References to studies

Included studies

Arechavaleta et al 2011

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Excluded studies

Studies awaiting classification

Ongoing studies

Other references

Additional references

Other published versions of this review

Classification pending references

Name of medicine (INN):	**Sitagliptin phosphate + Metformin hydrochloride 50/500 mg, 50/850 mg, 50/1000 mg film coated tablet**
Indication:	The drug is indicated as initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic contol in patients with type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone ; and used in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients with type 2 DM inadequately controlled with any two of the three agents : metformin, sitagliptin or a sulfonylurea.
Date of deliberation:	01 July 2015
Recommendation:	**DISAPPROVAL**
Clinical evidence:	The ERG report showed that in terms of effectiveness, the combination of sitagliptin + metformin resulted in decreased HbA1c level and fasting plasma glucose i.e., 0.07 (0.12-0.03 lower) and 0.32 (0.45-0.2), respectively. Likewise, the Council noted that greater number of patients achieved HbA1c level of less than 7% (115 more) and less than 6.5% (56 more) with the use of the said drug. However, it was noted that the body mass index (BMI) was also found to be higher by 0.6 (0.31-0.88). With regard to the safety of sitagliptin as an add-on to metformin, the FEC noted that decreased adverse events were observed in the following scenarios: (1) one or more AE (17 patients fewer per 1000), (2) drug-related AE (26 patients fewer per 1000) and (3) serious AE (9 patients fewer per 1000) compared to metformin alone. On the other hand, more patients experienced hypoglycemia with the drug, i.e., increased by 9 more per 1000 patients for hypoglycemia (OR 1.33, 95% CI 0.91 to 1.93), 2 more for serious hypoglycemia (OR 1.1, 95% CI 0.46 to 2.64) and 26 more for symptomatic hypoglycemia (RR 1.88, 95% CI 1.07 to 3.3). Overall, the Council discussed that add-on sitagliptin is effective and safe in achieving target HbA1c levels, however, this is only a surrogate outcome. The FEC considered a clinical outcome of paramount importance, hence, they concluded that there is insufficient evidence to justify the inclusion of the drug in the Formulary.

Cost data:	The Council acknowledged the cost of treatment presented in the report of the Evidence Review Group *(See Attachment)* and noted that the combination of sitagliptin and metformin would give a 3-month treatment cost ranging from Php 5,142.60 to Php 5,574.60 which is significantly more expensive than the combined cost of metformin and gliclazide which would only be around Php 1,017 for three (3) months. The Council discussed that the advantage of the drug is its efficacy in reducing blood sugar level but this is deemed insufficient to justify the very high cost of the drug.
Remarks:	The Secretary of Health has officially disapproved the proposal to include sitagliptin + metformin in the PNF. There was no appeal received within the set deadline, thus the recommendation of the Council still remains.

Question: Should Sitagliptin as an Add-on Treatment to Metformin vs Other Anti-diabetic Agents be used for DM Type 2?
Settings: Outpatient
Bibliography: Sitagliptin as an Add on to Metformin versus other anti-diabetic agents (sulfonylureas, pioglitazone) for DM Type 2.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sitagliptin as an Add-on Treatment to Metformin	Other Anti-diabetic Agents	Relative (95% CI)	Absolute		
HBA1C Level at Study EndPoint (follow-up 18-104 weeks; measured with: Blood Levels at end of study perio; Better indicated by lower values)												
10	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	2329	2101	-	MD 0.07 lower (0.12 to 0.03 lower)	⊕⊕⊕O MODERATE	CRITICAL
Fasting Plasma Glucose at Study End (follow-up 18-104 weeks; measured with: Blood Levels; Better indicated by lower values)												
10	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	2329	2101	-	MD 0.32 lower (0.45 to 0.2 lower)	⊕⊕⊕O MODERATE	CRITICAL
Proportion of Patients with HBA1c < 7% (follow-up 18-104 weeks; assessed with: Number of Patients with HBA1c less than 7%)												
11	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	1417/3138 (45.2%)	989/2916 (33.9%)	RR 1.34 (1.26 to 1.43)	115 more per 1000 (from 88 more to 146 more)	⊕⊕⊕O MODERATE	CRITICAL
								30.4%		103 more per 1000 (from 79 more to 131 more)		
Proportion of Patients with HBA1C < 6.5% (follow-up 32-44 weeks; assessed with: Number of Patients with HBA1c less than 6.5%)												

3	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	330/1256 (26.3%)	258/1251 (20.6%)	RR 1.27 (1.1 to 1.47)	56 more per 1000 (from 21 more to 97 more)	⊕⊕⊕O MODERATE	CRITICAL
								17.9%		48 more per 1000 (from 18 more to 84 more)		
Change in Body Mass Index (BMI) (follow-up 16-34 weeks; measured with: Body Mass Index Based on weight and height; Better indicated by lower values)												
2	randomised trials	serious	no serious inconsistency[5,6]	no serious indirectness	no serious imprecision	none	94	93	-	MD 0.6 higher (0.31 to 0.88 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Heterogeneity: Chi² = 143.62, df = 9 (P < 0.00001); I² = 94%
[2] Heterogeneity: Chi² = 61.96, df = 9 (P < 0.00001); I² = 85%
[3] Heterogeneity: Chi² = 106.72, df = 10 (P < 0.00001); I² = 91%
[4] Heterogeneity: Chi² = 27.22, df = 2 (P < 0.00001); I² = 93%
[5] Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
[6] Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Sitagliptin as an Add-on Treatment to Metformin compared to Other Anti-diabetic Agents for DM Type 2

