	1.0%	SD 0.1	High	
					HbA _{1c} <7%	71	262	88	244		
					Reduction in FBS	2.1 mmol/L	SD 0.1	1.4%	SD 0.1		
6	Ferrannini et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin/metformin vs glimepiride/metformin	Reduction in HbA _{1c}	0.44%	SD 0.02	0.53%	SD 0.02	High	
					HbA _{1c} <7%	756	1,389	768	1,383		
					Reduction in FBS	1.01 mmol/L	SD 0.06	1.14 mmol/L	SD 0.06		
7	Bosi et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin vs Metformin (2 arms of 4 arm RCT)	Reduction in HbA _{1c}	1.1%	SD 0.06	1.4%	SD 0.06	High	
					HbA _{1c} <7%	114	285	123	283		
					Reduction in FBS	1.26 mmol/L	SD 0.13	1.92 mmol/L	SD 0.13		
8	Bolli et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin/metformin vs Pioglitazone/metformin	Reduction in HbA _{1c}	0.6%	CI 0.7 and 0.4	0.6%	CI 0.7 and 0.5	High	
					Reduction in FBS	1.0 mmol/L	CI 1.3 and 0.6	1.6 mmol/L	CI 1.9 and 1.3		
9	Schweizer et al, Diab Obes Metab, 2009	RCT	Elderly DM Type 2	Vildagliptin vs Metformin	Reduction in HbA _{1c}	0.64%	SD 0.07	0.75%	SD 0.07	High	
10	Blonde et al, Diab Obes	RCT	DM Type 2	Vildagliptin/metformin vs	Reduction in HbA _{1c}	0.68%	SD 0.02	0.57%	SD 0.03	High	

	Metab, 2009			Thiazolidinedione/metformin							
11	Matthews et al, Diab Obes Metab, 2010	RCT	DM Type 2	Vildagliptin/metformin vs glimepiride/metformin	Reduction in HbA _{1c}	0.3%	SD 0.0%	0.3%	SD 0.0%	High	
					HbA _{1c} <7%	576	1,562	596	1,556		
					Reduction in FBS	0.5 mmol/L	SD 0.1	0.7 mmol/L	SD 0.1		

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

Among patients with Type 2 diabetes mellitus how safe is vildagliptin as monotherapy or as add on to monotherapy of metformin compared to other anti-diabetic agents (sulfonylureas, pioglitazone) for

- all adverse events
- total hypoglycemia
- severe hypoglycemia
- weight gain

EVIDENCE TABLE 1: (ADVERSE EVENTS MEASURES)

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES				GRADE OF EVIDENCE	REMARKS	
					EVENTS (including adverse events)	Vidagliptin with or without Metformin No. of events * Total # of patients	Other Oral Hypoglycemics No. of events * Total # of patients				
1	Schweizer et al, Diabet Med, 2007	RCT	DM Type 2	Vildagliptin vs Metformin	Any adverse event	111	511	109	249	High	
2	Filozof and Gautier, Diabet Med, 2010	RCT	DM Type 2	Vildagliptin/metformin vs gliclazide/metformin	Hypoglycemic Event Any Adverse Event Serious Adverse Events weight gain (kg)	6 317 34 +0.08	513	11 303 43 +1.36	494	High	P-value of <0.001 indicating significant difference, not included in meta-analysis since no SD reported
3	Hyun and Tae, Diabetes Metab, 2011	RCT	DM Type 2	Vildagliptin/metformin vs glimepiride/metformin	Hypoglycemic Event Any Adverse Event	1 5	51 51	10 10	51 51	High	P<0.05 meaning

					weight gain (kg)	+0.23	+/-0.69	+2.53	+/-1.21		significant differenc
4	Rosenstock et al, Diab Obes Metab, 2007	RCT	DM Type 2	Vildagliptin vs Pioglitazone (2 arms of 4 arm RCT)	Any Adverse Event	70	153	83	161	High	
5	Bolli et al, Diab Obes Metab, 2008	RCT	DM Type 2	Vildagliptin vs Pioglitazone	Any Adverse Event	157	262	138	244	High	P value <0.001 means significant difference
				Serious Adverse Event	5		11				
				weight gain (kg)	+0.30	+/-0.20	+1.9	+/-0.20			
6	Ferrannini et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin/metformin vs glimepiride/metformin	Hypoglycemic Events	23	1,389	224	1,383	High	P value <0.001 means significant difference
				Any Adverse Event	1,035		1,121				
				weight gain (kg)	-0.23	+/-0.11	+1.56	+/-0.12			
7	Bosi et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin vs Metformin (2 arms of 4 arm RCT)	Any Adverse Event	147	285	170	283	High	Comparators vildagliptin and metformin monotherapy
				weight gain (kg)	-0.59	+/-0.22	-1.62	+/-0.22			
8	Bolli et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin/metformin vs Pioglitazone/metformin	Any Adverse Event	200	295	192	281	High	P<0.001 which means significant difference
				weight gain (kg)	+0.20	+/-0.20	+2.60	+/-0.30			
9	Schweizer et al,	RCT	Elderly DM	Vildagliptin vs	Any Adverse	75	169	83	166	High	

	Diab Obes Metab, 2009		Type 2	Metformin	Event Hypoglycemia weight gain (kg)	0 -0.45	+/-0.20	2 -1.25	+/-0.19		P-value=0.004 which means significant difference
10	Blonde et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin/metformin vs Thiazolidinedione/metformin	Any Adverse Event weight gain (kg)	653 -0.58	1,653 +/-0.09	299 +0.33	825 +/-0.11	High	P<0.001 which means significant difference
11	Matthews et al, Diab Obes Metab, 2010	RCT	DM Type 2	Vildagliptin/metformin vs glimepiride/metformin	Hypoglycemic Event weight gain (kg)	36 -0.30	1,562 +/-0.10	283 +1.2	1,556 +/-0.10	High	P<0.001 which means significant difference

