State and Public School Life and Health Insurance Board Clinical and Fiscal Drug Utilization and Evaluation Committee
Minutes
February 7, 2011

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday, February 7, 2011 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

Members present:
Dr. William Golden
Matthew Hadley
Kat Neill
Larry Dickerson/Proxy
Dr. Hank Simmons
Mark McGrew

Members absent:
Robert Watson
Dr. Joe Stallings

Jason Lee, Executive Director, Employee Benefits Division of DFA.

OTHERS PRESENT
Jill Johnson, UAMS College of Pharmacy/EBRx; George Platt, Stella Greene, Shannon Roberts, Michelle Hazelett, Lori Eden, Amy Tustison, Latryce Taylor, Sherry Bryant; Cathy Harris, EBD; Pam Lawrence, AHH; Barbara Melugin, Health Advantage; Dwight Davis; Bridget Johnson, Pfizer, Wayne Whitley, Ronda Walthall, Colleen Adkins, UAMS; Julie Ryba; Informed Rx; Bryan Meldrum, Novasys; Frances Baumen, Novo Nordisk; Treg Long, ACR; American Cancer Society; Shonda Rocke, InformedRx; Warren Tyes, Merck; Wayne Whitley, AHTD

CALL TO ORDER
Meeting was called to order by Dr. Golden.

APPROVAL OF MINUTES
The motion was made by Dr Golden to approve the October 4, 2010 minutes. Minutes were approved by consensus.

CLASS REVIEW –ORAL TYPE II DIABETIC MEDICATIONS *by Jill Johnson*

Johnson presented evidence information for diabetes drugs for type 2 Diabetes Mellitus. Drugs included in the review:

- Pramlintide Amylin agonist
- Sitagliptin DPP-4 Inhibitor
- Saxagliptin DPP-4 Inhibitor
- Exenatide GLP-1 Analogs (Incretin mimetics),
- Liraglutide GLP-1 Analogs (Incretin mimetics),
- Pioglitazone TZD,
- Rosiglitazone TZD

Combination drugs included in the review were Rosiglitazone + Metformin, Pioglitazone + Metformin, Rosiglitazone + Glimepiride, Pioglitazone + Glimepiride and Sitagliptin + Metformin.

The committee requested information on plan costs and member utilizations for diabetes drugs in 2010.

a. TZD's-Thiazolidinediones (Rosiglitazone, Pioglitazone), (Avandia, Avandaryl, Avandamet, Actos, ActoplusMet)

Recommendation: Restrict the access to Rosiglitazone. Stop covering rosiglitazone (Avandia, Avandamet and Avandaryl) effective July 1, 2011. No Pioglitazone (Actos) without metformin (at a near maximum daily dose-1000mg daily) or a contraindication to metformin.

The committee decided by consensus to approve.

b. Exenatide (Byetta), Liraglutide (Victoza)

Recommendation: Option 1 – Discontinue covering Exenatide (Byetta), Liraglutide (Victoza) based on lack of outcomes evidence. Option 2- Deny if any insulin claim in past 30 days. Continue no monotherapy access for exenatide or liraglutide. PA all prescription. Criteria requires a current metformin fill for 90 of the past 120 days goal A1c, and then require inpatients who cannot tolerate metformin, the use of a sulfonylurea or the use of pioglitazone, unless contraindicated due to HF, edema, or fracture risk.

The committee by consensus was interested in option 2 but decided to present both options to the Board for consideration.

c. Sitagliptin (Janumet) Saxagliptin, (Onglyza, Kombiglyze XR)

Recommendation: Option 1- Discontinue covering Sitagliptin (Janumet) Saxagliptin, (Onglyza, Kombiglyze XR) based on lack of outcomes evidence. Option 2- Deny if any insulin claim in past 30 days. Continue no monotherapy access for sitagliptin or saxagliptin. PA all prescription, criteria requires a current metformin fill for 90 days of the past 120 days at the maximum or near maximum dose failure to reach goal A1C, and require the use of concomitant sulfonylurea and/or pioglitazone in patients who have not reached their HbA1C goal with metformin monotherapy, unless contraindicated due to HF, edema or fracture risk

The committee by consensus was interested in option 2 but decided to present both options to the Board for consideration.

d. Pramlintide (Symlin, SymlinPen)

Recommendation: Exclude

The committee decided by consensus to exclude.

MAXALT *by Jill Johnson*

Johnson reported the packaging has changed from 12 tablets to 18 tablets per package. Maxalt Generic Name: rizatriptan (RYE za TRIP tan) is used to treat migraine headaches. The current polity is12 tablets per 31 days.

Recommendation – Allow for 18 tablets per 45 days.

The committee decided by consensus to approve. The committee agreed to allow EBD to manage the prescription and co-pay adjustments and to inform the committee if needed.

FIRST REVIEW MEDICATIONS – NEW DRUGS Oct-Dec 2010 by Jill Johnson

Drug Name	Tier Status
GILENYA CAP 0.5MG	**T3 w PA. Specialty**

GILENYA (fingolimod) is the first oral therapy approved for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Drug Name	Tier Status
PRADAXA CAP 75, 150MG	**T3 w/ PA QL/2 a day per 31 days**

PRADAXA is FDA-approved for the prevention of stroke and blood clots in patients with abnormal heart rhythm (atrial fibrillation).

The committee decided by consensus to approve.

Meeting Adjourned.

The following pages were made available to attendees of the meeting

AGENDA

State and Public School Life and Health Insurance Board

Drug Utilization and Evaluation Committee

EBD Board Room - 501 Building - 5th Floor

February 7, 2011
1:00 p.m.

1. **Call to Order** ..... *Dr. William Golden, Chair*
2. **Approval of Minutes** ..... *Dr. William Golden, Chair*
3. **Class Review – Oral Type II Diabetic Medication** .... *Jill Johnson, UAMS*
4. **Maxalt** ..... Jill Johnson, UAMS
5. **First Review Medications** ..... *Jill Johnson, UAMS*
6. **Director's Report** ..... *Jason Lee, Executive Director*

Next Meeting
April 4, 2011

Jill T. Johnson, Pharm.D., BCPS
Associate Professor, UAMS College of Pharmacy
January 10, 2011

Review of Newer Diabetes Drugs for Type 2 Diabetes Mellitus

1

Drugs included in the review

Drug Class	Trade name How administered	Labeled indications	Dosing
Pramlintide Amylin agonist	Symlin Injectable	T1DM,T2DM, Adjunct w/ insulin	T1: 15-60mcg w/ meals, T2: 60-12 mcg w/ meals
Sitagliptin DPP-4 Inhibitor	Januvia Oral	T2DM; monotherapy or in combo w/ any antihyperglycemic	100mg once daily, 25-50mg if renal dysfxn
Saxagliptin DPP-4 Inhibitor	Onglyza Oral	T2DM; monotherapy or in combo w/ any antihyperglycemic	2.5-5mg once daily, 2.5mg if renal dysfxn
Exenatide GLP-1 Analogs (Incretin mimetics)	Byetta Injectable	T2DM; not recommended w/ insulin	5-10 mcg twice daily prior to meals
Liraglutide GLP-1 Analogs (Incretin mimetics)	Victoza Injectable	T2DM; not recommended w/ insulin	0.6-1.8mg once daily
Pioglitazone TZD	Actos Oral	T2DM, monotherapy or in combination w/ SU, Met, Insulin	15-45mg once daily
Rosiglitazone TZD	Avandia Oral	T2DM, monotherapy or in combination w/ SU, Met, Insulin	4-8mg once daily

2

Combinations included in this review

Combination drugs	Trade Names	Dosing
Rosiglitazone + Metformin	Avandamet	2mg/500mg, 2/1000, 4/500, 4/1000
Pioglitazone + Metformin	Actoplus Met	15mg/500mg, 15/850
Rosiglitazone + Glimepiride	Avandaryl	4mg/1mg, 4/2, 4/4, 8/2, 8/4
Pioglitazone + Glimepiride	Duetact	30mg/2mg, 30/4
Sitagliptin + Metformin	Janumet	50mg/500mg,50/1000

DERP, 2010.

3

Background: Evidence SUGGESTING tight glucose control may benefit T2DM patients

- UKPDS-33
  - In 1977 UK Prospective Diabetes Study was designed to establish whether, in patients with T2DM, intensive blood-glucose control reduced the risk of macrovascular or microvascular complications, and whether any particular therapy was advantageous.
  - Results:
    - Intensive glucose control by either SUs or insulin substantially decreased the risk of MICROvascular but not MACROvascular disease in pts with T2DM. No individual drug had an adverse effect on CV outcomes. All intensive treatments increased hypoglycemia.

UKPDS-33. Lancet. 1998;352:837-53.