Patient or population: patients with DM Type 2
Settings: Outpatient
Intervention: Sitagliptin as an Add-on Treatment to Metformin
Comparison: Other Anti-diabetic Agents

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Other Anti-diabetic Agents**	Corresponding risk **Sitagliptin as an Add-on Treatment to Metformin**				
HBA1C Level at Study EndPoint Blood Levels at end of study period Follow-up: 18-104 weeks		The mean hba1c level at study endpoint in the intervention groups was **0.07 lower** (0.12 to 0.03 lower)		4430 (10 studies)	⊕⊕⊕⊖ **moderate**[1]	
Fasting Plasma Glucose at Study End Blood Levels Follow-up: 18-104 weeks		The mean fasting plasma glucose at study end in the intervention groups was **0.32 lower** (0.45 to 0.2 lower)		4430 (10 studies)	⊕⊕⊕⊖ **moderate**[2]	
Proportion of Patients with HBA1c < 7% Number of Patients with HBA1c less than 7% Follow-up: 18-104 weeks	**Study population**		**RR 1.34** (1.26 to 1.43)	6054 (11 studies)	⊕⊕⊕⊖ **moderate**[3]	
	339 per 1000	**454 per 1000** (427 to 485)				
	Moderate					
	304 per 1000	**407 per 1000** (383 to 435)				
Proportion of Patients with HBA1C < 6.5% Number of Patients with HBA1c less than 6.5% Follow-up: 32-44 weeks	**Study population**		**RR 1.27** (1.1 to 1.47)	2507 (3 studies)	⊕⊕⊕⊖ **moderate**[4]	
	206 per 1000	**262 per 1000** (227 to 303)				
	Moderate					
	179 per 1000	**227 per 1000** (197 to 263)				
Change in Body Mass Index (BMI) Body Mass Index Based on weight and height Follow-up: 16-34 weeks		The mean change in body mass index (bmi) in the intervention groups was **0.6 higher** (0.31 to 0.88 higher)		187 (2 studies)	⊕⊕⊕⊖ **moderate**[5,6]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Heterogeneity: $Chi^2 = 143.62$, df = 9 ($P < 0.00001$); $I^2 = 94\%$
[2] Heterogeneity: $Chi^2 = 61.96$, df = 9 ($P < 0.00001$); $I^2 = 85\%$
[3] Heterogeneity: $Chi^2 = 106.72$, df = 10 ($P < 0.00001$); $I^2 = 91\%$
[4] Heterogeneity: $Chi^2 = 27.22$, df = 2 ($P < 0.00001$); $I^2 = 93\%$
[5] Heterogeneity: $Chi^2 = 0.05$, df = 1 ($P = 0.82$); $I^2 = 0\%$
[6] Heterogeneity: $Chi^2 = 0.05$, df = 1 ($P = 0.82$); $I^2 = 0\%$

Interventions for DM Type 2 in Adults

Outcomes	Intervention and Comparison intervention	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		With comparator	**With intervention**				
HBA1C Level at Study EndPoint							
	Sitagliptin as an Add-on Treatment to Metformin/Other Anti-diabetic Agents		The mean hba1c level at study endpoint in the intervention groups was **0.07 lower** (0.12 to 0.03 lower)		4430 (10 studies)	⊕⊕⊕⊖ **moderate**	
Fasting Plasma Glucose at Study End							
	Sitagliptin as an Add-on Treatment to Metformin/Other Anti-diabetic Agents		The mean fasting plasma glucose at study end in the intervention groups was **0.32 lower** (0.45 to 0.2 lower)		4430 (10 studies)	⊕⊕⊕⊖ **moderate**	
Proportion of Patients with HBA1c < 7%							
	Sitagliptin as an Add-on Treatment to Metformin/Other Anti-diabetic Agents	**Study population**		**RR 1.34** (1.26 to 1.43)	6054 (11 studies)	⊕⊕⊕⊖ **moderate**	
		339 per 1000	**454 per 1000** (427 to 485)				
		Moderate					
		304 per 1000	**407 per 1000** (383 to 435)				
Proportion of Patients with HBA1C < 6.5%							
	Sitagliptin as an Add-on Treatment to Metformin/Other Anti-diabetic Agents	**Study population**		**RR 1.27** (1.1 to 1.47)	2507 (3 studies)	⊕⊕⊕⊖ **moderate**	
		206 per 1000	**262 per 1000** (227 to 303)				
		Moderate					
		179 per 1000	**227 per 1000** (197 to 263)				
Change in Body Mass Index (BMI)							
	Sitagliptin as an Add-on Treatment to Metformin/Other Anti-diabetic Agents		The mean change in body mass index (bmi) in the intervention groups was **0.6 higher** (0.31 to 0.88 higher)		187 (2 studies)	⊕⊕⊕⊖ **moderate**	

Question: Should Sitagliptin as an Add-on Treatment to Metformin vs Other Anti-diabetic Agents be used for DM Type 2?

