AGENTS FOR TYPE 2 DIABETES
& Hypoglycemic Comparison Chart

The **RxFiles**

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The RxFiles Academic Detailing Program
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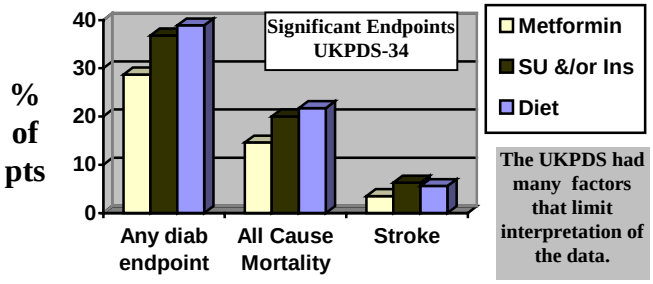
Type 2 diabetes is a **progressive disease** with modifiable risk factors. While some patients may initially be managed with **diet and exercise**, about 50% will require drug therapy within 1 year.[1] For optimal glycemic control, many patients will eventually need oral combination and/or insulin therapy. **Since diabetes is a multifactorial disease, optimal care must also emphasize control of blood pressure, lipids, etc.**

KEY FINDINGS FROM THE UKPDS

◆**The UKPDS-33** showed that intensive blood-glucose-control reduced the 10 year risk of **microvascular** endpoints by ~**25%** compared to patients allocated to the conventional treatment group.[2] Intensive glycemic control did not have a significant impact on **macrovascular** endpoints (e.g. risk of stroke or myocardial infarction), diabetes related mortality or all cause mortality. However, tight blood pressure control (UKPDS-38) reduced some macrovascular endpoints.[3]

◆**The UKPDS-34** studied treatment of **obese Type 2** patients with diabetes followed for a mean of 10 years.[4] **Metformin** *GLUCOPHAGE* showed the following benefits compared to conventional (primarily diet) therapy [reductions based on # of patients with endpoint]:
38% ↓ risk of stroke; (absolute risk reduction: ARR=2.1%)
32% ↓ risk of any diabetes related endpoint (ARR=10.2%)
33% ↓ in all-cause mortality (ARR=7.1%)

Treatment with sulfonylureas (SU) and insulin did not confer the same benefits. The authors postulated that since HbA_{1c} was similar in both metformin and SU/insulin groups, glycemic control alone could not explain the risk reduction.



The UKPDS had many factors that limit interpretation of the data.

CHOOSING AN ORAL HYPOGLYCEMIC

Obese Versus Non-obese

◆ **In non-obese patients, metformin or sulfonylureas (SU) are usually considered first-choice agents.**

◆ **In obese patients (BMI ≥30kg/m^2), metformin should be considered for first-line therapy. As noted above, it was the only agent to reduce overall mortality in the UKPDS.**[4]

Metformin should be avoided in patients with impaired **renal function**, hepatic disease, alcoholism, symptomatic CHF, and those undergoing intravascular radiocontrast study who are at risk of lactic acidosis.[5] Dosage adjustment may be required in the elderly (due to declining renal function; see **Table 2**).

Table 2: Metformin Dosing In The Elderly*

Lactic acidosis associated with metformin is rare (<1:10,000 treated patients) and may not be different than the background rate in the general population.[6,7] If metformin is used in the elderly, dosage may require adjustment based on estimated creatinine clearance (Following table derived from study of those age ≥74yr).[8]

CrCl (ml/min)	Maximum Metformin Dose
60	1,700 mg/day*
30	850 mg/day*
<30	contraindicated

* **Calculation of creatinine clearance (CrCl):**
◆CrCl ml/minute = $\frac{(140\text{-age}) \times \text{Weight (kg)}}{\text{Serum creatinine (umol/L)} \times (0.814)}$
◆Females: CrCl = 0.85 x CrCl (male)

*There are varying opinions regarding the safety of metformin in those with reduced renal function. **Some specialists are more cautious and avoid any use.** The "Glitazones" are an alternative in overcoming insulin resistance.[9]

Predominent Elevation in PPBG

◆Patients who have an elevated postprandial blood glucose (PPBG) > 10mmol/L and whose fasting plasma glucose (FPG) is < 7 may be considered for agents such as acarbose *PRANDASE* whose main effect is on PPBG. Repaglinide *GLUCONORM* and insulin lispro *HUMALOG* may be considered in patients who have suboptimal control of both PPBG and FPG. PPBG may be elevated early in the course of disease and there is some evidence it is related to poor macrovascular outcomes.[10]