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UKPDS-33

- Intensive = FPG < 108 was the target.
  - SUs were chlorpropamide 100-500mg daily, glibenclamide 2.5-20mg, or glipizide 2.5-40mg
  - Insulin
- Conventional = FPG <270 without symptoms of hyperglycemia was the aim.
  - received dietary advice

UKPDS-33, pg 840.

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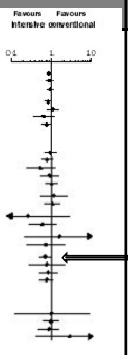
UKPDS-33

	Patients with clinical endpoints		Absolute risk: events per 1000 patient-years		Log-rank p	RR for intensive policy (CI)
	Intensive (n=2729)	Conventional (n=1138)	Intensive	Conventional		
AGGREGATE ENDPOINT						
Any diabetes-related endpoint	963	438	40·9	46·0	0·029	0·88 (0·79–0·99)
Diabetes-related death	252	142	10·4	15·5	0·34	0·90 (0·73–1·11)
All-cause mortality	483	213	17·9	18·9	0·44	0·94 (0·80–1·10)
Myocardial infarction	367	186	14·7	17·6	0·052	0·94 (0·71–1·00)
Stroke	148	55	5·6	5·0	0·52	1·11 (0·82–1·51)
Amputation or death from PVD	29	18	1·1	1·6	0·15	0·65 (0·36–1·18)
Microvascular	225	121	8·6	11·4	0·0059	0·75 (0·60–0·93)
SINGLE ENDPOINTS						
Fatal myocardial infarction	207	90	7·6	8·0	0·63	0·94 (0·66–1·30)
Non-fatal myocardial infarction	197	101	7·5	9·5	0·087	0·79 (0·59–1·09)
Fatal: sudden death	24	18	0·9	1·6	0·047	0·54 (0·24–1·21)
Heart failure	90	36	3·5	3·3	0·60	0·91 (0·54–1·52)
Angina	177	72	6·8	6·7	0·91	1·02 (0·71–1·46)
Fatal stroke	43	15	1·6	1·3	0·60	1·17 (0·54–2·54)
Non-fatal stroke	114	44	4·3	4·0	0·72	1·07 (0·68–1·68)
Death from peripheral vascular disease	2	3	0·1	0·3	0·12	0·26 (0·03–2·77)
Amputation	27	18	1·0	1·6	0·066	0·61 (0·28–1·33)
Death from renal disease	8	2	0·3	0·2	0·59	1·63 (0·21–12·49)
Renal failure	16	9	0·6	0·8	0·45	0·73 (0·25–2·14)
Retinal photocoagulation	207	117	7·9	11·0	0·0091	0·71 (0·53–0·96)
Vitreous haemorrhage	15	10	0·7	0·9	0·81	0·77 (0·28–2·11)
Blind in one eye	76	38	3·9	3·5	0·39	0·94 (0·61–1·40)
Cataract extraction	149	80	5·8	7·4	0·046	0·76 (0·55–1·06)
Death from hyperglycaemia	0	1	0	0·1		
Death from hypoglycaemia	1	0	0	0		
Fatal accident	5	2	0·2	0·2	0·99	1·01 (0·12–8·70)
Death from cancer	120	50	4·4	4·4	0·92	0·98 (0·64–1·52)
Death from any other specific cause	65	30	2·4	2·7	0·57	0·88 (0·50–1·56)
Death from unknown cause	14	2	0·5	0·2	0·14	2·88 (0·41–20·19)



RR=relative risk. 95% CI for aggregate and 99% CI for single endpoints. PVD=peripheral vascular disease.

UKPDS-33. Lancet. 1998;352:837-53.

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Background: Observational Evidence; association, no causation established

- White hair and mortality rates may be highly correlated, but that does not make white hair a cause of high mortality.
- And making a policy to allow access to hair color may not fix the underlying problem.

7

Background: Observational Evidence; association, no causation established

- UKPDS-35
  - Prospective observational study
  - N=3642 patients
  - Results SUGGEST for each 1% reduction in updated mean HbA1C was associated with reductions in risk of:
    - 21% for "any end point related to DM" (95%CI 17-24%)
    - 21% for deaths related to diabetes (95%CI 15-27%)
    - 14% for MI (8-21%)
    - 37% for microvascular complications (33-41%)

UKPDS 35. Stratton IM, et al. BMJ. 2000;321:405-12.

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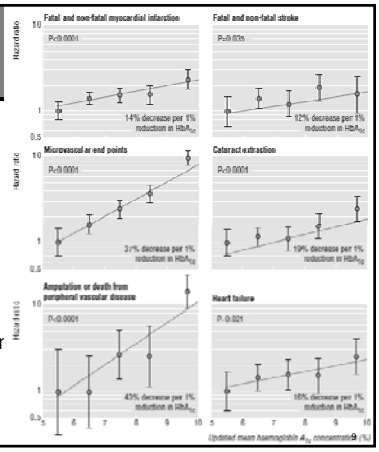
Background (continued)

- UKPDS-35
  - The rate of increase of risk for microvascular disease with hyperglycemia is greater than that for macrovascular disease.



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Background: Observational Evidence w/o intervention

- Effects of diabetes and level of glycemia on all-cause and CV mortality
- Prospective, observational cohort study
- N=4875 (65% Mexican-American)
- Results:
  - The RR for all-cause mortality, CVD were each 4.9 fold higher for pts w/ fasting glucose of <207 compared to those <144.
  - **Comment: HDL, TGs, & duration of DM each showed a statistical difference at baseline for which these results were not adjusted.

Wei M, et al. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. Diabetes Care. 1998;21(7):1167-1172.

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Background: Lower HbA1C failed to reduce CV events (ADVANCE)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

•N-11,140 pts, assigned to undergo either a strategy of intensive blood glucose control (target glycated hemoglobin value, ≤6.5%) or a strategy of standard glucose control (with target glycated hemoglobin levels defined on the basis of local guidelines).

•Median f/u was 5years.

N Engl J Med 2008;358:2560-72.

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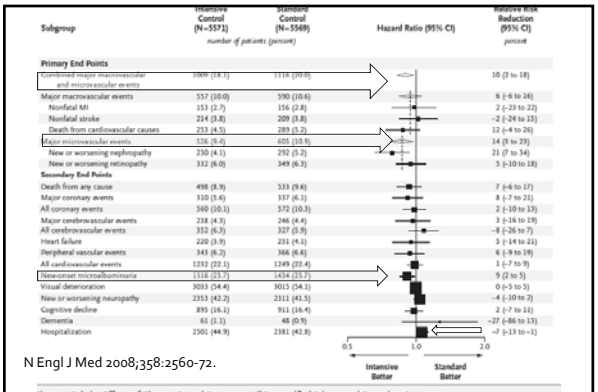

N Engl J Med 2008;358:2560-72.

Figure 4. Relative Effects of Glucose-Control Strategy on All Prespecified Primary and Secondary Outcomes.

The diamonds incorporate the point estimates, represented by the vertical dashed lines, and the 95% confidence intervals of the overall effects within categories; for subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% confidence intervals. The hazard ratios and relative risk reductions are given for intensive glucose control as compared with standard glucose control.

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Hypoglycemia with intensive glucose control

- Severe hypoglycemia occurred more frequently in the intensive-control group than in the standard control group:
  - 150 patients (2.7%) undergoing intensive control had at least one severe hypoglycemic episode, as compared with 81 patients (1.5%) undergoing standard control (hazard ratio, 1.86; 95% CI, 1.42 to 2.40; P<0.001).
  - These included one fatal episode in the standard-control group and one episode resulting in permanent disability in each group.
  - On average, the rate of severe hypoglycemic events was 0.7 event per 100 patients per year in the intensive-control group and 0.4 event per 100 patients per year in the standard-control group.
- Minor hypoglycemia also occurred more frequently in patients undergoing intensive control (120 events per 100 patients per year, vs. 90 with standard control).
- Approximately 47% of patients in the intensive-control group and 62% of those in the standard-control group remained free of any hypoglycemic event during the follow-up period.

N Engl J Med 2008;358:2560-72.

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Evidence lowering HbA1C does NOT lower events

- ACCORD trial
- N=10,251 patients
  - intensive therapy, targeted to achieve an A1c level below 6.0%, or
  - standard therapy, targeted to achieve a level of 7.0%-7.9%.
- Contrary to observational evidence, treatment groups did not significantly differ on the primary study outcome,
  - composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (HR = 0.90, 95% CI = 0.78-1.04).
- However, the intensive therapy group experienced significantly
  - higher rates of hypoglycemia requiring medical assistance (10.5% vs. 3.5%, *P < 0.001) and*
  - *weight gain greater than 10 kilograms* (27.8% vs. 14.1%, *P < 0.001).*
- *More importantly, all-cause mortality* rates were *higher in the intensive-treatment than in the standard-* treatment group (HR = 1.22, 95% CI = 1.01-1.46), prompting early termination of the trial by the National Institutes of Health after a mean of 3.5 years of follow-up.