Bibliography: Sitagliptin as an Add on to Metformin versus other anti-diabetic agents (sulfonylureas, pioglitazone) for DM Type 2.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Other Anti-diabetic Agents	**With Sitagliptin as an Add-on Treatment to Metformin**		**Risk with Other Anti-diabetic Agents**	**Risk difference with Sitagliptin as an Add-on Treatment to Metformin** (95% CI)
HBA1C Level at Study EndPoint (CRITICAL OUTCOME; measured with: Blood Levels at end of study period; Better indicated by lower values)											
4430 (10 studies) 18-104 weeks	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to inconsistency	2101	2329	-		The mean hba1c level at study endpoint in the intervention groups was **0.07 lower** (0.12 to 0.03 lower)
Fasting Plasma Glucose at Study End (CRITICAL OUTCOME; measured with: Blood Levels; Better indicated by lower values)											
4430 (10 studies) 18-104 weeks	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to inconsistency	2101	2329	-		The mean fasting plasma glucose at study end in the intervention groups was **0.32 lower** (0.45 to 0.2 lower)
Proportion of Patients with HBA1c < 7% (CRITICAL OUTCOME; assessed with: Number of Patients with HBA1c less than 7%)											
6054 (11 studies) 18-104	no serious risk of	serious[3]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[3] due to	989/2916 (33.9%)	1417/3138 (45.2%)	**RR 1.34** (1.26 to 1.43)	**Study population**	
										339 per 1000	**115 more per 1000** (from 88 more to 146 more)

weeks	bias					inconsistency				**Moderate**	
										304 per 1000	**103 more per 1000** (from 79 more to 131 more)
Proportion of Patients with HBA1C < 6.5% (CRITICAL OUTCOME; assessed with: Number of Patients with HBA1c less than 6.5%)											
2507 (3 studies) 32-44 weeks	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[4] due to inconsistency	258/1251 (20.6%)	330/1256 (26.3%)	**RR 1.27** (1.1 to 1.47)	**Study population**	
										206 per 1000	**56 more per 1000** (from 21 more to 97 more)
										Moderate	
										179 per 1000	**48 more per 1000** (from 18 more to 84 more)
Change in Body Mass Index (BMI) (IMPORTANT OUTCOME; measured with: Body Mass Index Based on weight and height; Better indicated by lower values)											
187 (2 studies) 16-34 weeks	serious	no serious inconsistency[5,6]	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[5,6] due to risk of bias	93	94	**-**		The mean change in body mass index (bmi) in the intervention groups was **0.6 higher** (0.31 to 0.88 higher)

[1] Heterogeneity: Chi² = 143.62, df = 9 (P < 0.00001); I² = 94%
[2] Heterogeneity: Chi² = 61.96, df = 9 (P < 0.00001); I² = 85%
[3] Heterogeneity: Chi² = 106.72, df = 10 (P < 0.00001); I² = 91%
[4] Heterogeneity: Chi² = 27.22, df = 2 (P < 0.00001); I² = 93%
[5] Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
[6] Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Sitagliptin as an Add-on Treatment to Metformin compared to Other Anti-diabetic Agents for DM Type 2

Bibliography: Sitagliptin as an Add on to Metformin versus other anti-diabetic agents (sulfonylureas, pioglitazone) for DM Type 2.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Other Anti-diabetic Agents	Risk difference with Sitagliptin as an Add-on Treatment to Metformin (95% CI)
HBA1C Level at Study End Point Blood Levels at end of study period	4430 (10 studies) 18-104 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to inconsistency			The mean hba1c level at study endpoint in the intervention groups was **0.07 lower** (0.12 to 0.03 lower)
Fasting Plasma Glucose at Study End Blood Levels	4430 (10 studies) 18-104 weeks	⊕⊕⊕⊖ **MODERATE**[2] due to inconsistency			The mean fasting plasma glucose at study end in the intervention groups was **0.32 lower** (0.45 to 0.2 lower)
Proportion of Patients with HBA1c < 7% Number of Patients with HBA1c less than 7%	6054 (11 studies) 18-104 weeks	⊕⊕⊕⊖ **MODERATE**[3] due to inconsistency	**RR 1.34** (1.26 to 1.43)	**Study population**	
				339 per 1000	**115 more per 1000** (from 88 more to 146 more)
				Moderate	
				304 per 1000	**103 more per 1000** (from 79 more to 131 more)
Proportion of Patients with HBA1C < 6.5% Number of Patients with HBA1c less than 6.5%	2507 (3 studies) 32-44 weeks	⊕⊕⊕⊖ **MODERATE**[4] due to inconsistency	**RR 1.27** (1.1 to 1.47)	**Study population**	
				206 per 1000	**56 more per 1000** (from 21 more to 97 more)
				Moderate	
				179 per 1000	**48 more per 1000** (from 18 more to 84 more)
Change in Body Mass Index (BMI) Body Mass Index Based on weight and height	187 (2 studies) 16-34 weeks	⊕⊕⊕⊖ **MODERATE**[5,6] due to risk of bias			The mean change in body mass index (bmi) in the intervention groups was **0.6 higher** (0.31 to 0.88 higher)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Heterogeneity: $Chi^2 = 143.62$, df = 9 ($P < 0.00001$); $I^2 = 94\%$
[2] Heterogeneity: $Chi^2 = 61.96$, df = 9 ($P < 0.00001$); $I^2 = 85\%$
[3] Heterogeneity: $Chi^2 = 106.72$, df = 10 ($P < 0.00001$); $I^2 = 91\%$
[4] Heterogeneity: $Chi^2 = 27.22$, df = 2 ($P < 0.00001$); $I^2 = 93\%$
[5] Heterogeneity: $Chi^2 = 0.05$, df = 1 ($P = 0.82$); $I^2 = 0\%$
[6] Heterogeneity: $Chi^2 = 0.05$, df = 1 ($P = 0.82$); $I^2 = 0\%$