Table 1: Tx GOALS – ADULT DIABETES

		OPTIMAL	SUBOPTIMAL		INADEQUATE	
GLUCOSE CONTROL[11] ◆ HbA_{1c} q3-6 months ◆ calibrate meter yearly	**HbA_{1c}** (%) **FPG** (mmol/L) **PPBG** (mmol/L)	TARGET < 7.0 4.0-7.0 5.0-11.0	7.0-8.4 7.1-10 11.1-14.0	⇨action may be necessary	> 8.4 > 10 > 14	⇨action required
BLOOD PRESSURE[12] ◆ q3-4mo	**BP** (mmHg)	< 130/80	< 140/90		> 140/90	
DYSLIPIDEMIA[13] ◆ q12 months; more often for patients with heart disease	**LDL** mmol/L **Total :HDL ratio** **TG** mmol/L	< 2.5 < 4 < 2.0	◆Based on fasting lipid profile; ◆All 3 target values should be achieved; ◆Modifying lipids more effective than modifying blood glucose to ↓ mortality in patients with heart disease & diabetes[14]			

HbA_{1c} = glycosolated hemoglobin A_{1C}; **FPG** = fasting plasma glucose; **PPBG** = postprandial (2hr)[15] blood glucose; **BP** = blood pressure; **TG** = triglycerides
****Target treatment goals need to be individualized** with consideration given to life expectancy, co-morbidity and risk of hypoglycemic side effects.

COMBINATION ORAL THERAPY

◆**Combination therapy will be required in most Type 2 patients to maintain glycemic control.** Many combinations have been studied in terms of their effects on glucose control. Other effects such as weight gain, changes in lipid profile, and additive risk of hypoglycemia have also been evaluated.

◆A variety of patient factors should be considered in agent selection. (see **Table 6 – Individualization of Therapy**).

◆Some dual combination regimens have been studied (See **Table 7: Combination Therapy**). Combinations of more than 2 agents may also be used, but data on these combinations is not available.

◆The combination of repaglinide & sulfonylureas is **not** recommended.[16]

INSULIN IN TYPE 2 DIABETES

◆**Most current guidelines suggest that when diet, exercise and oral agents fail to provide glycemic control, insulin is indicated.** Evidence regarding this is currently limited to studies evaluating glycemic control. Studies on the effects of insulin on clinical outcomes such as morbidity and mortality have not been done. **The UKPDS found that insulin therapy was often eventually necessary for glycemic control**. It found that tight glycemic control reduced the risk of microvascular complications. Hyperinsulinemia did not appear to contribute to cardiovascular risk, an issue that is still under some debate. Drawbacks to insulin therapy include the side effects of weight gain, hypoglycemia and patient reluctance to use insulin.

◆**Combinations of oral hypoglycemics and insulin are likely preferable to treatment with insulin alone**. A combination approach has an insulin sparing effect and usually leads to improved glycemic control. Some combinations are associated with less hypoglycemia and less weight gain.[17] Inclusion of metformin in the regimen minimizes the problems of weight gain and hypoglycemia. The FINFAT study compared different agents combined with bedtime insulin and found that a reduction in HbA_{1c} of 2.5% was greater for metformin than for other studied combinations (SU, SU+metformin, morning insulin).[18]

◆**Adding bedtime insulin to oral hypoglycemics is commonly recommended**. This approach allows lower doses of insulin to be used, and keeps the insulin regimen simple. (See page 3 – Approach … Add Insulin Therapy.)

Treatment of comorbidity is key!

Table 3: NOTES ON NEWER AGENTS (see also Table 8)

Thiazolidinediones (TZDs)

◆Agents: **rosiglitazone** ***AVANDIA*** and **pioglitazone** ***ACTOS***

◆TZDs are insulin sensitizers and are moderately effective in controlling hyperglycemia. Adverse effects include **weight gain** and **edema** (~4.8% versus 1.2% for placebo)[19]; caution in patients with heart failure/hypertension. Incidence of edema was higher in patients also on insulin.

◆Patients on TZDs require monitoring of **liver function tests (e.g. ALT)** at baseline, q2 months during the 1st year of therapy and periodically thereafter. Therapy should not be initiated in patients whose ALT is >2.5x the upper limit of normal and should be discontinued in patients whose ALT rises >3x upper limit of normal. (Troglitazone, the first agent in this class was withdrawn from the market due to severe hepatotoxicity and ≥ 60 deaths.)

◆There is some hope that if TZDs are **used early** in the course of Type 2 diabetes, they may be able to alter the progression of the disease.

