Drug Use Research & Management Program
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Month/Year of Review: April 2012
PDL Classes: DPP4 Inhibitors
GLP-1 agonists and analogs
Oral Hypoglycemics
Thiazolidinediones

Date of Last Review: June 2009
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Current Preferred Agents:

Dipeptidyl peptidase (DPP4) Inhibitors
Sitagliptan/metformin (Janumet®)
Sitagliptan (Januvia®)

Glucagon-like peptide (GLP)-1 Analogs
Pramlintide (Symlinpen 60 and 120®)

Thiazolidinediones (TZD's)
Pioglitazone (Actos®)

Oral hypoglycemics
Glimepiride
Glipizide
Glyburide
Metformin
Metformin ER

Current Non-Preferred Agents:

Oral hypoglycemics
Glyburide micronized
Chlorpropamide
Tolbutamide
Repaglinide (Prandin®)
Nateglinide (Starlix®)
Tolazamide

Thiazolidinediones
Rosiglitazone (Avandia®)

DPP4 Inhibitors
Linagliptan (Tradjenta®)
Saxagliptan (Onglyza®)

GLP-1 Analogs
Exenatide (Byetta®)
Liraglutide (Victoza®)

Combination Products
Rosiglitazone/Glimepiride (Avandaryl®)
Pioglitazone/Glimepiride (Duetact®)
Pioglitazone/metformin (Actoplus Met®)
Rosiglitazone/metformin (Avandamet®)
Glyburide/metformin
Glipizide/metformin
Repaglinide/metformin (Prandimet®)
Saxagliptan /metformin (Kombiglyze XR®)
Linagliptan/metformin (Jentadueto®)
Sitagliptan/metformin (Janumet XR®)

Previous Recommendations:

Oral Hypoglycemics

1. There is no clinically significant difference between any of the agents in these two drug classes (oral sulfonylureas and non-sulfonylurea secretagogues) in their ability to lower hemoglobin A1c (HbAlc).
2. There is no statistically significant difference between glyburide and chlorpropamide in the progression or occurrence of clinically relevant outcomes with the exception of retinopathy. Patients on glyburide had greater risk reduction of progression of retinopathy than those on chlorpropamide.
3. There is insufficient evidence on other sulfonylureas and nonsulfonylureas secretagogues to identify a difference in progression or occurrence of clinically relevant outcomes.
4. Chlorpropamide has a less favorable adverse effect profile compared to glyburide. There is no difference in safety or adverse effect profiles for other oral sulfonylureas and non-sulfonylureas secretagogues. Glimepiride, glipizide, glyburide, micronized glyburide and repaglinide do not differ in safety or adverse effect profile. No evidence exists for evaluation of tolbutamide, tolazamide or nateglinide.

TZDs

1. Good quality evidence shows that pioglitazone and rosiglitazone have similar effects on A1C, yielding a decrease of approximately 1%. There are no significant differences between these two drugs for effect on A1c .
2. TZDs have a similar effect on A1C as metformin, glibenclamide, or glimepiride.

3. There is no difference between TZDs and metformin or sulfonylureas in their ability to lower A1c.

DPP4-Inhibitors

1. Data are insufficient to determine the long term clinical effectiveness of sitagliptin.
2. No studies provided evidence on benefits or harms for follow-up periods longer than 52 weeks.
3. There was no evidence of increased adverse events for sitagliptin vs. placebo.
4. Sitagliptin had lower rates of abdominal pain, nausea, vomiting and diarrhea than metformin.
5. Sitagliptin and metformin as monotherapy or in combination have a lower incidence of hypoglycemia than glipizide.

GLP-1 agonists and analogs

1. Data are insufficient to determine long term effectiveness of pramlintide in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy.
2. Pramlintide + insulin treated patients had an increased incidence of nausea, vomiting and anorexia than insulin treated patients.
3. Data are insufficient to determine long term clinical effectiveness of pramlintide in Type 2 Diabetes when added to prandial insulin compared to conventional insulin therapy with or without concurrent oral agents.
4. No studies meeting inclusion criteria examined exenatide as monotherapy or combined therapy for long term health outcomes.
5. Nausea and vomiting were more common in exenatide vs. insulin groups.

PA Criteria/QL: Prior Authorization criteria for incretin enhancers, incretin mimetics, and amylin analogs to promote use of preferred agents and require a trial of metformin and sulfonylurea therapy or have contraindications before approval of a non-preferred agent in these classes.