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ACCORD

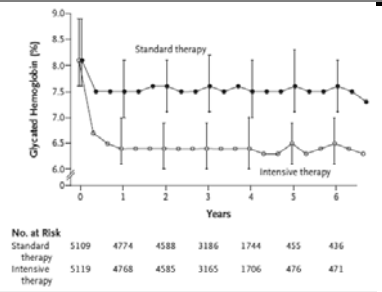

Figure 1. Median Glycated Hemoglobin Levels at Each Study Visit.
I bars denote interquartile ranges.

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ACCORD

Table 2. Prescribed Glucose-Lowering Drugs.*

Drug Class and Name	Intensive Therapy (N=5128)		Standard Therapy (N=5123)	
	no. of patients (%)	person-years	no. of patients (%)	person-years
Single class				
Metformin	4856 (94.7)	14,444	4452 (86.9)	12,693
Secretagogue†	4443 (86.6)	12,021	3779 (73.8)	10,059
Glimepiride	4010 (78.2)	9,142	3465 (67.6)	8,955
Repaglinide	2574 (50.2)	4,447	908 (17.7)	1,293
Thiazolidinedione‡	4702 (91.7)	12,844	2986 (58.3)	6,719
Rosiglitazone	4677 (91.2)	12,639	2946 (57.5)	6,563
α-Glucosidase inhibitor§	1191 (23.2)	941	263 (5.1)	200
Incretin¶	911 (17.8)	566	251 (4.9)	175
Exenatide	622 (12.1)	415	204 (4.0)	155
Any insulin	3965 (77.3)	11,902	2837 (55.4)	7,842
Any bolus insulin	2834 (55.3)	6,806	1794 (35.0)	4,336
Combination of classes				
No. of classes without insulin				
1 or 2	2798 (54.6)	2,011	3224 (62.9)	6,612
3	3030 (59.1)	3,641	1681 (32.8)	2,545
4 or 5	539 (10.5)	332	109 (2.1)	67
No. of classes with insulin				
0	916 (17.9)	829	892 (17.4)	1,495
1 or 2	3311 (64.6)	6,603	2375 (46.4)	5,284
3	2668 (52.0)	4,126	834 (16.3)	1,027
4 or 5	526 (10.3)	344	64 (1.2)	36

Metformin, glimepiride, repaglinide, rosiglitazone, acarbose, and exenatide were provided by a study-supervised formulary.
Patients could receive more than one medication or combination of medications and may therefore be counted in more than one category. All individual medications that are listed were prescribed to at least 10% of patients in either group.
Patients received glimepiride, glyburide, gliclazide, repaglinide, or nateglinide.
Patients received rosiglitazone or pioglitazone.
All the patients in this category received acarbose except one who received miglitol.
‖Patients received exenatide or sitagliptin.

ACCORD

Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001
Fatal or nonfatal heart failure — no. (%)	152 (3.0)	124(2.4)	0.10
Motor vehicle accident in which patient was driver — no./total no. (%)	9/5033 (0.2)	14/5036 (0.3)	0.40
Any nonhypoglycemic serious adverse event — no. (%)	113 (2.2)	82 (1.6)	0.03
Fluid retention — no./total no. (%)‡	3541/5053 (70.1)	3378/5054 (66.8)	<0.001
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.001
Alanine aminotransferase >3 times ULN — no./total no. (%)§	51/5065 (1.0)	77/5061 (1.5)	0.02
Low-density lipoprotein cholesterol — mg/dl¶	90.8±33.5	90.6±34.0	0.74
Blood pressure — mm Hg¶			
Systolic	126.4±16.7	127.4±17.2	0.002
Diastolic	66.9±10.5	67.7±10.6	<0.001

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Table 4. Primary and Secondary Outcomes.*

Outcome	Intensive Therapy (N=5128)		Standard Therapy (N=5123)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per yr	no. of patients (%)	% per yr		
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.35 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	235 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74
Fatal or nonfatal congestive heart failure	152 (3.0)	0.90	124 (2.4)	0.75	1.18 (0.93–1.49)	0.17
Causes of death						
Any	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Unexpected or presumed cardiovascular disease†	86 (1.7)		67 (1.3)			
Fatal myocardial infarction†	19 (0.4)		13 (0.3)			
Fatal congestive heart failure†	23 (0.4)		16 (0.3)			
Fatal procedure†						
For cardiovascular disease	10 (0.2)		3 (0.1)			
For noncardiovascular disease	1 (<0.1)		3 (0.1)			
Fatal arrhythmia†	4 (0.1)		10 (0.2)			
Fatal stroke†	9 (0.2)		11 (0.2)			
Other cardiovascular disease†	8 (0.2)		10 (0.2)			
Cancer	65 (1.3)		63 (1.2)			
Condition other than cancer or cardiovascular disease‡	50 (1.0)		35 (0.7)			
Undetermined	7 (0.1)		11 (0.2)			

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Risk of using Surrogate Endpoints

"The difference between a surrogate and a true endpoint is like the difference between a cheque and cash. You can often get the cheque earlier but then, of course, it might bounce."

Statistical Issues in Drug Development, 2nd Ed.

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Patient Oriented Evidence that Matters *contradicts* Disease Oriented Evidence

Disease & intervention	DOE	POEM
Asymptomatic Vent. Arrhythmia,encainide & flecainide	Suppression of V arrhythmia	Decreased survival
AF & quinidine to maintain NSR after conversion	Improved maintenance of NSR	3X's mortality
Postmenopausal osteoporosis treatment w/ fluoride therapy	Increased bone mineral density	↑ in non-vert fractures
Post-menopausal HRT	Decrease in LDL-C	↑ in MI
Heart failure and milrinone	Improved CO and exercise tolerance	↑'d mortality
COX-2 inhibitors and fewer GIB	↓'d endoscopically determined GU	No beneficial effect after 6 m
BP lowering with doxazosin	Lowered BP	Increased CHF
Insulin receptor sensitivity and better control of BS w/ Rosiglitazone	Lower HbA1C	Increased CV events

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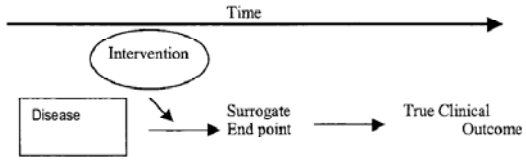
FDA significantly restricts access to the diabetes drug Avandia

09-23-2010] The U.S. Food and Drug Administration announced that it will significantly restrict the use of the diabetes drug Avandia (rosiglitazone) to patients with Type 2 diabetes who cannot control their diabetes on other medications. These new restrictions are in response to data that suggest an elevated risk of cardiovascular events, such as heart attack and stroke, in patients treated with Avandia.

21

When a surrogate may represent true outcome reduction

A. The setting which provides the greatest potential for the surrogate to be valid



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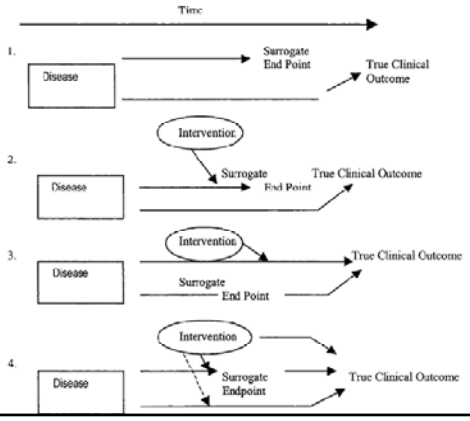
B. Reasons for failure of surrogate end points.



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The problem with surrogate endpoints

- To prove the surrogate endpoints are adequate, you have to run the sort of trial the endpoints were supposed to enable you to avoid.

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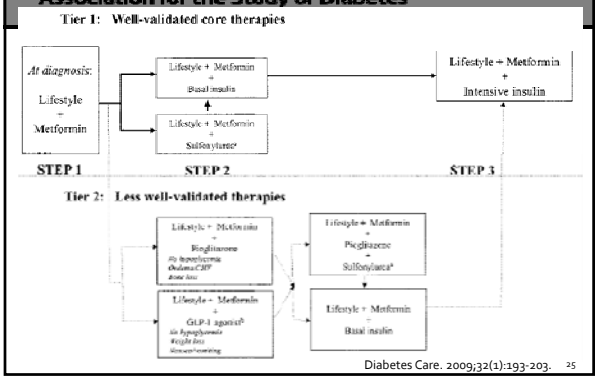
A Consensus statement of the ADA & the European Association for the Study of Diabetes



Diabetes Care. 2009;32(1):193-203.

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Metformin's effects

ADVANTAGES

- Lowers A1C ~ 1.5%
- Well-tolerated, GI effects
- Not usually accompanied by hypoglycemia
- Weight stability or modest weight loss
- Has demonstrated a reduction in CV outcomes

DISADVANTAGES

- Contraindicated in renal dysfunction
  - Lactic acidosis (1 case per 100,000 treated patients) but potentially fatal complication
  - Safe unless the estimated GFR <30mL/min

Nathan DM, et al. Medical management of hyperglycemia in T2DM: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 32:193-203.