◆Studies on morbidity/mortality outcomes not yet available

◆Long-term safety remains to be established

Acarbose ***PRANDASE***

◆Acarbose is useful in reducing peak postprandial blood glucose (PPBG) concentrations.

◆**Side effects** of flatulence, abdominal discomfort and diarrhea limit patient acceptance of this agent. These side effects can be minimized by **starting with low dosages** (e.g. 25mg with each meal) & **titrating up over several months**.

◆**Safety advantages**: it does not cause hypoglycemia

◆Studies on morbidity/mortality outcomes not yet available

◆Long-term safety remains to be established

Repaglinide ***GLUCONORM***

◆Repaglinide is rapid but short acting and is useful in lowering **PPBG** and HbA_{1c} . It has a lower risk of hypoglycemia than sulfonylureas and appears to be well tolerated. **It may be especially useful in individuals with irregular eating habits**.

◆Studies on morbidity/mortality outcomes not yet available

◆Long term safety remains to be established

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References available on website or on request

Table 4: NOTES ON COMORBIDITY ⇨ diabetics are at 2-4-fold higher risk for cardiovascular disease than non-diabetics

Pharmacological Treatment of HYPERTENSION

◆Benefits of intensive hypertensive control may have a **greater** impact on reducing **macrovascular** morbidity (e.g. stroke) and mortality than intensive blood glucose control.[20,21]

◆**Up to 3 antihypertensives often needed to meet target.**

{See 1999 Canadian Recommendations–CMAJ 1999;161(12 Suppl):S1}

Pharmacological Treatment of DYSLIPIDEMIA

◆*The lower the better*; potential outcome benefit of lowering lipids is **greater** in diabetics than non-diabetics. (good evidence for 2° prevention; studies for 1° prevention ongoing)[22]

◆Patients with diabetes without previous MI are as high-risk for an event as nondiabetic patients with previous MI.[23,13]

ASA to Prevent CORONARY ARTERY DISEASE (CAD)

◆**Low-dose ASA** (81-325mg po OD) is recommended for all patients (age ≥30 yrs) with diabetes unless contraindicated.[24]

Treatment of MICROALBUMINURIA (MAU)

◆MAU is a marker for diabetic nephropathy and cardiovascular disease. With early recognition & therapy, diabetic risk reduction does occur.

◆Treatment of MAU: **ACE Inhibitor** – start low & titrate up; Angiotensin II Receptor Blockers (ARBs) may be considered if patients unable to tolerate ACEI. Recent data suggest that the ARBs may protect against the progression of kidney disease.[25,26,27] Early treatment of hypertension is also important.

Table 5: APPROACH TO MANAGEMENT OF TYPE 2 DIABETES

Nonpharmacologic Therapy

- **Lifestyle Modifications** & **Patient Education** are important at all levels!!! [28,29]

If individualized goals for glucose are not achieved in 2-4 months,
⇨*reassess; advance to next level of therapy*

See Health Canada's Food & Fitness Guides

Oral Hypoglycemic Monotherapy

MF target dose in UKPDS (age ≤65): 1700mg am + 850mg @supper

If obese (BMI ≥30)

- ⇨ start metformin (**MF**) **500mg po OD** or BID
  (↑dose over 3-4 weeks; usual ≤2,000mg/day; lower doses in elderly-see Table 2)
- ⇨ alternative agents used if metformin contraindicated/not tolerated
  (e.g. acarbose, sulfonylureas, repaglinide, "glitazones"; see chart)

If non-obese

- ⇨ start sulfonylurea (SU) or metformin (↑dose over 3-4 weeks)
- ⇨ consider acarbose or repaglinide if main target is **PPBG**
- ⇨ alternative agents such as "glitazones" may also be considered (note these agents can take a long time before effect seen (8-16 weeks). There are theoretical advantages to early use, but await studies on morbidity and mortality outcomes

Repeat HbA_{1c}; Reassess lifestyle modifications in 2-4 months,
⇨*If targets for glucose control not achieved, advance combination therapy*
(Combination therapy will be required in most Type 2 patients)

Oral Combination Therapy

- a variety of 2-drug (& sometimes 3 drug) combinations may be considered
- combination of repaglinide and sulfonylureas not usually recommended

Repeat HbA_{1c}; Reassess lifestyle modifications in 2-4 months,
⇨*If targets for glucose control not achieved, advance to next level of therapy*