Methods:

A MEDLINE OVID search was conducted using all included drugs in adults and limits for humans, English language, and controlled clinical trials or meta-analysis from July 2010 (end of literature search in recent systematic review) to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews:

The Oregon Evidence-based Practice Center (EPC) for the Drug Effectiveness Review Project (DERP) produced an original report on newer diabetes medications, TZD's, and combinations in February 2011.[1] The full report can be found on the Evidence-based Practice Center website: http://derp.ohsu.edu/about/final-document-display.cfm. This review compared the effectiveness and adverse event profiles of amlyin agonists, DDP-4 inhibitors, incretin mimetics, TZDs, and certain combination products for people with type 2 diabetes and for people with type 1 diabetes for pramlintide only.

Most of the evidence was limited to adult populations which evaluated intermediate outcomes, such as HbA1c or weight. Very few studies reported health outcomes or were longer than 6 months. All of the included medications were found to be efficacious for reducing HbA1c and none of the newer medications appeared to cause weight gain. Little data was available to evaluate the long-term effectiveness of the newer medications compared with more established treatments. Overall, there was insufficient evidence to determine how fixed-dose combination products (FDCPs) compared with other treatments for their impact on health outcomes and there were no head-to-head trials that compared 2 FDCPs. There was insufficient evidence to draw conclusions based on subgroups of patients based on demographics, comorbidities, or other medications. The following additional conclusions were made for each drug class.

Amylin Agonists

There was insufficient evidence to determine how pramlintide compares with other treatments for their impact on health outcomes. There was moderate strength evidence that a greater reduction in HbA1c was demonstrated with pramlinitde added to fixed doses of insulin compared with placebo and insulin (range 0.13% to 0.4%) and low evidence that there is no statistically significant differences when added to insulin glargine or determir compared with rapid acting insulin (1.1% vs. 1.3%, p=0.46).[1] There was moderate strength evidence demonstrating nausea as the most commonly reported adverse event which occurred more frequently with pramlintide plus insulin than with placebo plus insulin.

DPP-IV Inhibitors

There was insufficient evidence to compare the direct effectiveness of sitagliptan and saxagliptin and all included studies focused on intermediate outcomes.. There was low quality evidence that sitagliptin monotherapy resulted in slightly less HbA1c reduction than either metformin monotherapy over 54 weeks (between group difference −0.16 for metformin 1000 and −0.47 for metformin 2000 mg/d) or glipizide monotherapy over 12 weeks (between group difference −0.22%). [1] There was moderate strength evidence that there is no significant difference in reduction in HbA1c between rosiglitazone and sitagliptin when added to metformin therapy.

GLP-1 Agonists

No studies examined the impact of treatment on health outcomes as the primary outcomes. One head-to-head trial demonstrated low quality evidence that liraglutide 1.8mg once daily reduced mean HbA1c significantly more than exenatide 10 mcg twice daily (treatment difference -0.33%; 95% CI -0.47 to -0.18) and resulted in similar weight loss.[1] This trial also demonstrated no significant difference in withdrawal rates between groups. There is moderate strength evidence that there is no significant difference in reduction in HbA1c between exenatide and insulin when also taking oral diabetic agents (exenatide range -1.0% to -1.4%, insulin range -0.9% to -1.4%)

TZDs:

Moderate evidence from a meta-analysis of 8 head-to-head randomized controlled trials suggests no statistically significant difference between pioglitazone and rosiglitazone for their ability to improve glycemic control (mean difference in reduction in HbA1c -0.09, 95% CI -0.23 to 0.05) when used in either monotherapy or combination therapy.[1] There is also moderate strength evidence that there is no difference between pioglitazone or rosiglitazone and sulfonylureas for reduction in HbA1c and high quality evidence for no difference between pioglitazone and metformin. There is high quality evidence that both TZDs increase the risk of heart failure (Odds ratio from 1.32 to 2.18) and the risk of edema (Odds ratio from 2.26 to 2.18).[1] There is low strength evidence that there is no increased all-cause mortality or cardiovascular mortality with pioglitazone. There is also moderate strength evidence that the risk of fractures is increased among patients exposed to TZDs (OR 1.45, 95% CI 1.18 to 1.79, from meta-analysis of 10 randomized controlled trials with 13,715 patients). This risk appears to be increased among women compared to men.[1]