Question: Should Sitagliptin as an Add-on Therapy vs Other Anti-diabetic Drugs be used for DM Type 2?
Bibliography: Sitagliptin as an Add on to Metformin versus other anti-diabetic agents (sulfonylureas, pioglitazone) for DM Type 2.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sitagliptin as an Add-on Therapy**	**Other Anti-diabetic Drugs**	**Relative (95% CI)**	**Absolute**		
One or More Adverse Events (follow-up 18-104 weeks; assessed with: Number of Reported Adverse Events)												
8	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	1315/2453 (53.6%)	1217/2207 (55.1%)	RR 0.97 (0.92 to 1.02)	17 fewer per 1000 (from 44 fewer to 11 more)	⊕⊕⊕O MODERATE	CRITICAL
								53.1%		16 fewer per 1000 (from 42 fewer to 11 more)		
Drug-Related Adverse Events (follow-up 18-104 weeks; assessed with: Number of Reported Drug-Related Adverse Events)												
8	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	340/2760 (12.3%)	381/2522 (15.1%)	OR 0.8 (0.69 to 0.94)	26 fewer per 1000 (from 8 fewer to 42 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								10.6%		19 fewer per 1000 (from 6 fewer to 30 fewer)		

Serious Adverse Events (follow-up 18-44 weeks; assessed with: Number of Reported Adverse Events)												
4	randomised trials	serious[3]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	47/1441 (3.3%)	59/1436 (4.1%)	OR 0.78 (0.53 to 1.16)	9 fewer per 1000 (from 19 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
								3.5%		7 fewer per 1000 (from 16 fewer to 5 more)		
Serious Hypoglycemia (follow-up 26-48 weeks; assessed with: Reported Serious Hypoglycemia)												
2	randomised trials	serious[5]	no serious inconsistency[6]	no serious indirectness	serious[7]	none	11/625 (1.8%)	10/624 (1.6%)	OR 1.1 (0.46 to 2.64)	2 more per 1000 (from 9 fewer to 25 more)	⊕⊕OO LOW	CRITICAL
								2.6%		3 more per 1000 (from 14 fewer to 40 more)		
Symptomatic Hypoglycemia (follow-up 26-54 weeks; assessed with: Number of Reported Symptomatic Hypoglycemia)												
3	randomised trials	serious	no serious inconsistency[8]	no serious indirectness	serious	none	33/582 (5.7%)	17/565 (3%)	RR 1.88 (1.07 to 3.3)	26 more per 1000 (from 2 more to 69 more)	⊕⊕OO LOW	CRITICAL
								3.9%		34 more per 1000 (from 3 more to 90 more)		

Hypoglycemia (follow-up 18-44 weeks; assessed with: Number of Reported Hypoglycemia)												
6	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	no serious imprecision	none	66/1972 (3.3%)	47/1745 (2.7%)	OR 1.33 (0.91 to 1.93)	9 more per 1000 (from 2 fewer to 24 more)	⊕⊕⊕O MODERATE	CRITICAL
								2.2%		7 more per 1000 (from 2 fewer to 20 more)		
Presence of Weight Gain (assessed with: Weight Gain)												
1	randomised trials					none	5/175 (2.9%)	5/178 (2.8%)	OR 1.02 (0.29 to 3.58)	1 more per 1000 (from 20 fewer to 66 more)		CRITICAL
								2.8%		1 more per 1000 (from 20 fewer to 65 more)		

[1] Heterogeneity: Chi² = 14.27, df = 7 (P = 0.05); I² = 51%

[2] Heterogeneity: Chi² = 30.39, df = 7 (P < 0.0001); I² = 77%

[3] All four studies have undertermined acceptable random sequence generation, Two studies have undertermined adequate method of concealment and blinding.

[4] Heterogeneity: Chi² = 1.94, df = 3 (P = 0.58); I² = 0%

[5] One study has 44% lost to follow-up. Another has undetermined random sequence generation.