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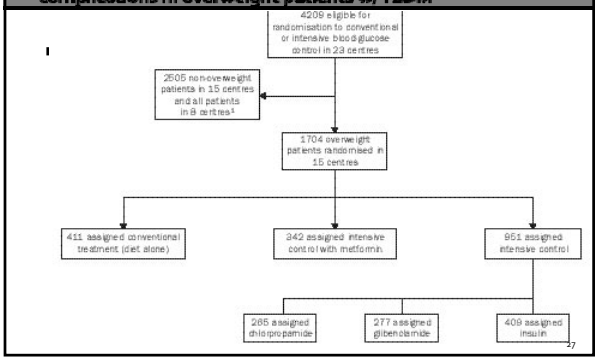
Metformin-UKPDS-34:

Effect of intensive blood-glucose control w/ metformin on complications in overweight patients w/ T2DM



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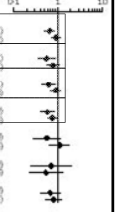
Metformin-UKPDS-34

AGGREGATE ENDPOINT	p for metformin vs other intensive	Patients with aggregate endpoints: Metformin or intensive	Patients with aggregate endpoints: Conventional	Absolute risk (events per 1000 patient-years): Metformin or intensive	Absolute risk (events per 1000 patient-years): Conventional	Log-rank 2p	RR (95% CI) vs conventional
Any diabetes-related endpoint	p=0·0034						
Metformin		98	160	29·8	43·3	0·0023	0·68 (0·53–0·87)
Intensive		350	160	40·1	43·3	0·46	0·93 (0·77–1·12)
Diabetes-related death	p=0·11						
Metformin		28	55	7·5	12·7	0·017	0·58 (0·37–0·91)
Intensive		108	55	10·3	12·7	0·19	0·80 (0·58–1·11)
All-cause mortality	p=0·021						
Metformin		50	89	13·9	20·9	0·011	0·64 (0·45–0·91)
Intensive		190	89	18·9	20·6	0·49	0·92 (0·71–1·18)
Myocardial infarction	p=0·12						
Metformin		39	73	11·0	18·0	0·01	0·61 (0·41–0·89)
Intensive		139	73	14·4	18·0	0·11	0·79 (0·60–1·05)
Stroke	p=0·092						
Metformin		12	23	3·3	5·5	0·13	0·59 (0·29–1·18)
Intensive		60	23	6·2	5·5	0·60	1·14 (0·70–1·84)
Peripheral vascular disease	p=0·62						
Metformin		6	9	1·6	2·1	0·67	0·74 (0·26–2·09)
Intensive		12	9	1·2	2·1	0·18	0·56 (0·24–1·33)
Microvascular	p=0·39						
Metformin		24	38	6·7	9·2	0·19	0·71 (0·43–1·19)
Intensive		74	38	7·7	9·2	0·38	0·84 (0·57–1·24)



Intensive therapy= chlorpropamide, glibenclamide, or insulin
Metformin=maximum dose was 2550mg daily

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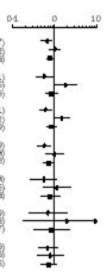
UKPDS-34

AGGREGATE ENDPOINT	Patients with aggregate endpoint/total: Added metformin	Patients with aggregate endpoint/total: Conventional/ sulphonylurea	Absolute risk (events per 1000 patient-years): Added metformin	Absolute risk (events per 1000 patient-years): Conventional/ sulphonylurea	Log-rank 2p	RR (95%CI) for conventional/ metformin
Any diabetes-related endpoint						
Metformin	98/342	160/411	29·8	43·3	0·0023	0·68 (0·53–0·87)
Sulphonylurea plus metformin	81/268	82/269	60·5	58·4	0·78	1·04 (0·77–1·42)
Combined groups	179/610	242/680	38·7	47·5	0·033	0·81 (0·67–0·98)
Diabetes-related death						
Metformin	28/342	55/411	7·5	12·7	0·017	0·58 (0·37–0·91)
Sulphonylurea plus metformin	26/268	14/269	16·8	8·6	0·036	1·96 (1·02–3·75)
Combined groups	54/610	69/680	10·3	11·6	0·47	0·88 (0·61–1·25)
All-cause mortality						
Metformin	50/342	89/411	13·9	20·6	0·011	0·64 (0·45–0·91)
Sulphonylurea plus metformin	47/268	31/269	30·3	19·1	0·041	1·60 (1·02–2·52)
Combined groups	97/610	120/680	18·4	20·2	0·49	0·91 (0·70–1·19)
Myocardial infarction						
Metformin	39/342	73/411	11·0	18·0	0·010	0·61 (0·41–0·89)
Sulphonylurea plus metformin	33/268	31/269	22·0	20·2	0·73	1·09 (0·67–1·78)
Combined groups	72/610	104/680	14·2	18·6	0·077	0·76 (0·56–1·03)
Stroke						
Metformin	12/342	23/411	3·3	5·5	0·13	0·59 (0·29–1·18)
Sulphonylurea plus metformin	15/268	13/269	9·9	8·2	0·61	1·21 (0·58–2·55)
Combined groups	27/610	36/680	5·2	6·2	0·49	0·84 (0·51–1·38)
Peripheral vascular disease						
Metformin	6/342	9/411	1·6	2·1	0·57	0·74 (0·26–2·09)
Sulphonylurea plus metformin	2/268	1/269	1·3	0·6	0·53	2·12 (0·19–23·3)
Combined groups	8/610	10/680	1·7	1·7	0·82	0·80 (0·35–2·07)
Microvascular disease						
Metformin	24/342	38/411	6·7	9·2	0·19	0·71 (0·43–1·19)
Sulphonylurea plus metformin	15/268	19/269	10·1	12·1	0·62	0·84 (0·43–1·66)
Combined groups	39/610	57/680	7·7	10·0	0·20	0·77 (0·54–1·15)



The authors dismissed their finding of ↑'d 'diabetes-related death' with SU + Met due to the observation that the SU pts were ≤ y older, more hyperglycemic (163.8 vs 145.8), less overweight, and f/u for ≤ y less.[29]

DERP study selection

- Included populations
  - Adults & kids-T2DM for all included medications
  - Adults & kids-T1 DM for pramlintide only
- Excluded
  - Gestational diabetes, pre-diabetes, metabolic syndrome w/o DM, PCOS
- Included outcomes:
  - All-cause mortality
  - Microvascular dz: CKD (renal dialysis, renal transplantation, ESRD, renal failure with proteinuria, retinopathy including proliferative retinopathy & blindness; peripheral neuropathy

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DERP study selection

- Outcomes (continued)
  - Macrovascular dz: CV mortality (MI & PAD), stroke/TIA, CHD, CV procedures, extremity amputation
  - Lower extremity ulcers
  - QOL
  - Hospitalization and medical visits related to diabetes care

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DERP study selection (continued)

- Included harms/adverse events outcomes
  - Overall adverse events
  - Withdrawals due to adverse events
  - Major adverse events (DKA, nonketotic hyperosmolar coma)
  - Specific events (cancers/infections, hypoglycemmia, liver toxicity, liver function abnormalities, GI effects, CHF, adverse changes in lipid concentrations, pancreatitis, weight gain, fractures)

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DERP study selections

- Included study designs
  - For intermediate outcomes
    - RCTs and good-quality systematic reviews
  - For health and utilization outcomes
    - RCT, good-quality systematic reviews, and observational studies if they were cohort studies with a comparison group or case-control studies
  - For harms:
    - RCTs, controlled clinical trials, good and fair-quality systematic reviews, population-based comparative cohort studies focused on adverse events, case-control studies
- Duration: all study designs were ≥12 w of f/u
- Sample size: any size

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Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence the evidence reflects the true effect. Further research is very unlikely to change the confidence in the estimate of effect.
Moderate	Moderate confidence the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.
Low	Low confidence the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

34

Rosiglitazone (Avandia)
Pioglitazone (Actos)

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Pioglitazone

ADVANTAGES

- Some evidence of reduction in CV events
- Same HbA1C lowering as SUs, Met (0.5-1.4%)
- Similar to Met for hypoglycemia risk
- Less hypoglycemia than SUs

DISADVANTAGES

- Contraindicated in heart failure
- Edema
- Weight gain
- Fracture risk

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Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus
A Meta-analysis of Randomized Trials

Lincoff and colleagues examined the effect of pioglitazone on ischemic cardiovascular disease complications in diabetes using a database of individual patient data from Takeda Pharmaceuticals, the manufacturers of pioglitazone. The primary composite endpoint (death, nonfatal myocardial infarction, and nonfatal stroke) was decreased with pioglitazone as mono- or combination therapy with a variety of antidiabetic drugs (hazard ratio 0.82 [95% CI 0.72 to 0.94; 18 *P=0.005]). For placebo-controlled trials the hazard ratio was 0.09 (95% CI 0.01 to 0.84). The risk of serious heart failure was increased with pioglitazone (hazard ratio 1.41 [95% CI 1.14 to 20 1.76; P=0.002]).*

37

Pioglitazone, Rosiglitazone

- Evidence from systematic reviews, RCTs, and observational studies indicate that both pioglitazone and rosiglitazone:
  - increase the risk of:
    - heart failure (odds ratios range from 1.32 to 2.18 in various meta-analyses).
    - edema (odds ratios range from 2.26 to 4.62 in various meta-analyses)
  - Decrease the risk of:
    - hypoglycemia when compared with sulfonylureas; the risk is similar to the risk with metformin.

