



Republic of the Philippines  
Department of Health  
**OFFICE OF THE SECRETARY**

<b>Name of medicine (INN):</b>	Vildagliptin + Metformin hydrochloride 50 mg/ 500 mg, 50mg/850mg, 50mg/1000mg film coated tablet
<b>Indication:</b>	Indicated as initial therapy in patients with type 2 diabetes mellitus whose diabetes is not adequately controlled by diet and exercise alone; as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus whose diabetes is not adequately controlled on Metformin hydrochloride or Vildagliptin alone or who are already treated with the combination of Vildagliptin and Metformin, as separate tablets; in combination with a Sulphonylurea (SU) (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and sulphonylurea ; as add-on to insulin as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control.
<b>Date/s of deliberation:</b>	05 June 2015 26 November 2015
<b>Recommendation:</b>	<b>DISAPPROVAL</b>
<b>Clinical evidence:</b>	Overall, vildagliptin compared with other hypoglycemic is less effective in lowering HbA1c, FBS and achievement of HbA1c 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.  <i>(See Attachment for the full ERG evaluation)</i>
<b>Cost data:</b>	The average monthly cost of treatment is P 1,293 for vildagliptin + metformin compared to P 527 to Php 652.40 for metformin alone.  <i>(See Attachment for the full ERG evaluation)</i>

**Remarks:**

The ERG evaluated the documents submitted by the proponent to support their appeal and it was noted that the additional article compared vildagliptin with placebo among patients with diabetes and renal impairment, and it was pointed out that placebo comparison is not the objective of the clinical question. The revised evidence tables and cost-effectiveness tables were likewise examined by the ERG. With regards to the evidence table, the overall results confirmed the initial findings 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:

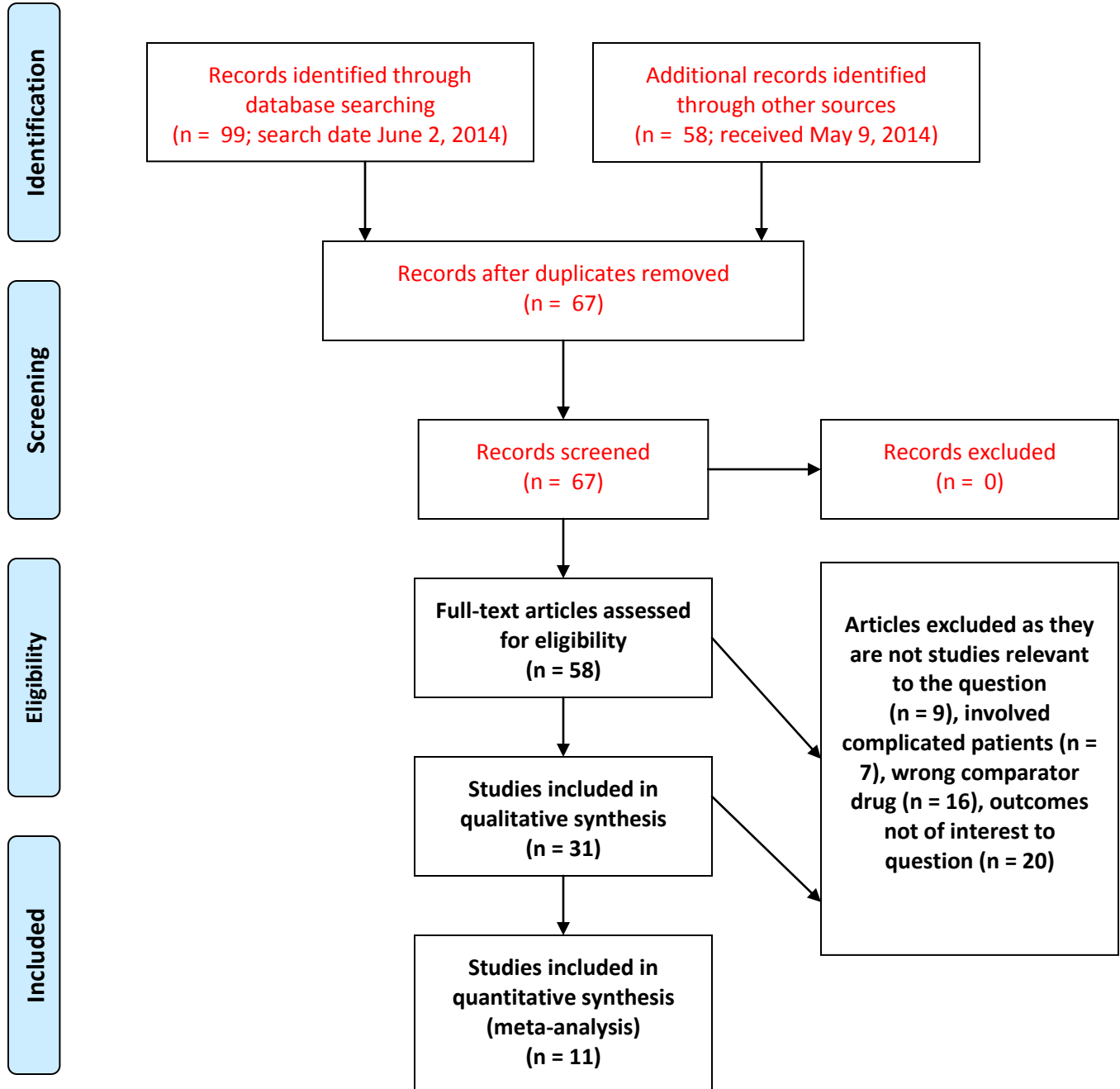
- The cost-effectiveness table from the manufacturer used MIMS price for both drugs. The ERG as directed used the DPRI price for the control drug (metformin) and the company submission for the new drug being evaluated.
- The manufacturer also assumed that the treatment of hypoglycemia/other side effect 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 acknowledging the documents submitted for reconsideration as well as the re-evaluation of the ERG, the Council still recommends the disapproval of vildagliptin+metformin since its prohibitive cost compared to metformin does not justify its minimal efficacy and safety advantage.