<u>Agency for Healthcare Research and Quality</u>

The Agency for Healthcare Research and Quality (AHRQ) published an update to the comparative effectiveness review on Oral Diabetes Medications for Adults with Type 2 Diabetes in March 2011 to summarize the benefits and harms of medications as monotherapy and in combination, for the treatment of adults with type 2 diabetes.[2] There was low or insufficient evidence for all comparisons when focusing on long term clinical outcomes of all-cause mortality, cardiovascular disease, nephropathy, and neuropathy, as most studies were generally of short duration and had few long-term events. Metformin was associated with slightly lower all-cause mortality and cardiovascular disease mortality than the sulfonylureas. There was moderate strength evidence from two larger trials that pioglitazone is better than metformin at reducing short-term nephropathy. In both trials, the urinary

albumin-to-creatinine ratio declined in patients receiving pioglitazone by 15 percent and 19 percent, respectively but remained unchanged in patients with metformin with statistically significant differences between groups in both trials.[2]

Intermediate outcomes were the most frequently evaluated outcomes. Most diabetes medications reduced HbA1c to a similar degree, by about 1 absolute percentage point (moderate to high strength of evidence). There was moderate strength of evidence that metformin was more efficacious than the DPP-4 inhibitors in lowering HbA1c (by about 0.4 absolute percentage points, 95% CI -0.5% to -0.2%) based on three randomized controlled trials.[2] There was high strength of evidence that TZD's and sulfonylureas had a more unfavorable effect on weight compared to metformin (mean difference of -2.6kg; 95% CI -4.1 kg to -1.2 kg, mean difference of -2.7kg; 95% CI -3.5 kg to -1.9 kg for TZDs and sulfonylureas, respectively).[2] Three RCTs comparing rosiglitazone directly with pioglitazone showed a greater increase in LDL with rosiglitazone, (pooled between-group difference of 14.3 mg/dL, 95 percent CI 5.8 mg/dL to 22.7 mg/dL) and that pioglitazone increased HDL more than rosiglitazone (pooled between group difference of -2.3 mg/dL, 95 percent CI -3.5 mg/dL to -1.2 mg/dL).[2] All comparisons with the GLP-1 agonists were based on insufficient or low evidence. Comparisons of two-drug combinations showed little to no difference in HbA1c reduction, but some combinations increased risk for hypoglycemia and other adverse events.

Metformin was associated with high risk of gastrointestinal side effects than all other medications and there was high strength of evidence that TZDs were associated with a 1.5-fold higher risk of bone fractures than was with metformin alone or in combination with a sulfonylurea and women were taking rosiglitazone were at higher risk for bone fractures than men.[2] No other conclusions regarding differences in subgroups of patients could be made. Sulfonylureas had a fourfold higher risk of mild/moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a fivefold increased risk compared with metformin plus TZDs. TZDs also had an increased risk of congestive heart failure relative to sulfonylureas and bone fractures relative to metformin.

Other

Another meta-analysis was performed that included 43 randomized (n=19,101) controlled trials lasting at least 12 weeks involving DPP-4 inhibitors.[3] Of participants evaluated for the primary endpoint, 10,467 were treated with a DPP-4 inhibitor and 8,634 treated with placebo or a comparator drug. DPP-4 inhibitors showed a statistically significant reduction in HbA1c compared to placebo and approximately 40 percent of participants achieved the HbA1c goal of < 7 percent, which was associated with weight neutrality and no greater hypoglycemia. Baseline HbA1c was the best predictor for achievement of HbA1C target ($p<0.001$).[3]

New Trials:

A total of 233 citations resulted from the original Medline literature search. After title and abstract review, 43 citations resulted and after further review for inclusion of population and outcomes, eleven potentially relevant clinical trials were identified (Appendix 1). Four trials evaluated linagliptin and are included in the individual drug monograph. The table below briefly describes the identified clinical trials.

Study	Comparison	Population	Primary Outcome	Results
Yang, 2011[4] R, PC, DB	saxagliptin 5mg + metformin vs. placebo + metformin (n = 570).	Asian patients with type 2 diabetes with inadequate control on metformin alone	HbA1c change from baseline to week 24	Adjusted mean decrease in HbA1c: Sax/Met: -0.78% Pla/met: -0.37% P<0.0052
Nowicki, 2011[5] RCT, DB	Saxagliptin 2.5 mg vs. placebo added to other	Type 2 diabetes and renal impairment	Change in HbA1c and fasting plasma glucose	mean decrease in HbA1c: Sax: -1.08%; 95% CI (-1.37 to -0.8%) Pla: -0.36%%; 95% CI (-0.63 to -0.08%)