DERP, 2010.

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TZDs (both)

- Both TZDs resulted in a similar weight increase. The increase is similar to that with sulfonylureas.
- 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 RCTs involving 13,715 participants).
  - This risk appears to be increased among women (OR 2.23, 95% CI 1.65 to 3.10) but not among men (OR 1.00, 95% CI 0.73 to 1.39).
    - These findings are consistent with the results of the ADOPT trial.

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Pio- vs Rosi-

Relevance?

Table F-21. Pioglitazone compared with rosiglitazone

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
5; 1209	Low RCTs/Fair	Consistent	Indirect	Precise	WMD -0.09, 95% CI: -0.23, 0.05	Moderate
Weight change						
5; 1209	Medium RCTs/Fair Systematic reviews	Consistent	Indirect	Precise	Both TZDs resulted in a similar weight increase. The increase is similar to sulfonylureas	Moderate
Heart Failure						
Multiple systematic reviews, trials and observational studies	Low Systematic reviews RCTs	Consistent	Direct	Precise	Both pioglitazone and rosiglitazone increase the risk of heart failure (odds ratios range from 1.32 to 2.18 in various meta-analyses)	High
Edema						
Multiple systematic reviews, trials and observational studies	Low Systematic reviews RCTs	Consistent	Direct	Precise	Both pioglitazone and rosiglitazone increase the risk of edema (odds ratios range from 2.26 to 4.62 in various meta-analyses).	High
Fractures						
including meta-analysis of 10 RCTs involving 13,715 participants	Systematic reviews RCTs	Consistent	Direct	Precise	Risk of fractures is increased among patients exposed to TZDs (OR 1.45, 95% CI 1.18 to 1.79); Risk appears to be increased among women (OR 2.23, 95% CI 1.65 to 3.10) but not among men (OR 1.00, 95% CI 0.73 to 1.39)	Moderate

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Pio- vs SU's

Table F-22. Pioglitazone compared with sulfonylureas (monotherapy or add-on)

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
10; 1787	Medium RCTs/Fair	Consistent[a]	Indirect	Precise	No difference (7/10 trials found no difference, 2 favored pio and 1 favored glimepiride)	Moderate
Outcome# 2: Weight change						
10; 1787	Medium RCTs/Fair	Inconsistent	Indirect (intermediate outcome)			

[a]most of the evidence was consistent, finding no difference; with a large number of studies it is consistent with random error to have a few studies finding a small difference in favor of one treatment or the other

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Pio- vs Met

Table F-23. Pioglitazone compared with metformin (monotherapy or add-on)

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
5; 1456	Low 2 RCTs/Good 3 RCTs/Fair	Consistent	Indirect	Precise	No difference	High
Outcome# 2: Weight change						
3;1182	Medium 2 RCTs/Good 3 RCTs/Fair	Inconsistent	Indirect (intermediate outcome)			

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Rosi- vs SUs

Table F-24. Rosiglitazone compared with sulfonylureas

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
8; 6337	Low 1 RCT/Good 7 RCTs/Fair	Consistent[a]	Indirect	Precise	No difference (6 of 8 trials found no difference, 1 favored rosiglitazone and 1 favored the sulfonylurea group)	Moderate
Outcome# 2: Weight change						
8; 6337	Medium 1 RCT/Good 7 RCTs/Fair	inconsistent	Indirect (intermediate outcome)			

[a]most of the evidence was consistent, finding no difference; with a large number of studies it is consistent with random error to have a few studies finding a small difference in favor of one treatment or the other

Relevance?

43

Rosi- vs metformin

Table F-25. Rosiglitazone compared with metformin

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
4; 8925	Medium RCTs/Fair	Consistent	Indirect	Precise	No difference (3 of 4 trials found no difference; 1 reported a very small difference favoring rosiglitazone, 0.13% between group difference)	Moderate
Outcome# 2: Weight change						
3;1182	Medium RCT/Fair	Inconsistent	Indirect (intermediate outcome)			

Relevance?

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Met + Rosi- vs monotx

Table F-26. Avandamet® or dual therapy with metformin and rosiglitazone compared with monotherapy

	Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; # of subjects	Risk of Bias; Design / Quality	Consistency	Directness	Precision		Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c							
3; 1,686	Medium 3 RCT/Fair	Consistent	Indirect	Imprecise		Greater reduction in A1c with Avandamet® or dual therapy than with monotherapy (range 0.13% to 0.7%)	Moderate[a]
Weight							
2; 977	Medium 2 RCTs/Fair	Consistent	Indirect	Precise		No weight change with Avandamet® (0.0kg to 0.01 kg) compared with slight weight gain with rosiglitazone monotherapy, and slight weight gain (1.9kg) or weight loss (-2.9kg) with metformin	Moderate
Edema							
3; 1,686	Medium 3 RCTs/Fair	Consistent	Indirect	Imprecise		Higher rates of edema with Avandamet® or dual therapy than with metformin monotherapy	Moderate
Gastrointestinal adverse effects							
3; 1,686	Medium 3 RCTs/Fair	Consistent	Direct	Imprecise		Rates of gastrointestinal adverse effects with Avandamet® or dual therapy were high (28	Moderate

Relevance?

45

Rosi- + glimepiride vs monotx

Table F-27. Avandaryl® or dual therapy with rosiglitazone and glimepiride compared with monotherapy

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; # of subjects	Risk of Bias; Design / Quality	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
2; 914	Low[a] 1 RCT/Fair 1 RCT/Good	Consistent	Indirect	Precise	Greater reduction in A1c with Avandaryl® or dual therapy than with monotherapy (range 0.6% to 0.8%)	High
Weight						
2; 914	Low[a] 1 RCT/Fair 1 RCT/Good	Consistent	Indirect	Precise	Weight gain was slightly greater with Avandaryl® or dual therapy than with monotherapy	Moderate
Hypoglycemia						
2; 914	Low[a] 1 RCT/Fair 1 RCT/Good	Consistent	Indirect	Precise	Rates of hypoglycemia were greater with Avandaryl® or dual therapy than with monotherapy	Moderate

[a]Risk of bias rated low because the Good study has a low risk of bias and contributes 96% of the total sample N

Relevance?

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Pio + Met vs monotx

Table F-28. Dual therapy with pioglitazone and metformin compared with monotherapy

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
# of studies; # of subjects	Risk of Bias; Design / Quality	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
1; 271	Low 1 RCT/Good	Unknown (single study)	Indirect	Precise	Greater reduction in A1c with dual therapy than with monotherapy (range 0.9% to 1.1%)	Moderate

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TZDs

CURRENT

- No edits for EBD members

PROPOSED

- Restrict the access to rosiglitazone.
- No edits for pioglitazone.

48

Exenatide (Byetta injection)
Liraglutide (Victoza injection)

Exenatide (Byetta injection)
Liraglutide (Victoza injection)

ADVANTAGES

- Lower HbA1C by 0.5-1%
- Weight loss—may be a result of GI SEs

DISADVANTAGES

- No evidence for event reduction
- Slows gastric motility
- Causes a relatively high frequency of GI disturbances (30-45% experience 1 or more episodes of N/V/D

Liraglutide vs exenatide

Table F-12. Liraglutide compared with exenatide

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
1; 464	Medium 1 RCT/Good	Unknown	Indirect	Precise	Estimated treatment difference -0.33; 95% CI -0.47 to -0.18; *P*<0.0001	Low
Weight change						
1; 464	Medium 1 RCT/Good	Unknown	Indirect	Imprecise	No significant difference (treatment difference -0.38 kg; 95% CI -0.99 to 0.23; *P*=0.2235)	Low
Hypoglycemia						
1; 464	Medium 1 RCT/Good	Unknown	Direct	Imprecise	Rate ratio 0.55 for minor hypoglycemia, CI 0.34 to 0.88; *P*=0.0131	Low