**The Secretary of Health has officially disapproved the proposal to include vildagliptin + metformin in the PNF.**

PRISMA Table

PubMed search strategy was MESH search of “vildagliptin AND metformin” limited to “randomized controlled trials” and studies on “human” subjects. The yield was 99 articles. Additional records were reviewed from the search conducted by PNDP 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<sub>1c</sub>) [mean difference]
- achievement of target glycosylated haemoglobin (HbA<sub>1c</sub>) level of  $\leq 7\%$

**EVIDENCE TABLE 1 (EFFECTIVENESS MEASURES)**

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTI ON	INTERVENTI ON	RESULTS/OUTCOMES					GRADE OF EVIDENC E	REMARK S
					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 <sub>1c</sub>  Reduction in FBS  HbA <sub>1c</sub> <7%	1.0%  0.9 mmol/L  179	SD 0.1  SD 0.1  511	1.4%  1.9 mmol/L  112	SD 0.1  SD 0.2  249	High	
2	Filozof and Gautier, Diabet Med, 2010	RCT	DM Type 2	Vildagliptin/me tformin vs gliclazide/metfo rmin	Reduction in HbA <sub>1c</sub>  HbA <sub>1c</sub> <7%	0.81%  176	SD 0.06  513	0.85%  158	SD 0.06  494	High	
3	Hyun and Tae, Diabetes Metab, 2011	RCT	DM Type 2	Vildagliptin/me tformin vs glimepiride/met formin	Reduction in HbA <sub>1c</sub>  HbA <sub>1c</sub> <7%  Reduction in FBS	0.94%  25  1.54 mmol/L	SD 1.15  51  SD 2.41	1.0%  28  2.16 mmol/L	SD 1.32  51  SD 2.51	High	
4	Rosenstock et	RCT	DM Type 2	Vildagliptin vs	Reduction in	1.1%	SD 0.1	1.4%	SD 0.1	High	

	al, Diab Obes Metab, 2007			Pioglitazone (2 arms of 4 arm RCT)	HbA <sub>1c</sub> HbA <sub>1c</sub> <7% Reduction in FBS	58 136 1.9 mmol/L	SD 0.2	57 133 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 <sub>1c</sub> HbA <sub>1c</sub> <7% Reduction in FBS	0.9% 71 2.1 mmol/L	SD 0.1	1.0% 88 1.4%	SD 0.1 244 SD 0.1	High	
6	Ferrannini et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin/metformin vs glimepiride/metformin	Reduction in HbA <sub>1c</sub> HbA <sub>1c</sub> <7% Reduction in FBS	0.44% 756 1.01 mmol/L	SD 0.02	0.53% 768 1.14 mmol/L	SD 0.02 1,383 SD 0.06	High	
7	Bosi et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin vs Metformin (2 arms of 4 arm RCT)	Reduction in HbA <sub>1c</sub> HbA <sub>1c</sub> <7% Reduction in FBS	1.1% 114 1.26 mmol/L	SD 0.06	1.4% 123 1.92 mmol/L	SD 0.06 283 SD 0.13	High	
8	Bolli et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin/metformin vs Pioglitazone/metformin	Reduction in HbA <sub>1c</sub> Reduction in FBS	0.6% 1.0 mmol/L	CI 0.7 and 0.4	0.6% 1.6 mmol/L	CI 0.7 and 0.5 CI 1.9 and 1.3	High	
9	Schweizer et al, Diab Obes Metab, 2009	RCT	Elderly DM Type 2	Vildagliptin vs Metformin	Reduction in HbA <sub>1c</sub>	0.64%	SD 0.07	0.75%	SD 0.07	High	
10	Blonde et al,	RCT	DM Type 2	Vildagliptin/me	Reduction in	0.68%	SD 0.02	0.57%	SD 0.03	High	