	antidiabetic drugs (n=170)		(FPG) at week 52	Diff -0.73%; 95% CI -1.11% to -0.34% P<0.001 Reductions similar in patients with ESRD	
Borges, 2011[6] RCT, PG, DB	Avandamet (AVM) vs. metformin N=688	Type 2 diabetes, drug naive	Two hour pain relief	<u>Reduction in HbA1c:</u> AVM: Met: P<0.0001	<u>Reduction in FPG:</u> AVM: Met: P<0.001
Goke, 2010[7] RCT	saxagliptin 5 mg or glipizide from 5 to 20 mg x 52 weeks.	Type 2 diabetes with inadequate control on metformin alone N=858	Change from baseline in HbA1c; Non-inferiority	<u>Adjusted mean decrease in HbA1c:</u> Sax/Met: -0.74% Glp/Met: -0.80% Diff 0.06% (95% CI -0.05% to 0.16) *Discontinuation rates due to adverse events similar between groups (~4%)	
Reasner, 2010[8] RCT, DB	Sitagliptin/ Metformin 50/500 bid vs. metformin 500 bid (N=1250)	Type 2 diabetes, drug naïve Mean baseline HbA1c 9.9%	Mean reduction in HbA1c at week 18	<u>Mean change in HbA1c</u> Sita/met: -2.4% Met: -1.8% p < 0.001	
Hollander, 2011[9] DB, PC	Saxagliptin (SX) 2.5mg vs. SX 5mg vs. placebo added to TZD	Type 2 diabetes with inadequate control on TZD monotherapy N=565	Mean reduction in HbA1c at week 18 at 76 weeks	<u>Mean change in HbA1c</u> SX 2.5mg: -0.59% SX 5 mg: -1.09% PLA: -0.2% P=0.0019 for SX 2.5mg vs. placebo p < 0.0001 for SX 5 mg vs. placebo *Only 63.8% of patients completed the study	
Buse, 2011[10] RCT, DB, PC	Exenatide vs. placebo	Type 2 diabetes, HbA1c 7.1 to 10.5% on insulin glargine alone or in combination with metformin and/or pioglitazone	Mean reduction in HbA1c at week 30 weeks	<u>Mean change in HbA1c</u> Exen: -1.74% Pla: -1.04% P<0.001 <u>Achieved HbA1c <7.0%</u> Exen: 60% Pla: 35% * Thirteen exenatide patients and one placebo patient discontinued due to adverse events (p<0.010).	

New drugs:

Linagliptin (Tradjenta) is a dipeptidyl peptidase-4 (DPP-4) Inhibitor FDA approved in 2011 and used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. See full drug monograph for further information and details (http://pharmacy.oregonstate.edu/drug_policy/meetings).

New Formulations:

Exenatide extended–release (Bydureon), once weekly injection (EQW) is a glucagon-like peptide-1 (GLP-1) agonist approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. EQW is an extended release formulation of the twice daily injectable product exenatide (Byetta) which was FDA approved in 2005. See full drug summary for further information and details (http://pharmacy.oregonstate.edu/drug_policy/meetings).

New Combination Products:

Sitagliptin/simvastatin (Juvisync) is a new combination product that combines a DPP-4 Inhibitor with the cholesterol lowering agent, simvastatin. It was FDA approved in October 2011 for patients in whom treatment with

both sitagliptin and simvastatin is appropriate.[11] Sitagliptin/simvastatin was approved based on studies demonstrating its bioequivalence to the single agents administered together. In a randomized open-label, crossover study (n=29), steady-state sitagliptin did not alter the pharmacokinetics of a single dose of simvastatin. This study did not specifically evaluate the effects of simvastatin on sitagliptin pharmacokinetics, although none is expected. It has not been studied in patients with a history of pancreatitis and use is not recommended in patients with moderate or severe renal impairment or end stage renal disease (ESRD) since doses appropriate for these patients are not available in this combination product.[11]

Linagliptan/metformin (Jentadueto) is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product approved in January, 2012 and indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.[12] It is not indicated for the treatment of type 1 diabetes or diabetic ketoacidosis. Jentadueto has not been studied with insulin. There have been no clinical efficacy studies performed with linagliptin/metformin (Jentadueto). However, coadministration of the single entity medications has been studied in type 2 diabetes mellitus patients who were not well controlled in their diet and exercise and in combination with a sulfonylurea.[12] The bioequivalence of Jentadueto to linagliptin and metformin administered together as single entities was demonstrated in healthy subjects. There are currently three additional biguanide/DDP-4 combination products available.