[6] Heterogeneity: Chi² = 1.37, df = 1 (P = 0.24); I² = 27%

[7] Confidence Interval in one of out the three study was wide 95% CI.0.33 [0.03, 3.20]

[8] Heterogeneity: Chi² = 1.81, df = 2 (P = 0.40); I² = 0%

[9] Heterogeneity: Chi² = 16.71, df = 5 (P = 0.005); I² = 70%

Sitagliptin as an Add-on Therapy compared to Other Anti-diabetic Drugs for DM Type 2

Patient or population: patients with DM Type 2
Intervention: Sitagliptin as an Add-on Therapy
Comparison: Other Anti-diabetic Drugs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Other Anti-diabetic Drugs**	Corresponding risk **Sitagliptin as an Add-on Therapy**				
One or More Adverse Events Number of Reported Adverse Events Follow-up: 18-104 weeks	**Study population**		**RR 0.97** (0.92 to 1.02)	4660 (8 studies)	⊕⊕⊕⊖ **moderate**[1]	
	551 per 1000	**535 per 1000** (507 to 562)				
	Moderate					
	531 per 1000	**515 per 1000** (489 to 542)				
Drug-Related Adverse Events Number of Reported Drug-Related Adverse Events Follow-up: 18-104 weeks	**Study population**		**OR 0.8** (0.69 to 0.94)	5282 (8 studies)	⊕⊕⊕⊖ **moderate**[2]	
	151 per 1000	**125 per 1000** (109 to 143)				
	Moderate					
	106 per 1000	**87 per 1000** (76 to 100)				
Serious Adverse Events Number of Reported Adverse Events Follow-up: 18-44 weeks	**Study population**		**OR 0.78** (0.53 to 1.16)	2877 (4 studies)	⊕⊕⊕⊖ **moderate**[3,4]	
	41 per 1000	**32 per 1000** (22 to 47)				
	Moderate					
	35 per 1000	**28 per 1000** (19 to 40)				
Serious Hypoglycemia Reported Serious Hypoglycemia Follow-up: 26-48 weeks	**Study population**		**OR 1.1** (0.46 to 2.64)	1249 (2 studies)	⊕⊕⊖⊖ **low**[5,6,7]	
	16 per 1000	**18 per 1000** (7 to 41)				
	Moderate					
	26 per 1000	**29 per 1000** (12 to 66)				

Symptomatic Hypoglycemia Number of Reported Symptomatic Hypoglycemia Follow-up: 26-54 weeks	**Study population**		**RR 1.88** (1.07 to 3.3)	1147 (3 studies)	⊕⊕⊖⊖ **low**[8]
	30 per 1000	**57 per 1000** (32 to 99)			
	Moderate				
	39 per 1000	**73 per 1000** (42 to 129)			
Hypoglycemia Number of Reported Hypoglycemia Follow-up: 18-44 weeks	**Study population**		**OR 1.33** (0.91 to 1.93)	3717 (6 studies)	⊕⊕⊕⊖ **moderate**[9]
	27 per 1000	**36 per 1000** (25 to 51)			
	Moderate				
	22 per 1000	**29 per 1000** (20 to 42)			
Presence of Weight Gain Weight Gain	**Study population**		**OR 1.02** (0.29 to 3.58)	353 (1 study)	See comment
	28 per 1000	**29 per 1000** (8 to 94)			
	Moderate				
	28 per 1000	**29 per 1000** (8 to 93)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Heterogeneity: $Chi^2 = 14.27$, df = 7 (P = 0.05); $I^2 = 51\%$
[2] Heterogeneity: $Chi^2 = 30.39$, df = 7 (P < 0.0001); $I^2 = 77\%$
[3] All four studies have undertermined acceptable random sequence generation, Two studies have undertermined adequate method of concealment and blinding.
[4] Heterogeneity: $Chi^2 = 1.94$, df = 3 (P = 0.58); $I^2 = 0\%$
[5] One study has 44% lost to follow-up. Another has undetermined random sequence generation.
[6] Heterogeneity: $Chi^2 = 1.37$, df = 1 (P = 0.24); $I^2 = 27\%$
[7] Confidence Interval in one of out the three study was wide 95% CI.0.33 [0.03, 3.20]
[8] Heterogeneity: $Chi^2 = 1.81$, df = 2 (P = 0.40); $I^2 = 0\%$
[9] Heterogeneity: $Chi^2 = 16.71$, df = 5 (P = 0.005); $I^2 = 70\%$

Interventions for DM Type 2 in Adults

Outcomes	Intervention and Comparison intervention	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		With comparator	**With intervention**				
One or More Adverse Events							
	Sitagliptin as an Add-on Therapy/Other Anti-diabetic Drugs	**Study population**		**RR 0.97** (0.92 to 1.02)	4660 (8 studies)	⊕⊕⊕⊖ **moderate**	
		551 per 1000	**535 per 1000** (507 to 562)				
		Moderate					
		531 per 1000	**515 per 1000** (489 to 542)				
Drug-Related Adverse Events							
	Sitagliptin as an Add-on Therapy/Other Anti-diabetic Drugs	**Study population**		**OR 0.8** (0.69 to 0.94)	5282 (8 studies)	⊕⊕⊕⊖ **moderate**	
		151 per 1000	**125 per 1000** (109 to 143)				
		Moderate					
		106 per 1000	**87 per 1000** (76 to 100)				
Serious Adverse Events							
	Sitagliptin as an Add-on Therapy/Other Anti-diabetic Drugs	**Study population**		**OR 0.78** (0.53 to 1.16)	2877 (4 studies)	⊕⊕⊕⊖ **moderate**	
		41 per 1000	**32 per 1000** (22 to 47)				
		Moderate					
		35 per 1000	**28 per 1000** (19 to 40)				
Serious Hypoglycemia							
	Sitagliptin as an Add-on Therapy/Other Anti-diabetic Drugs	**Study population**		**OR 1.1** (0.46 to 2.64)	1249 (2 studies)	⊕⊕⊖⊖ **low**	
		16 per 1000	**18 per 1000** (7 to 41)				
		Moderate					
		26 per 1000	**29 per 1000** (12 to 66)				