	Diab Obes Metab, 2009			tformin vs Thiazolidinedione/metformin	HbA <sub>1c</sub>						
11	Matthews et al, Diab Obes Metab, 2010	RCT	DM Type 2	Vildagliptin/metformin vs glimepiride/metformin	Reduction in HbA <sub>1c</sub>	0.3%	SD 0.0%	0.3%	SD 0.0%	High	
					HbA <sub>1c</sub> <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)	Vildagliptin 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	Any adverse event	111	511	109	249	High	
2	Filozof and Gautier, Diabet Med, 2010	RCT	DM Type 2	Vildagliptin/me tformin vs gliclazide/metfo rmin	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/me tformin vs glimepiride/met formin	Hypoglycemic Event  Any Adverse	1  5	51  51	10  10	51  51	High	

					Event							P<0.05 meaning significant difference
					weight gain (kg)	+0.23	+/-0.69	+2.53	+/-1.21			
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		
					Serious Adverse Event	5		11				
					weight gain (kg)	+0.30	+/-0.20	+1.9	+/-0.20			P value <0.001 means significant difference
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		
					Any Adverse Event	1,035		1,121				
					weight gain (kg)	-0.23	+/-0.11	+1.56	+/-0.12			P value <0.001 means significant difference
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		
					weight gain (kg)	-0.59	+/-0.22	-1.62	+/-0.22			Comparators vildagliptin and metformin monotherapy
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		
					weight gain (kg)	+0.20	+/-0.20	+2.60	+/-0.30			P<0.001 which means significant difference



9	Schweizer et al, Diab Obes Metab, 2009	RCT	Elderly DM Type 2	Vildagliptin vs Metformin	Any Adverse Event	75	169	83	166	High	P-value=0.004 which means significant difference
					Hypoglycemia	0		2			
					weight gain (kg)	-0.45	+/-0.20	-1.25	+/-0.19		
10	Blonde et al, Diab Obes Metab, 2009	RCT	DM Type 2	Vildagliptin/me tformin vs Thiazolidinedio ne/metformin	Any Adverse Event	653	1,653	299	825	High	P<0.001 which means significant difference
					weight gain (kg)	-0.58	+/-0.09	+0.33	+/-0.11		
11	Matthews et al, Diab Obes Metab, 2010	RCT	DM Type 2	Vildagliptin/me tformin vs glimepiride/met formin	Hypoglycemic Event	36	1,562	283	1,556	High	P<0.001 which means significant difference
					weight gain (kg)	-0.30	+/-0.10	+1.2	+/-0.10		

\*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		
<b>Outcome: Reduction in HbA1c</b>												
11	RCT	No	No	No	No		Vildagliptin	Others		-0.12% (SD 0.02)	High	Critical
<b>Outcome: Reduction in FBS</b>												
8	RCT	No	No	No	No		Vildagliptin	Others		-0.24 (SD 0.02)	High	Critical
<b>Outcome: Proportion of HbA1c &lt;7.0%</b>												
8	RCT	No	No	No	No		Vildagliptin	Others	0.94 (95% CI 0.91 and 0.99)		High	Critical
<b>Outcome: Any adverse event</b>												
10	RCT	No	No	No	No		Vildagliptin	Others	0.86 (95% CI 0.84 and 0.90)		High	Critical
<b>Outcome: Hypoglycemic event</b>												
5	RCT	No	No	No	No		Vildagliptin	Others	0.12 (95% CI 0.10 and 0.16)		High	Critical
<b>Outcome: Serious adverse event</b>												
2	RCT	No	No	No	No		Vildagliptin	Others	0.69 (95% CI 0.46 and 1.02)		High	Critical
<b>Outcome: weight gain</b>												
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 1,293 for vildagliptin + metformin compared to P 527 to Php 652.40 for metformin alone.

**DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS**

<p align="center"><b>PARAMETER</b> (Indicate information for intended recipient)* <i><u>INTENDED RECIPIENT:</u></i></p>	<p align="center"><b>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</b></p>	<p align="center"><b>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</b></p>	<p align="center"><b>REFERENCES</b></p>
<p>COST PER DOSAGE UNIT (in PhP)                      a. Proposed list price to the government                      b. Current prevailing market price</p>	<p>a) Php 26.41 per tablet</p>	<p>Metformin                      Php 0.90 per 500 mg tablet                      Php 1.00 per 500 mg film coated tablet                      Php 5.08 per 850 mg tablet</p>	<p>Company submission and DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p align="center">30</p>	<p align="center">30</p>	<p>Lowest maintenance</p>
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>Php 792.30 per month</p>	<p>Php 27 to Php 152.40 per month</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (in PhP)                      a. Intervention costs: (management of adverse drug reactions)</p>	<p align="center">500</p>	<p align="center">500</p>	<p align="center">Laboratory</p>
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p align="center">Php 1,292.30</p>	<p align="center">Php 527 to Php 652.40</p>	
<p>ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION</p>	<p align="center">7.1% of total population</p>	<p align="center">7.1% of total population</p>	<p align="center">NNHeS 2008 of FNRI</p>

WHO WILL USE THE MEDICINE			
QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)			
DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)			

## **Response to appeal on the reviewers' recommendation on vildagliptin+metformin**

The Evidence Review Group's (ERG) recommendation was based on the clinical question: "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 Council 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 company submission 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.