Exenatide vs insulin

Table F-13. Exenatide compared with insulin

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
4; 1245	Medium 4 RCTs/Fair	Consistent	Indirect	Precise	No difference between groups for reduction	Moderate
Weight						
4; 1245	Medium 4 RCTsFair	Consistent	Indirect	Imprecise	Greater weight loss with exenatide (treatment difference range 4.1 kg to 5.4 kg)	Moderate
Hypoglycemia						
4; 1245	Medium 4 RCTs/Fair	Consistent	Direct	Imprecise	Similar rates of hypoglyemia between exenatide and insulin	Moderate

5.4kg=11.9 pounds

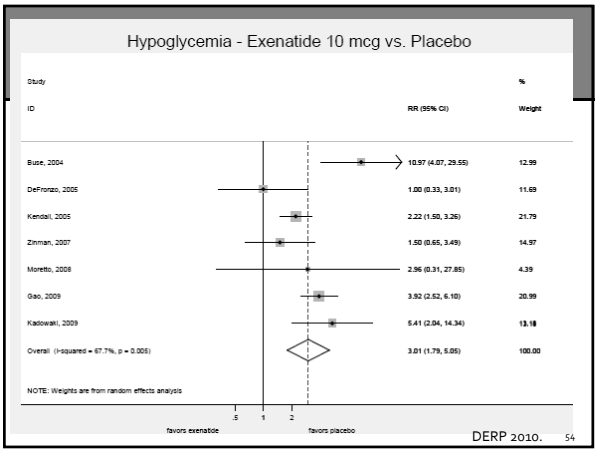
Exenatide vs placebo

Table F-14. Exenatide 5 mcg BID compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
5; 1832	Low 1 RCT/Good 4 RCTs/Fair	Consistent	Indirect	Precise	WMD -0.72 (-0.99 to -0.45)	Moderate
Weight						
5; 1832	Low 1 RCT/Good 4 RCTs/Fair	Inconsistent	Indirect	Imprecise	WMD -0.61 kg (-1.28 to 0.06)	Low
Hypoglycemia						
5; 1832	Low 1 RCT/Good 4 RCTs/Fair	Consistent	Indirect	Imprecise	RR 2.37 (1.20 to 4.27)	Moderate
Nausea						
5; 1832	Low 1 RCT/Good 4 RCTs/Fair	Consistent	Indirect	Imprecise	RR 2.42 (1.47 to 4.16)	Moderate

Table F-15. Exenatide 10 mcg BID compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
7; 2531	Low 2 RCTs/Good 5 RCTs/Fair	Consistent	Indirect	Precise	WMD -0.96 (-1.12 to -0.81)	High
Weight						
7; 2531	Low 2 RCTs/Good 5 RCTs/Fair	Consistent	Indirect	Precise	WMD -1.18 kg, (-1.54 to -0.80)	High
Hypoglycemia						
7; 2531	Low 2 RCTs/Good 5 RCTs/Fair	Consistent	Indirect	Imprecise	RR 3.011 (1.79 to 5.05)	Moderate
Nausea						
7; 2531	Low 2 RCTs/Good 5 RCTs/Fair	Consistent	Indirect	Imprecise	RR 4.37 (2.41 to 7.93)	Moderate



DERP 2010.

Liraglutide vs glimepiride

Table F-16. Liraglutide compared with glimepiride

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
3; 2030	Medium 3 RCTs/Fair	Inconsistent	Indirect	Imprecise	Studies with heterogenous results; either no difference between groups or slightly greater reduction in A1c with liraglutide	Insufficient
Weight						
3; 2030	Medium 3 RCTs/Fair	Inconsistent	Indirect	Imprecise	Some evidence that liraglutide leads to greater weight loss	Low

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Liraglutide vs glargine

Table F-17. Liraglutide compared with insulin glargine

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
1; 581	Low 1 RCT/Good	Unknown	Indirect	Imprecise	Between group difference -0.24% (-0.08 to -0.39)	Low
Weight						
1; 581	Low 1 RCT/Good	Unknown	Indirect	Imprecise	Between group difference -1.39 kg (-2.10 to -0.69)	Low

1.39kg=3 pounds

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Liraglutide vs placebo

Table F-19. Liraglutide 1.2 to 1.25 mg daily compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
3; 1789	Medium 3 RCT/Fair	Consistent	Indirect	Imprecise	WMD -1.27 (CI –1.70 to –0.84)	Moderate
Weight						
2; 1624	Medium 2 RCT/Fair	Consistent	Indirect	Precise	WMD -1.31kg (–1.85 to –0.77)	Moderate
Hypoglycemia						
2; 1624	Medium 2 RCT/Fair	Consistent	Indirect	Precise	RR 1.44 (0.74 to 3.04)	Moderate
Gastrointestinal side effects						
2; 1624	Medium 2 RCT/Fair	Consistent	Indirect	Precise	RR 2.33 (1.78 to 3.04)	Moderate

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Liraglutide vs placebo

Table F-20. Liraglutide 1.8 to 1.9 mg daily compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
A1c						
4; 2370	Medium 3 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	WMD -1.23, 95% CI -1.52 to -0.94, $P<0.001$	Moderate
Weight						
3; 2205	Medium 2 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	WMD -1.76 kg, 95% CI –2.61 to –0.92, $P<0.001$	Moderate
Hypoglycemia						
3; 2205	Medium 2 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	RR 1.57 (1.10 to 2.25)	Moderate
Gastrointestinal side effects						
3; 2205	Medium 2 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	RR 3.14 (2.49 to 3.94)	Moderate

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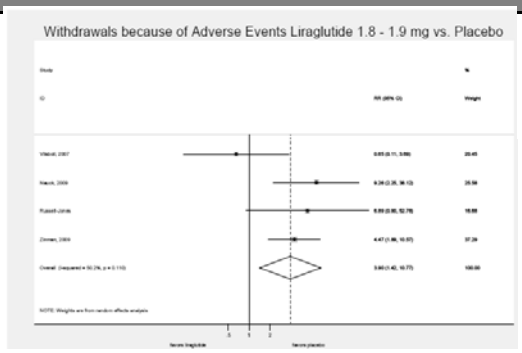
Liraglutide vs Placebo



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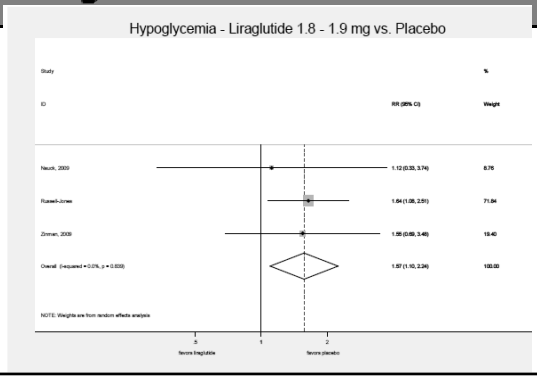
Liraglutide vs Placebo



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Exenatide/Liraglutide

CURRENT

- No monotherapy allowed
- 120 day lookback for 1 fill of metformin, sulfonylurea, or TZD.

PROPOSED

- Option 1.
  - Discontinue covering these drugs based on lack of outcomes evidence.
- Option 2.
  - Deny if any insulin claim in past 30d.
  - Continue no monotherapy access for exenatide or liraglutide.
  - PA all prescriptions, criteria:
    - require a current metformin fill for 90 of the past 120 days at the maximum or near-maximum dose failure to reach goal A1C, AND then
    - Require, in patients who cannot tolerate metformin, the use of pioglitazone, unless contraindicated due to HF, edema, or fracture risk.
- If renal function will not allow metformin (CrCl <30mL/min), then should not take exenatide either.

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Sitagliptin Saxagliptin (DPP-4 inhibitors)

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Sitagliptin & Saxagliptin trials

Applicability to General Diabetes Populations

Patients enrolled in the sitagliptin trials represented a highly selected population: primarily white, middle-aged, obese adults with moderately elevated baseline A1c (< 9%) and diabetes for less than 10 years. These populations were further selected during long dose-stabilization and run-in periods, where only persons with > 75% adherence to placebo went on to randomization. Moreover, these trials did not provide sufficient baseline information on comorbidities and other characteristics and laboratory values that would enable inference about the applicability of study findings to general diabetic populations. The available data appear to be limited to persons with diabetes without related comorbidities and who are highly motivated.