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

EVIDENCE TABLE 3: 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: Reduction in HbA1c												
11	RCT	No	No	No	No		Vildagliptin	Others		-0.12% (SD 0.02)	High	Critical
Outcome: Reduction in FBS												
8	RCT	No	No	No	No		Vildagliptin	Others		-0.24 (SD 0.02)	High	Critical
Outcome: Proportion of HbA1c <7.0%												
8	RCT	No	No	No	No		Vildagliptin	Others	0.94 (95% CI 0.91 and 0.99)		High	Critical
Outcome: Any adverse event												
10	RCT	No	No	No	No		Vildagliptin	Others	0.86 (95% CI 0.84 and 0.90)		High	Critical
Outcome: Hypoglycemic event												
5	RCT	No	No	No	No		Vildagliptin	Others	0.12 (95% CI 0.10 and 0.16)		High	Critical
Outcome: Serious adverse event												
2	RCT	No	No	No	No		Vildagliptin	Others	0.69 (95% CI 0.46 and 1.02)		High	Critical
Outcome: weight gain												
8	RCT	no	no	no	no		Vildagliptin	Others		-1.37 (95% CI -1.37,-1.36)	High	Critical

Summary of Recommendation

We have reviewed 99 abstract we search from Medline and 58 articles provided by the PNDF secretariat. We selected 11 articles that are randomized controlled trials and met the criteria using the Grade Profiler.

Overall, vildagliptin compared with other hypoglycemic is less effective in lowering HbA1c, FBS and achievement of NbA1c less than 7%. However the difference is small and may not be clinically significant. In terms of safety, vildagliptin showed lesser incidence of any adverse events, weight gain, hypoglycemia and severe adverse event.

The fewer side effects in vildagliptin is moderate and may be clinically significant.

The average monthly cost of treatment is P 1,227 for vildagliptin compared to P 650 for metformin.

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS (Attach Evidence Tables)

<p>PARAMETER (Indicate information for intended recipient) * <u>INTENDED RECIPIENT:</u></p>	<p>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</p>	<p>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</p>	<p>REFERENCES</p>
<p>COST PER DOSAGE UNIT (in PhP) a. Proposed list price to the government b. Current prevailing market price</p>	<p>Php 24.23 per 50 mg tablet</p>	<p>Metformin P 5 per 850 mg tablet</p>	<p>Company submission and DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>30</p>	<p>30</p>	<p>Lowest maintenance</p>
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>Php 726.90 per month</p>	<p>Php 150 per month</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP) a. Intervention costs: (management of adverse drug reactions)</p>	<p>500</p>	<p>500</p>	<p>Laboratory</p>
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p>Php 1,226.90</p>	<p>Php 650</p>	
<p>ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE</p>	<p>7.1% of total population</p>	<p>7.1% of total population</p>	<p>NNHeS 2008 of FNRI</p>
<p>QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			
<p>DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			

Response to appeal on the reviewers' decision on vildagliptin

The Evidence Review Group's (ERG) recommendation was based on the clinical question by the FEC which was "Among patients with Type 2 diabetes mellitus how effective is vildagliptin as monotherapy or as add on to monotherapy of metformin compared to other anti-diabetic agents and how safe is vildagliptin as monotherapy or as add on to monotherapy of metformin compared to other anti-diabetic agents and lastly how cost-effective is vildagliptin as monotherapy or as add on to monotherapy of metformin compared to other anti-diabetic agents?" The ERG findings showed vildagliptin to have very minimal efficacy advantage but safer than other oral hypoglycemic drugs. However, the cost-effectiveness table developed by the ERG showed that vildagliptin will cost twice than metformin (the reference oral hypoglycemic drug). In a CEA decision plane, the vildagliptin is safer by approximately 15% but more expensive by 100% (vildagliptin is not a dominant choice; is the 15% reduction in overall adverse event worth the 100% increase in cost). We referred the decision to FEC about inclusion or non-inclusion to PNF. The FEC apparently decided for non-inclusion probably because of the cost implication. The ERG is inclined to agree with this decision.

The appeal included additional article which compared vildagliptin with placebo among patients with diabetes and renal impairment. Placebo comparison is not the objective of the clinical question. The other documents were guidelines, product registration documents and manufacturing certificates that again are not relevant to the clinical question.

The appeal however included revised evidence tables and cost-effectiveness tables that merit examination. With regards to the evidence table, the overall results confirmed the findings of the ERG that Vildagliptin has minimal efficacy advantage in terms of HbA1C and other glucose control parameters but safer in terms of hypoglycemia over other oral hypoglycemic drugs.

The appeal also included a new cost-effectiveness table with estimates that differed from the ERG table. The reasons for the difference are the following:

- The cost-effectiveness table from the manufacturer used MIMS price for both drugs. The ERG as directed used the DPRI price for the control drug (metformin) and the MIMS price for the new drug being evaluated.
- The manufacturer also assumed that the treatment of hypoglycemia/other side effect is P 300 per episode, while the ERG did not factor this cost as the intervention may just be a simple glass of juice or lifestyle modification. The incidence of severe hypoglycemia/other side effect is not significantly different from other oral hypoglycemic.

After reviewing the appeal documents, the ERG still agree with FEC decision of non-inclusion to the PNF.