New FDA safety alerts:
In September 2010, the FDA restricted access for rosiglitazone and combination products that contain rosiglitazone due to an increased risk of cardiovascular adverse events as a result of review of cardiovascular safety data from the long-term clinical study, Rosiglitazone Evaluted for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD).[13]

In May 2011, the FDA outlined the risk evaluation and mitigation strategy (REMS), which applies to all rosiglitazone-containing products.[14] Under the REMS, healthcare providers and patients must enroll in a special program in order to prescribe and receive these drugs. The REMS, called the Avandia-Rosiglitazone Medicines Access Program, limits the use of rosiglitazone medicines to patients already being successfully treated with these medicines and patients whose blood sugar cannot be controlled with other anti-diabetic medicines and who, after consulting with their healthcare provider, do not wish to use pioglitazone-containing medicines. As of November 18, 2011, rosiglitazone medicines are no longer available through retail pharmacies.

In June 2011, the FDA issued a safety announcement that the use of pioglitazone (Actos) for more than one year may be associated with an increased risk of bladder cancer based on two three-year trials demonstrating increased reports of bladder cancer in patients taking pioglitazone compared to placebo or glyburide (44% vs. 14%).[15] Consequently, pioglitazone should not be used in patients with active bladder cancer and should be used with caution in those with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.

In 2011, the REMS requirement for exenatide, sitagliptin and sitagliptin/metformin were removed by the FDA.

Recommendations:
1) No further review or research needed.
2) Maintain new combination products sitaglipin/simvastatin and linagliptin/metformin as non-preferred agents on the PDL.

References:

1. Jonas DD, Van Scoyoc EE, Gerrald KK, et al. Drug Class Review: Newer Diabetes Medications, TZDs, and Combinations. 2011. Available at: http://derp.ohsu.edu/about/final-document-display.cfm.

2. Bennett W, Wilson L, Bolen S, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 27. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 11-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality. 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

3. Esposito K, Cozzolino D, Bellastella G, et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2011;13(7):594–603.

4. Yang W, Pan CY, Tou C, Zhao J, Gause-Nilsson I. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. *Diabetes Res. Clin. Pract.* 2011;94(2):217–224.

5. Nowicki M, Rychlik I, Haller H, et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. *Int. J. Clin. Pract.* 2011;65(12):1230–1239.

6. Borges JLC, Bilezikian JP, Jones-Leone AR, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naïve type 2 diabetes mellitus patients. *Diabetes Obes Metab*. 2011;13(11):1036–1046.

7. Göke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. *Int. J. Clin. Pract.* 2010;64(12):1619–1631.

8. Reasner C, Olansky L, Seck TL, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2011;13(7):644–652.

9. Hollander PL, Li J, Frederich R, Allen E, Chen R. Safety and efficacy of saxagliptin added to thiazolidinedione over 76 weeks in patients with type 2 diabetes mellitus. *Diab Vasc Dis Res*. 2011;8(2):125–135.

10. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann. Intern. Med.* 2011;154(2):103–112.

11. Juvisync. Prescribing Information. Merck & Co., Inc. Available at: http://www.merck.com/product/usa/pi_circulars/j/juvisync/juvisync_pi.pdf.

12. Jentadueto prescribing information. Ridgefield, CT; Boehringer Ingelheim Pharmaeuticals.

13. FDA Drug Safety Communication. Ongoing review of Avandia (rosiglitazone) and cardiovascular safety. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm201418.htm.

14. FDA Drug Safety Communication. Updated Risk Evaluation and Migitation Strategy (REMS) to Restrict access to rosiglitazone-containing medicines ncluding Avandia, Avandamet, and Avandaryl. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm.

15. FDA Drug Safety Communication. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm.

Appendix 1: New Trials

1. Yang W, Pan CY, Tou C, Zhao J, Gause-Nilsson I. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract. 2011 Nov;94(2):217-24. Epub 2011 Aug 26.