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Sitagliptin Saxagliptin

ADVANTAGES

- Reduce HbA1C 0.6-0.9%

DISADVANTAGES

- No evidence of event reduction
- Weight gain
- Less HbA1C reduction than with Metformin or SUs

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Sitagliptin vs placebo

Table F-3. Sitaglipitin 100mg monotherapy compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
7; 4333	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with sitagliptin (WMD -0.79, 95% CI -0.93 to -0.66)	Moderate
Outcome# 2: Weight change						
5;3035	Medium RCTs/Fair	inconsistent	Indirect	Precise	Less weight loss with sitagliptin than with placebo (WMD 0.66, 95% CI 0.43 to 0.89)	Moderate
Outcome #3: Hypoglycemia						
7; 4333	Medium RCTs/Fair	Inconsistent	Indirect	Imprecise	No difference (RR 1.26, 95% CI 0.48 to 3.25)	Low

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Sitagliptin monotx vs active control

Table F-4. Sitaglipitin monotherapy compared with active control

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c for studies comparing sitagliptin to metformin						
1;1091	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Reduction greater with metformin (-0.16 to -0.47% between group difference at 24 weeks, p NR)	Low
Outcome #1: A1c for studies comparing sitagliptin to glipizide						
1; 743	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Reduction greater with glipizide (between group difference -0.22%)	Low
Outcome# 2: Weight change for studies comparing sitagliptin to metformin						
1;1091	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Reduction greater with metformin (between group difference -0.9 to -1.1kg at 24 weeks; -1.6 to -2.1 at 54 weeks)	Low
Outcome #2: Weight change for studies comparing sitagliptin to glipizide						
1; 743	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater weight gain with glipizide (between group difference +0.5)	Low

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Sitagliptin added to metformin

Table F-5. Sitaglipitin compared with placebo, as add-on therapy to metformin

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
Outcome#1: A1c						
3; 1164	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with sitagliptin (between group difference -0.51 to -1.0)	Moderate
Outcome# 2: Weight change						
3; 1164	Medium RCTs/Fair	Inconsistent	Indirect	Precise	Similar change in weight between groups	Low

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Met + Sita- vs Monotx

Table F-29. Dual therapy with metformin and sitagliptin compared with monotherapy

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
# of studies; # of subjects	**Risk of Bias; Design / Quality**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
A1c						
1; 1,091*	Medium 1 RCT/Fair	Unknown (single study)	Indirect	Precise	Greater reduction in A1c with dual therapy than with monotherapy (range 0.4% to 1.2%)	Moderate
Weight						
1; 1,091*	Medium 1 RCT/Fair	Unknown (single study)	Indirect	Precise	Similar weight loss of sitagliptin plus metformin (-0.7 to -1.7kg) and metformin monotherapy (-1.0 to -1.5kg)	Low
Gastrointestinal adverse effects						
1; 1,091*	Medium 1 RCT/Fair	Unknown (single study)	Indirect	Precise	Similar between sitagliptin 100 plus metformin 2000 vs. metformin 2000 monotherapy (24 weeks: 34.7 vs. 25.3%, 54 weeks: 29 vs. 31%); Higher rates for sitagliptin 100 plus metformin 1000 vs. sitagliptin or metformin 1000 monotherapy (24 weeks: 17.9 vs. 15.1 vs. 15.9%; 54 weeks: 26 vs. 20 vs. 20%)	Low
Total cholesterol						
1; 1,091*	Medium 1 RCT/Fair	Unknown (single study)	Indirect	Precise	Combinations resulted in slightly greater improvements in total cholesterol (at 24 weeks: -3.3 to -7.1, at 54 weeks: -6.6 to -8.8 mg/dl) compared with metformin or sitagliptin monotherapy (at 24 weeks: -1.5 to +2.7; at 54 weeks: -0.2 to +0.5 mg/dl)	Low

*This includes data from 2 publications, one being a 30-week extension of the other. Number of subjects is from the initial study (not double-counting subjects).

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Sitagliptin added onto pioglitazone

Table F-6. Sitaglipitin compared with placebo, as add-on therapy to pioglitazone

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
Outcome#1: A1c						
1; 353	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater reduction with sitagliptin (between group difference -0.7)	Low
Outcome# 2: Weight change						
1; 353	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater weight gain with sitagliptin (between group difference +0.3kg)	Low

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Sitagliptin added to glimepiride

Table F-7. Sitagliptin compared with placebo, as add-on therapy to glimepiride

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
Outcome#1: A1c						
1; 441	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater reduction with sitagliptin (between group difference -0.57)	Low
Outcome# 2: Weight change						
1;441	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater weight gain with sitagliptin combination (between group difference +1.1kg)	Low

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Saxagliptin monotx vs placebo

Table F-8. Saxagliptin monotherapy compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
Outcome#1: A1c						
2; 741	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with saxagliptin (between group difference -0.45 to -0.65%)	Moderate
Outcome# 2: Weight change						
2; 741	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with placebo (between group difference -0.09 to -1.3kg)	Moderate

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Saxa- added to metformin

Table F-9. Saxaglipitin compared with placebo, as add-on therapy to metformin

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
Outcome#1: A1c						
1; 743	Medium RCT/Fair	Unknown (single study)	Indirect	Precise	Greater reduction with saxagliptin (between group difference -0.72 to -0.82%)	Low
Outcome# 2: Weight change						
1; 743	Medium RCT/Fair	Unknown (single study)	Indirect	Precise	Greater reduction with saxagliptin 2.5mg, but not saxagliptin 5mg, compared with placebo	Low

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Saxa- added to glyburide

Table F-10. Saxaglipitin compared with placebo, as add-on therapy to glyburide

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
1; 768	Medium RCT/Fair	Unknown	Indirect	Precise	Greater reduction seen with saxagliptin (between group difference -0.62 to -0.72)	Low
Outcome# 2: Weight change						
1; 768	Medium RCT/Fair	Unknown	Indirect	Precise	Greater weight gain seen with saxagliptin (between group difference +0.4 to +0.5kg)	Low

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Saxa- added to TZD (not stratified by which TZD pts were taking)

Table F-11. Saxaglipitin compared with placebo, as add-on therapy to thiazolidinedione

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
1; 565	Medium RCT/Fair	Unknown (single study)	Indirect	Precise	Greater reduction seen with saxagliptin (between group difference -0.36 to -0.64)	Low
Outcome# 2: Weight change						
1; 565	Medium RCT/Fair	Unknown (single study)	Indirect	Precise	Greater weight gain seen with saxagliptin (between group difference +0,4 to 0.5kg)	Low

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Sitagliptin Saxagliptin

CURRENT

- No monotherapy allowed
- 120 day lookback for 1 fill of metformin, sulfonylurea, or a TZD

PROPOSED

- Continue no monotherapy
- 180 day lookback for 75% fill rate of metformin or pioglitazone

75

Sitagliptin Saxagliptin

CURRENT

- No monotherapy allowed
- 120 day lookback for 1 fill of metformin

PROPOSED

- Option 1.
  - Discontinue covering these drugs based on lack of outcomes evidence.
- Option 2.
  - Deny if any insulin claim in past 30d.
  - Continue no monotherapy access for sitagliptin or saxagliptin.
  - PA all prescriptions, criteria:
    - Require a current metformin fill for 90 of the past 120 days at the maximum or near-maximum dose failure to reach goal A1C, AND
    - Require the use of concomitant pioglitazone in patients who have not reached their HbA1C goal with metformin monotherapy, unless contraindicated due to HF, edema, or fracture risk.

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Pramlintide (injection) (Symlin)

77

Pramlintide

ADVANTAGES

- Reduces HbA1C 0.5-0.7%

DISADVANTAGES

- No evidence it reduces events
- Injectable only
- Slows gastric emptying
- 30% develop nausea
- Only given with insulin

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Pramlintide (injectable only)

Table F-1. Pramlintide compared with placebo in type 2 diabetes

	Domains pertaining to strength of evidence				Magnitude of effect[a]	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c for studies adding pramlintide to flexible dose insulin regimens						
1; 212	Medium RCT/Fair	Unknown/NA	Indirect	Imprecise	Slight or no improvement with Pram (0.36% between group difference, P and CI NR)	Low
Outcome#1: A1c for studies adding pramlintide to fixed dose insulin regimens						
2; 1194	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater improvement with Pram (between group difference -0.13 to -0.4%)	Moderate
Outcome# 2: Weight change						
3; 1406	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with Pram (1.1 to 1.8 kg more than placebo at 52 weeks)	Moderate
Outcome #3: Severe hypoglycemia						
2; 749	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater frequency with pramlintide	Moderate

[a]Outcomes/effect sizes are for approved doses only (up to 120mcg for pramlintide)

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Pramlintide

Table F-2. Pramlintide compared with rapid acting insulin analog in type 2 diabetes

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome#1: A1c						
1; 113	Medium RCT/Fair	Unknown/NA	Indirect	Imprecise	No difference (-0.2 between group difference, *P*=0.46)	Low
Outcome# 2: Weight						
1; 113	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Weight gain seen with RAIA (+4.7kg between group difference, *P*<0.0001)	Low
Outcome #3: Hypoglycemia						
1; 113	Medium RCT/Fair	Unknown/NA	Direct	Precise	More frequent with RAIA	Low

RAIA=rapid acting insulin analog

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Pramlintide

CURRENT

- No edits

PROPOSED

- Exclude

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Any questions?