Symptomatic Hypoglycemia					
Sitagliptin as an Add-on Therapy/Other Anti-diabetic Drugs	**Study population**		**RR 1.88** (1.07 to 3.3)	1147 (3 studies)	⊕⊕⊖⊖ **low**
	30 per 1000	**57 per 1000** (32 to 99)			
	Moderate				
	39 per 1000	**73 per 1000** (42 to 129)			
Hypoglycemia					
Sitagliptin as an Add-on Therapy/Other Anti-diabetic Drugs	**Study population**		**OR 1.33** (0.91 to 1.93)	3717 (6 studies)	⊕⊕⊕⊖ **moderate**
	27 per 1000	**36 per 1000** (25 to 51)			
	Moderate				
	22 per 1000	**29 per 1000** (20 to 42)			
Presence of Weight Gain					
Sitagliptin as an Add-on Therapy/Other Anti-diabetic Drugs	**Study population**		**OR 1.02** (0.29 to 3.58)	353 (1 study)	See comment
	28 per 1000	**29 per 1000** (8 to 94)			
	Moderate				
	28 per 1000	**29 per 1000** (8 to 93)			

Question: Should Sitagliptin as an Add-on Therapy vs Other Anti-diabetic Drugs be used for DM Type 2?

Bibliography: Sitagliptin as an Add on to Metformin versus other anti-diabetic agents (sulfonylureas, pioglitazone) for DM Type 2.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Other Anti-diabetic Drugs	**With Sitagliptin as an Add-on Therapy**		**Risk with Other Anti-diabetic Drugs**	**Risk difference with Sitagliptin as an Add-on Therapy** (95% CI)
One or More Adverse Events (CRITICAL OUTCOME; assessed with: Number of Reported Adverse Events)											
4660 (8 studies) 18-104 weeks	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[1] due to inconsistency	1217/2207 (55.1%)	1315/2453 (53.6%)	**RR 0.97** (0.92 to 1.02)	**Study population**	
										551 AE per 1000	**17 fewer AE per 1000** (from 44 fewer to 11 more)
										Moderate	
										531 AE per 1000	**16 fewer AE per 1000** (from 42 fewer to 11 more)
Drug-Related Adverse Events (CRITICAL OUTCOME; assessed with: Number of Reported Drug-Related Adverse Events)											
5282 (8 studies) 18-104 weeks	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[2] due to inconsistency	381/2522 (15.1%)	340/2760 (12.3%)	**OR 0.8** (0.69 to 0.94)	**Study population**	
										151 AE per 1000	**26 fewer AE per 1000** (from 8 fewer to 42 fewer)
										Moderate	
										106 AE per 1000	**19 fewer AE per 1000** (from 6 fewer to 30 fewer)

Serious Adverse Events (CRITICAL OUTCOME; assessed with: Number of Reported Adverse Events)											
2877 (4 studies) 18-44 weeks	serious[3]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[3,4] due to risk of bias	59/1436 (4.1%)	47/1441 (3.3%)	**OR 0.78** (0.53 to 1.16)	**Study population**	
										41 AE per 1000	**9 fewer AE per 1000** (from 19 fewer to 6 more)
										Moderate	
										35 AE per 1000	**7 fewer AE per 1000** (from 16 fewer to 5 more)
Serious Hypoglycemia (CRITICAL OUTCOME; assessed with: Reported Serious Hypoglycemia)											
1249 (2 studies) 26-48 weeks	serious[5]	no serious inconsistency[6]	no serious indirectness	serious[7]	undetected	⊕⊕⊖⊖ **LOW**[5,6,7] due to risk of bias, imprecision	10/624 (1.6%)	11/625 (1.8%)	**OR 1.1** (0.46 to 2.64)	**Study population**	
										16 per 1000	**2 more per 1000** (from 9 fewer to 25 more)
										Moderate	
										26 per 1000	**3 more per 1000** (from 14 fewer to 40 more)
Symptomatic Hypoglycemia (CRITICAL OUTCOME; assessed with: Number of Reported Symptomatic Hypoglycemia)											
1147 (3 studies) 26-54 weeks	serious	no serious inconsistency[8]	no serious indirectness	serious	undetected	⊕⊕⊖⊖ **LOW**[8] due to risk of bias, imprecision	17/565 (3%)	33/582 (5.7%)	**RR 1.88** (1.07 to 3.3)	**Study population**	
										30 AE per 1000	**26 more AE per 1000** (from 2 more to 69 more)
										Moderate	
										39 AE per 1000	**34 more AE per 1000** (from 3 more to 90 more)