To assess efficacy and safety of saxagliptin added to metformin versus placebo plus metformin in Asian patients with type 2 diabetes mellitus (T2DM) and inadequate glycemic control on metformin alone. METHODS: Adults (HbA(1c) 7.0-10.0%, on stable metformin ≥ 1500 mg/day) were randomized 1:1 to saxagliptin 5mg daily plus metformin (n = 283) or placebo plus metformin (n = 287). The primary end point was HbA(1c) change from baseline to Week 24. RESULTS: Saxagliptin plus metformin provided significant adjusted mean decreases versus placebo plus metformin ($p \leq 0.0052$) in HbA(1c) (-0.78% versus -0.37%), fasting plasma glucose (-1.14 mmol/L versus -0.58 mmol/L), and postprandial glucose area under the curve from 0 to 180 min (-315 mmol min/L versus -160 mmol min/L). Significantly more saxagliptin-treated patients achieved a therapeutic glycemic response (HbA(1c)<7.0%) (46.5% versus 30.5%; $p = 0.0001$). The proportion of patients experiencing adverse events (excluding hypoglycemia) was similar for saxagliptin plus metformin (42.8%) versus placebo plus metformin (40.8%). Hypoglycemic events were reported in 1.4% of patients in each group. CONCLUSION: Saxagliptin added to metformin significantly improved glycemic control and was well tolerated in Asian patients with T2DM who had inadequate glycemic control with metformin and diet and lifestyle modification.

2. Nowicki M, Rychlik I, Haller H, Warren M, Suchower L, Gause-Nilsson I, Schützer KM. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. Int J Clin Pract. 2011 Dec;65(12):1230-9. doi: 10.1111/j.1742-1241.2011.02812.x. Epub 2011 Oct 7.

OBJECTIVE: Therapeutic options are limited for diabetes patients with renal disease. This report presents 52-week results from a study assessing the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus (T2DM) and renal impairment. DESIGN: Double-blind study in patients stratified by baseline renal impairment (moderate, severe or end-stage renal disease [ESRD] on haemodialysis) randomised to saxagliptin 2.5 mg once daily or placebo added to other antidiabetic drugs in use at baseline, including insulin.PATIENTS: A total of 170 adults with glycated haemoglobin (HbA(1c)) 7-11% and creatinine clearance < 50 ml/min or ESRD were randomised and treated. Absolute changes in HbA(1c) and fasting plasma glucose (FPG) from baseline to week 52 were evaluated using analysis of covariance (ANCOVA) with last observation carried forward. Repeated-measures analyses were also performed. RESULTS: Adjusted mean decrease in HbA(1c) was greater with saxagliptin than placebo (difference, -0.73%, $p < 0.001$ [ANCOVA]). Reductions in adjusted mean HbA(1c) were numerically greater with saxagliptin than placebo in patients with renal impairment rated as moderate (-0.94% vs. 0.19% respectively) or severe (-0.81% vs. -0.49%), but similar to placebo for those with ESRD (-1.13% vs. -0.99%). Reductions in adjusted mean FPG were numerically greater with saxagliptin in patients with moderate or severe renal impairment. Saxagliptin was generally well tolerated; similar proportions of patients in the saxagliptin and placebo groups reported hypoglycaemic events (28% and 29% respectively). CONCLUSIONS: Saxagliptin 2.5 mg once daily offers sustained efficacy and good tolerability for patients with T2DM and renal impairment

3. Borges JL, Bilezikian JP, Jones-Leone AR, Acusta AP, Ambery PD, Nino AJ, Grosse M, Fitzpatrick LA, Cobitz AR. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naïve type 2 diabetes mellitus patients. Diabetes Obes Metab. 2011 Nov;13(11):1036-46. doi: 10.1111/j.1463-1326.2011.01461.x.

The purpose of this study was to evaluate if superior glycaemic control could be achieved with Avandamet® (rosiglitazone/metformin/AVM) compared with metformin (MET) monotherapy, and if glycaemic effects attained with AVM are durable over 18 months of treatment. Bone mineral density (BMD) and bone biomarkers were evaluated in a subgroup of patients. METHODS: This was a phase IV, randomized, double-blind, multi-centre study in 688, drug naïve, male and female patients who had an established clinical diagnosis of type 2 diabetes mellitus (T2DM). Patients were randomized in a 1 : 1 ratio either to AVM or MET.RESULTS: As initial therapy in patients with T2DM, AVM was superior to MET in achieving statistically significant reductions in glycated haemoglobin (HbA1c) ($p < 0.0001$) and fasting plasma glucose (FPG) ($p < 0.001$), with more patients reaching recommended HbA1c and FPG targets for intensive glycaemic control. The glycaemic effects attained with AVM compared to MET monotherapy were durable over 18 months of treatment. In the bone substudy, AVM was associated with a significantly lower BMD in comparison with MET at week 80 in the lumbar spine and total hip ($p < 0.0012$ and $p = 0.0005$, respectively). Between-treatment differences were not statistically significant for distal one-third of radius BMD, femoral neck BMD or total BMD. CONCLUSION: Superior glycaemic control was achieved with AVM compared with MET monotherapy. The superior glycaemic effects were shown to be durable over 18 months of treatment. AVM was associated with a significantly reduced BMD in comparison with MET at week 80 in the lumbar spine and total hip.