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DUEC New Drugs Oct-Dec 2010

GPI	Drug	Generic Name	Other Drugs in Same Class (AWP Pricing)		AWP per unit	Estimated AWP/month	Indications	Notes	Consultant's Notes	DUEC Vote	Insurance Vote
27574020100320	CYCLOSET TAB 0.8MG	BROMOCRIPTINE MESYLATE TAB 0.8 MG (BASE EQUIVALENT)	metformin $42-$108 per 30 dyas, sufonylureas $10-$93, per 30 days	Actos 15-45mg $173.40--$287.40 per month, januvia $226.50 per month	1.8 per 0.8mg tab	2- 6 ta/day ($108-$324 per month)	Cycloset, an ergot derivative, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Cycloset should not be used as a treatment of type 1 diabetes or diabetic ketoacidosis. There is limited efficacy data for the use of Cycloset in combination use with thiazolidinediones, and efficacy has not been confirmed in combination with insulin.	Cycloset is a novel therapy directly targeting the body's dopamine activity to improve glycemic control. It provides physicians with another treatment option for their patients with type 2 diabetes. • Unlike many other currently available drugs that stimulate insulin release, Cycloset improves glycemic control without increasing circulating insulin levels.	Exclude at this time. Has not been compared to metformin. No outcomes except HbA1C.		
27992502607520	KOMBIGLYZE TAB 2.5-1000	SAXAGLIPTIN-METFORMIN HCL TAB SR 24HR 2.5-1000 MG	Janumet 50-500mg and 50-1000mg 3.77	$226.30 per month	3.67	$110.10 per month	For the treatment of type 2 diabetes mellitus in combination with diet and exercise when treatment with both saxagliptin and metformin is appropriate	Tier 3 with step (like Janumet)	Discuss w/ DM review		
27992502607540	KOMBIGLYZE TAB 5-1000MG	SAXAGLIPTIN-METFORMIN HCL TAB SR 24HR 5-1000 MG	Janumet 50-500mg and 50-1000mg 3.77		7.34	$220.20 per month		Tier 3 with step (like Janumet)	"		
27992502607530	KOMBIGLYZE TAB 5-500MG	SAXAGLIPTIN-METFORMIN HCL TAB SR 24HR 5-500 MG	Janumet 50-500mg and 50-1000mg 3.77		7.34	$220.20 per month		Tier 3 with step (like Janumet)	"		
25400070100320	ELLA TAB 30MG	ULIPRISTAL ACETATE TAB 30 MG	Plan B, Plan B one step, Next Choice	Plan b $15.88 per tab= $31.76 per dose, plan B one step $40.62, Next Chcice average generic $14.62	42.90		ELLA can be used up to 5 days after unprotected intercourse or a known or suspected contraceptive failure. In comparison, PLAN B and PLAN B ONE-STEP should be used within 3 days per FDA	A disadvantage to ELLA is its Rx-only availability. PLAN B and PLAN B ONE-STEP are available over-the-counter (OTC) for patients > 17 years of age; both are Rx for those < 17 years of age. ► PLAN B is available generically as NEXT . exclude, same as Plan B	Exclude, OTC alternatives		
30044530002030	XGEVA INJ	DENOSUMAB INJ 120 MG/1.7ML	Same drug as Prolia, different indications	Prolia 60mg $990/unit	1164.71	$1165 (120mg every 4 weeks)	For the treatment of osteoporosis in postmenopausal women at high risk for fracture and For the prevention of skeletal-related events in patients with bone metastases from solid tumors	exclude (same as Prolia)	Medical N/A		

30908230000320	CARBAGLU TAB 200MG	CARGLUMIC ACID TAB 200 MG	There are 2 currently marketed products known as “nitrogen scavengers,” Medicis Pharmaceutical Corp’s AMMONUL (sodium phenylacetate/sodium benzoate) and BUPHENYL (sodium phenylbutyrate), approved by the FDA to treat hyperammonemia in urea cycle disorders.	Ammonul $2,866.80 per 50 mL single-use vial Child: $5,733.60 Adult: $11,467.20 for 30 day supply. Buphenyl $7.72 per tablet; $3,857.38 per 250 gram can Child: $3,857.38 - $7,714.76 Adult: $8,106.00 - $10,653.60 for 30 day supply	159.60	$5586 per day	CARBAGLU (carglumic acid) is a Carbamoyl Phosphate Synthetase 1 (CPS 1) activator indicated as: (1) adjunctive therapy for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) and (2) maintenance therapy for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS).	CARBAGLU is the only product FDA-approved as a specific treatment of hyperammonemia due to NAGS deficiency. Other available treatments are unspecific for this indication.	PA T3. Specialty		
86805005102060	BROMDAY SOL 0.09%	BROMFENAC SODIUM OPHTH SOLN 0.09% (BASE EQUIV) (ONCE-DAILY)	Xibrom		91.18	1.700ML					
62407025100120	GILENYA CAP 0.5MG	FINGOLIMOD HCL CAP 0.5 MG (BASE EQUIV)	Avonex, Betaseron, COPAXONE, EXTAVIA, NOVANTRONE, REBIF, TYSABRI	(vs. $2,800 - $3,200 month for injectable therapies)	158.08	$4426 per 28 day supply	GILENYA (fingolimod) is the first oral therapy approved for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. GILENYA belongs to a new class of drugs called sphingosine-1-phosphate receptor (S1P) modulator	Current treatment guidelines recommend that initiation of interferon beta or glatiramer acetate should be considered when a diagnosis of relapsing disease is made. Natalizumab is generally reserved for patients who had an inadequate response or were unable to tolerate other MS therapies. Mitoxantrone is reserved for relapsing patients with worsening disease or patients with secondary progressive disease, whether or not relapses are occurring. first in class drug that prevents white cell release from lymph nodes, which attach the myelin sheath...* risk of toxicity for the heart, lung & eye along with increase risk of infection.	T3 w PA. Specialty		

45100010102020	GLASSIA INJ	PROTEINASE INHIBITOR (HUMAN) INJ 1000 MG/50ML	ARALAST - PROLASTIN –ZEMAIRA -		11.04	Single use vial 1 gram Alpha1-PI in 50 mL Solution 60 mg/kg body weight administered once weekly by intravenous infusion			Exclude. Specialty		
25990003200320	BEYAZ TAB	DROSPIRENONE-ETHINYL ESTRAD-LEVOMEFOLATE TAB 3-0.02-0.451 MG	compared to about $50 for the generic without folate (*Gianvi*) plus $2 for a folate supplement.		3.04286	85.12		Beyaz (bee-YAZ) is a new version of Yaz with folate. recommend using a generic OC plus a separate multivitamin or folic acid supplement	Exclude		
90550085206420	PEDIADERMTA KIT	*TRIAMCINOLONE CREAM 0.1% & EMOLLIENT CREAM KIT**			1.45043			exclude kits	Exclude		
90150080506420	PEDIADERMAF KIT COMPLETE	*NYSTATIN CREAM 100000 UNIT/GM & DIAPER RASH CREAM KIT**			1.15833			exclude kits	Exclude		
833370302001**	PRADAXA CAP 75, 150MG	DABIGATRAN ETEXILATE MESYLATE CAP	warfarin $23/month		4.05	$8.10 per day and/or $243 per 30 day supply.	PRADAXA is the first oral direct thrombin inhibitor (a type of anticoagulant). It is FDA-approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). PRADAXA will be competing with warfarin (COUMADIN, JANTOVEN), the existing "gold standard" oral anticoagulant that has been on the market for over 50 years. PRADAXA was designed to overcome the disadvantages of warfarin, specifically regarding onset of action and dissipation, predictability of anticoagulant effect, probability of food-drug interactions, and need for monitoring. PRADAXA is also being studied for other conditions such as venous thromboembolism (which will open the market for it to compete against heparin and low molecular weight heparins (LMWH)).	* Significant decrease risk of bleeding complications as compared to warfarin. Cost effectiveness study in the Annals of Internal Medicine supports this. * More predictable anticoagulant action thus less frequent coagulation monitoring & dosage adjustments * More rapid onset and offset of action. * Low risk of drug interactions To mitigate the risks of bleeding associated with the use of PRADAXA, the drug will be subject to a risk evaluation and mitigation strategy (REMS). A Medication Guide will be required to be dispensed along with each prescription informing patients of the serious risks associated with PRADAXA, particularly the increased risk of bleeding and how such symptoms should be recognized. : Cover with a daily dose limit of 2 per day.	T3		

30042065100635	ATELVIA TAB	RISEDRONATE SODIUM TAB DELAYED RELEASE 35 MG	Actonel 35mg		30.45	$121.76			T3		
30150085102120	EGRIFTA INJ 1MG	TESAMORELIN ACETATE FOR INJ 1 MG (BASE EQUIV)			39.29				Exclude. Whether Egrifta decreases the risk of cardiovascular disease or improves compliance with antiretroviral drugs has not been studied.		
68000050002020	KRYSTEXXA INJ 8MG/ML	PEGLOTICASE INJ 8 MG/ML (FOR IV INFUSION)			1,380.00				N/A Medical.		