Hypoglycemia (CRITICAL OUTCOME; assessed with: Number of Reported Hypoglycemia)											
3717 (6 studies) 18-44 weeks	no serious risk of bias	serious[9]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[9] due to inconsistency	47/1745 (2.7%)	66/1972 (3.3%)	**OR 1.33** (0.91 to 1.93)	**Study population**	
										27 per 1000	**9 more per 1000** (from 2 fewer to 24 more)
										Moderate	
										22 per 1000	**7 more per 1000** (from 2 fewer to 20 more)
Presence of Weight Gain (CRITICAL OUTCOME; assessed with: Weight Gain)											
353 (1 study)						See comment	5/178 (2.8%)	5/175 (2.9%)	**OR 1.02** (0.29 to 3.58)	**Study population**	
										28 per 1000	**1 more per 1000** (from 20 fewer to 66 more)
										Moderate	
										28 per 1000	**1 more per 1000** (from 20 fewer to 65 more)

[1] Heterogeneity: Chi² = 14.27, df = 7 (P = 0.05); I² = 51%

[2] Heterogeneity: Chi² = 30.39, df = 7 (P < 0.0001); I² = 77%

[3] All four studies have undertermined acceptable random sequence generation, Two studies have undertermined adequate method of concealment and blinding.

[4] Heterogeneity: Chi² = 1.94, df = 3 (P = 0.58); I² = 0%

[5] One study has 44% lost to follow-up. Another has undetermined random sequence generation.

[6] Heterogeneity: Chi² = 1.37, df = 1 (P = 0.24); I² = 27%

[7] Confidence Interval in one of out the three study was wide 95% CI.0.33 [0.03, 3.20]

[8] Heterogeneity: Chi² = 1.81, df = 2 (P = 0.40); I² = 0%

[9] Heterogeneity: Chi² = 16.71, df = 5 (P = 0.005); I² = 70%

Sitagliptin as an Add-on Therapy compared to Other Anti-diabetic Drugs for DM Type 2

Bibliography: Sitagliptin as an Add on to Metformin versus other anti-diabetic agents (sulfonylureas, pioglitazone) for DM Type 2.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Other Anti-diabetic Drugs	Risk difference with Sitagliptin as an Add-on Therapy (95% CI)
One or More Adverse Events Number of Reported Adverse Events	4660 (8 studies) 18-104 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to inconsistency	**RR 0.97** (0.92 to 1.02)	**Study population**	
				551 AE per 1000	**17 fewer AE per 1000** (from 44 fewer to 11 more)
				Moderate	
				531 AE per 1000	**16 fewer AE per 1000** (from 42 fewer to 11 more)
Drug-Related Adverse Events Number of Reported Drug-Related Adverse Events	5282 (8 studies) 18-104 weeks	⊕⊕⊕⊖ **MODERATE**[2] due to inconsistency	**OR 0.8** (0.69 to 0.94)	**Study population**	
				151 AE per 1000	**26 fewer AE per 1000** (from 8 fewer to 42 fewer)
				Moderate	
				106 AE per 1000	**19 fewer AE per 1000** (from 6 fewer to 30 fewer)
Serious Adverse Events Number of Reported Adverse Events	2877 (4 studies) 18-44 weeks	⊕⊕⊕⊖ **MODERATE**[3,4] due to risk of bias	**OR 0.78** (0.53 to 1.16)	**Study population**	
				41 AE per 1000	**9 fewer AE per 1000** (from 19 fewer to 6 more)
				Moderate	
				35 AE per 1000	**7 fewer AE per 1000** (from 16 fewer to 5 more)
Serious Hypoglycemia Reported Serious Hypoglycemia	1249 (2 studies) 26-48 weeks	⊕⊕⊖⊖ **LOW**[5,6,7] due to risk of bias, imprecision	**OR 1.1** (0.46 to 2.64)	**Study population**	
				16 per 1000	**2 more per 1000** (from 9 fewer to 25 more)
				Moderate	
				26 per 1000	**3 more per 1000** (from 14 fewer to 40 more)
Symptomatic Hypoglycemia Number of Reported Symptomatic	1147 (3 studies) 26-54 weeks	⊕⊕⊖⊖ **LOW**[8] due to risk of bias,	**RR 1.88** (1.07 to 3.3)	**Study population**	
				30 AE per 1000	**26 more AE per 1000** (from 2 more to 69 more)