4. Göke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I; D1680C00001 Investigators. **Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial.** Int J Clin Pract. 2010 Nov;64(12):1619-31. doi: 10.1111/j.1742-1241.2010.02510.x. Epub 2010 Sep 16.

Purpose: To assess the efficacy and safety of saxagliptin vs. glipizide as add-on therapy to metformin in patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone. METHODS: A total of 858 patients [age ≥ 18 years; glycated haemoglobin (HbA(1c)) > 6.5 - 10.0%; on stable metformin doses ≥ 1500 mg/day] were randomised 1 : 1 to saxagliptin 5 mg/day or glipizide up-titrated as needed from 5 to 20 mg/day for 52 weeks. The primary objective was to assess if the change from baseline HbA(1c) achieved with saxagliptin plus metformin was non-inferior to glipizide plus metformin. RESULTS: The per-protocol analysis demonstrated non-inferiority of saxagliptin vs. glipizide; adjusted mean changes from baseline HbA(1c) were -0.74% vs. -0.80%, respectively; the between-group difference was 0.06% (95% CI, -0.05% to 0.16%). Treatment with saxagliptin vs. glipizide was associated with a significantly smaller proportion of patients with hypoglycaemic events (3.0% vs. 36.3%; $p < 0.0001$) and a divergent impact on body weight (adjusted mean change from baseline -1.1 kg with saxagliptin vs. 1.1 kg with glipizide; $p < 0.0001$). There was a significantly smaller rise in HbA(1c) (%/week) from week 24 to 52 with saxagliptin vs. glipizide (0.001% vs. 0.004%; $p = 0.04$) indicating a sustained glycaemic effect beyond week 24. Excluding hypoglycaemic events, the proportion of patients experiencing adverse events (AEs) was similar (60.0% saxagliptin vs. 56.7% glipizide); treatment-related AEs were less common with saxagliptin vs. glipizide (9.8% vs. 31.2%), attributable to the higher frequency of hypoglycaemia in glipizide patients. Discontinuation rates resulting from AEs were similar (~4%). CONCLUSION: Saxagliptin plus metformin was well tolerated, provided a sustained HbA(1c) reduction over 52 weeks, and was non-inferior to glipizide plus metformin, with reduced body weight and a significantly lower risk of hypoglycaemia.

5. Reasner C, Olansky L, Seck TL, Williams-Herman DE, Chen M, Terranella L, Johnson-Levonas AO, Kaufman KD, Goldstein BJ. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011 Jul;13(7):644-52. doi: 10.1111/j.1463-1326.2011.01390.x.

This study was conducted to compare the glycaemic efficacy and safety of initial combination therapy with the fixed-dose combination of sitagliptin and metformin versus metformin monotherapy in drug-naive patients with type 2 diabetes. METHODS: This double-blind study (18-week Phase A and 26-week Phase B) randomized 1250 drug-naïve patients with type 2 diabetes [mean baseline haemoglobin A1c (HbA1c) 9.9%] to sitagliptin/metformin 50/500 mg bid or metformin 500 mg bid (uptitrated over 4 weeks to achieve maximum doses of sitagliptin/metformin 50/1000 mg bid or metformin 1000 bid). Results of the primary efficacy endpoint (mean HbA1c reductions from baseline at the end of Phase A) are reported herein. RESULTS: At week 18, mean change from baseline HbA1c was -2.4% for sitagliptin/metformin FDC and -1.8% for metformin monotherapy ($p < 0.001$); more patients treated with sitagliptin/metformin FDC had an HbA1c value <7% ($p < 0.001$) versus metformin monotherapy. Changes in fasting plasma glucose were significantly greater with sitagliptin/metformin FDC (-3.8 mmol/l) versus metformin monotherapy (-3.0 mmol/l; $p < 0.001$). Homeostasis model assessment of β-cell function (HOMA-β) and fasting proinsulin/insulin ratio were significantly improved with sitagliptin/metformin FDC versus metformin monotherapy. Baseline body weight was reduced by 1.6 kg in each group. Both treatments were generally well tolerated with a low and similar incidence of hypoglycaemia. Abdominal pain (1.1 and 3.9%; $p = 0.002$) and diarrhoea (12.0 and 16.6%; $p = 0.021$) occurred significantly less with sitagliptin/metformin FDC versus metformin monotherapy; the incidence of nausea and vomiting was similar in both groups. CONCLUSION: Compared with metformin monotherapy, initial treatment with sitagliptin/metformin FDC provided superior glycaemic improvement with a similar degree of weight loss and lower incidences of abdominal pain and diarrhoea