Hypoglycemia		imprecision		**Moderate**	
				39 AE per 1000	**34 more AE per 1000** (from 3 more to 90 more)
Hypoglycemia Number of Reported Hypoglycemia	3717 (6 studies) 18-44 weeks	⊕⊕⊕⊖ **MODERATE**[9] due to inconsistency	**OR 1.33** (0.91 to 1.93)	**Study population**	
				27 per 1000	**9 more per 1000** (from 2 fewer to 24 more)
				Moderate	
				22 per 1000	**7 more per 1000** (from 2 fewer to 20 more)
Presence of Weight Gain Weight Gain	353 (1 study)	See comment	**OR 1.02** (0.29 to 3.58)	**Study population**	
				28 per 1000	**1 more per 1000** (from 20 fewer to 66 more)
				Moderate	
				28 per 1000	**1 more per 1000** (from 20 fewer to 65 more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Heterogeneity: $Chi^2 = 14.27$, df = 7 (P = 0.05); $I^2 = 51\%$
[2] Heterogeneity: $Chi^2 = 30.39$, df = 7 (P < 0.0001); $I^2 = 77\%$
[3] All four studies have undertermined acceptable random sequence generation, Two studies have undertermined adequate method of concealment and blinding.
[4] Heterogeneity: $Chi^2 = 1.94$, df = 3 (P = 0.58); $I^2 = 0\%$
[5] One study has 44% lost to follow-up. Another has undetermined random sequence generation.
[6] Heterogeneity: $Chi^2 = 1.37$, df = 1 (P = 0.24); $I^2 = 27\%$
[7] Confidence Interval in one of out the three study was wide 95% CI.0.33 [0.03, 3.20]
[8] Heterogeneity: $Chi^2 = 1.81$, df = 2 (P = 0.40); $I^2 = 0\%$
[9] Heterogeneity: $Chi^2 = 16.71$, df = 5 (P = 0.005); $I^2 = 70\%$

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** ***(*where there is no comparator medicine in the formulary, use the cost of the best existing standard of care)***	**REFERENCES**
COST PER DOSAGE UNIT (in PhP) a. Proposed list price to the government b. Current prevailing market price	[2]**Sitagliptin + Metformin** • **50/500 mg tablet: Php 28.57** • **50/850 mg tablet: Php 30.07** • **50/1000 mg tablet: Php 30.97**	[1]**Metformin 500 mg tab:** Php 1 [1]**Gliclazide 80 mg tab:** Php 4.15	[1]DPRI [2]Company submission
NUMBER OF DOSAGE UNITS PER UNIT COURSE	**1 tab BID**	**Metformin 500 mg TID + Gliclazide 80 mg BID**	
TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)	**For 3 months:** • 50/500 mg tablet: **Php 5,142.60** • 50/850 mg tablet: **Php 5,412.60** • 50/1000 mg tablet: **Php 5,574.60**	Gliclazide 80 mg + Metformin 500 mg (3x daily) Php 1 x 3= 3 Php 4.15 x 2 = 8.30 Total Tx cost = Php 11.30 **Php 1,017 for three months**	
ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP) a. Implementation costs: (cost of drug	**Laboratory Work** **FBS= Php 221** **HBA1C = Php 658** **Transportation Cost**	**Laboratory Work** **FBS= Php 221** **HBA1C = Php 658** **Transportation**	

administration, monitoring, additional diagnostic services, additional equipment, travel, caregiver, etc.) *– transportation cost: use Php 8 (multiplied by the number of visits to the hospital)* b. Intervention costs: (management of adverse drug reactions) c. Indirect costs: (lost production costs) –use the daily minimum wage (both for the patient and caregiver)	**a. lab work= 16.00** **Php 8 x2 (blood extraction/release of results, 2 visits)** **consult = Php 16.00** **Php 8 x 2 (consult; back to home and to clinic)** **Additional Cost laboratory and transpo:** **Php 911.00** **Indirect cost:** **Daily minimum wage: Php 475** **Px = 2 days lost (Lab and clinic visit)** **Caregiver = 2 days Lost)** **Indirect cost** **Php 475 x 4 = 1,900**	**Cost a. lab work= 16.00** **Php 8 x2 (blood extraction/release of results, 2 visits)** **consult = Php 16.00** **Php 8 x 2 (consult; back to home and to clinic)** **Additional Cost laboratory and transpo:** **Php 911.00** **Indirect cost:** **Daily minimum wage: Php 475** **Px = 2 days lost (Lab and clinic visit)** **Caregiver = 2 days Lost)** **Indirect cost** **Php 475 x 4 = 1,900**	
TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs	• 50/500 mg tablet: **Php 7,953.60** • 50/850 mg tablet: **Php 8,223.60** • 50/1000 mg tablet: **Php 8,385.60** **Total Cost per Patient for 3 months of Treatment until repeat HB1AC**	**Php 3,828** **Total Cost per Patient for 3 months of Treatment until repeat HB1AC**	
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)			

SUMMARY OF FINDINGS:

Effectiveness

- HBA1c Level: has decreased by 0.07 (0.12 – 0.03)
- Fasting Plasma Glucose : has decreased by 0.32 (0.45-0.2)
- Proportion of Patient:
  - greater number of patients with HBA1c <7% (115 more)
  - greater number of patients with HBA1c <6.5% (56 more)
- Change in BMI
  - BMI is higher by 0.6 (0.31-0.88)

Safety

- One or More AE: Decreased adverse events with Sitagliptin
- Drug-Related AE: Decreased
- Serious AE: Decreased
- Hypoglycemia: increase by 9 more per 1000
- Serious Hypoglycemia: increase by 2 more per 1000
- Symptomatic Hypoglycemia: increase by 26 more per 1000

Overall Recommendation

- Add-on sitagliptin is effective and safe in achieving target HBA1c levels, however it is more expensive than the currently listed oral hypoglycemic agents.