6. Hollander PL, Li J, Frederich R, Allen E, Chen R; CV181013 Investigators. Safety and efficacy of saxagliptin added to thiazolidinedione over 76 weeks in patients with type 2 diabetes mellitus. Diab Vasc Dis Res. 2011 Apr;8(2):125-35.

To assess the long-term efficacy and safety of saxagliptin in patients with type 2 diabetes mellitus inadequately controlled with thiazolidinedione monotherapy, 565 patients were randomised to saxagliptin (2.5 mg or 5 mg) or placebo added to thiazolidinedione over 76 weeks (24-week short-term + 52-week long-term extension period) in this phase 3, double-blind, placebo-controlled trial; 360 patients completed the study. At 76 weeks, adjusted mean changes from baseline HbA(1C) (repeated measures model; 95% CI) for saxagliptin 2.5 mg, 5 mg, and placebo were -0.59% (-0.75, -0.43), -1.09% (-1.26, -0.93), and -0.20% (-0.39, -0.01), respectively (post hoc and nominal p=0.0019 and p<0.0001 for saxagliptin 2.5 mg and 5 mg vs. placebo, respectively). Adverse event frequency was similar between groups. Confirmed hypoglycaemic events were 1.0% and 0% vs. 0.5% for saxagliptin 2.5 mg and 5 mg vs. placebo, respectively. Results should be interpreted with caution given the proportion of patients who discontinued or required glycaemic rescue therapy during the 76-week course of study. Saxagliptin added to thiazolidinedione provided sustained incremental efficacy vs. placebo with little hypoglycaemia for up to 76 weeks and was generally well tolerated.

7. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin–treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011;154

Objective: To test whether twice-daily exenatide injections reduce HbA_1(c) levels more than placebo in people receiving insulin glargine. DESIGN: Parallel, randomized, placebo-controlled trial, blocked and stratified by HbA_1(c) level at site,performed from October 2008 to January 2010. Participants, investigators, and personnel conducting the study were masked to treatment assignments. (ClinicalTrials.gov registration number: NCT00765817) Adults with type 2 diabetes and an HbA_1(c) level of 7.1% to 10.5% who were receiving insulin glargine alone or in combination with metformin or pioglitazone (or both agents). Assignment by a centralized, computer-generated, random-sequence interactive voice-response system to exenatide, 10 µg twice daily, or placebo for 30 weeks. The primary outcome was change in HbA_1(c) level. Secondary outcomes included the percentage of participants with HbA_1(c) values of 7.0% or less and 6.5% or less, 7-point self-monitored glucose profiles, body weight, waist circumference, insulin dose, hypoglycemia, and adverse events. RESULTS: 112 of 138 exenatide recipients and 101 of 123 placebo recipients completed the study.

The HbA_1(c) level decreased by 1.74% with exenatide and 1.04% with placebo (between-group difference, -0.69% [95% CI, -0.93% to -0.46%]; P < 0.001). Weight decreased by 1.8 kg with exenatide and increased by 1.0 kg with placebo (between-group difference, -2.7 kg [CI, -3.7 to -1.7]). Average increases in insulin dosage with exenatide and placebo were 13 U/d and 20 U/d. The estimated rate of minor hypoglycemia was similar between groups. Thirteen exenatide recipients and 1 placebo recipient discontinued the study because of adverse events (P < 0.010); rates of nausea (41% vs. 8%), diarrhea (18% vs. 8%), vomiting (18% vs. 4%), headache (14% vs. 4%), and constipation (10% vs. 2%) were higher with exenatide than with placebo. CONCLUSION: Adding twice-daily exenatide injections improved glycemic control without increased hypoglycemia or weight gain in participants with uncontrolled type 2 diabetes who were receiving insulin glargine treatment. Adverse events of exenatide included nausea, diarrhea, vomiting, headache, and constipation.