Add Insulin Therapy +/- Oral Agents

- **Option 1: Bedtime insulin** (e.g. Humulin N/Novolin N) **+ daytime oral hypoglycemics**
  - ⇨**if** on SU + other oral agent, may consider discontinuing / reducing the SU
  - **add intermediate acting insulin, 10-15units at HS (initial max 0.25units/kg)**
  - -↑ insulin dose by **2 units every 3-4 days** until fasting glucose of 4 -7
  - -may result in better control, lower insulin dose, less weight gain than insulin alone
  - -if target BG not achieved at 30units/day, or if daytime BG rises, may switch to split-mixed insulin or a more intensive regimen (usual range: 0.25-1unit/kg/d)

- **Option 2: Switch to insulin therapy 1-4x/day**
  - ⇨may discontinue oral hypoglycemic agents
  - -adjust insulin dose and frequency to achieve target levels
  - **e.g. Split-mixed insulin regimen**
  - -estimate total starting daily dose (0.3-0.6 units/kg)
  - -divide daily dose: 2/3 in morning before breakfast; 1/3 in evening before supper
  - -divide each dose: 2/3 intermediate-acting & 1/3 short-acting insulin (or 30/70 mix)

Some patients may eventually require very high doses of insulin due to insulin resistance (max 400U/day in UKPDS)

(Note: insulin temporarily indicated in any patient with metabolic decompensation, severe fasting hyperglycemia, or severe illness.)

BMI (kg/m²)		WEIGHT (Kg; *lbs*)																	
		45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130
		99	*110*	*121*	*132*	*143*	*154*	*165*	*176*	*187*	*198*	*209*	*220*	*231*	*242*	*253*	*264*	*275*	*286*
HEIGHT (Cm; *inches*)	150 *59*	20	22	24½	26½	29	31	33	35½	38	40	42	44½	46½	49	51	53	55½	58
	155 *61*	18½	21	23	25	27	29	31	33	35½	37½	39½	41½	43½	46	48	50	52	54
	160 *63*	17½	19½	21½	23½	25½	27	29	31	33	35	37	39	41	43	45	47	49	51
	165 *65*	16½	18½	20	22	24	26	27½	29½	31	33	35	36½	38½	40½	42	44	46	48
	170 *67*	15½	17	19	21	22½	24	26	27½	29½	31	33	34½	36	38	40	41½	43	45
	175 *69*	14½	16	18	19½	21	23	24½	26	28	29½	31	32½	34½	36	37½	39	41	42½
	180 *71*	14	15½	17	18½	20	21½	23	24½	26	28	29	31	32½	34	35½	37	38½	40
	185 *73*	13	14½	16	17½	19	20½	22	23½	25	26	28	29	30½	32	33½	35	36½	38
	190 *75*	12½	14	15	16½	18	19½	21	22	23½	25	26	27½	29	30½	32	33	34½	36
	195 *77*	12	13	14½	16	17	18½	19½	21	22½	23½	25	26	27½	29	30	31½	33	34

Underweight = <18.5kg/m²; **Normal** = 18.5-24.9kg/m²; Overweight = 25-29.9kg/m²; **Obese = ≥30kg/m²**

Table 6: Individualization of Drug Therapy: Special Considerations

Patient Factor	Consider ⇨
Renal failure	**"Glitazones"**, **Repaglinide**; also tolbutamide or gliclazide [30]
Hypoglycemia	**Metformin**, **"Glitazones"**, **Acarbose**; also Repaglinide
Obese	**Metformin**; Acarbose; also "Glitazones"
Irregular mealtimes	**Repaglinide** (may be preferred over SU)
PPBG >10mmol/l & FPG minimally ↑'d	**Repaglinide** or **Acarbose** **Insulin lispro** *HUMALOG* (**if PPBG very high**)

Table 7: Combination Therapy/Insulin Therapy in Type 2 Diabetes [19,31,32,33]

Drug combination	↓ in HbA_{1C}	hypo-glyc.	Wt	Comments (long-term outcomes not well studied!)
SU + MF	↓↓↓	↑↑	↑	•if SU initial agent, may add MF or a TZD; (SU+MF may ↓HbA_{1c} by additional 1.7%; one study found ↑mortality with combination [34]) •if MF initial agent, may add SU or repaglinide •MF combos generally result in less weight gain than SU combinations; •MF+pioglitazone had positive lipid effects; •MF+acarbose: ↓ weight / PPBG but ↑GI SEs; •for hypoglyc. on acarbose: must treat with glucose as sucrose not absorbed
SU + TZD [35]	↓↓	↑↑	↑↑	
SU + acarbose	↓	↑↑	↑	
MF+ repaglinide [36]	↓↓	↑	↑	
MF+ TZD [37,38]	↓↓	↑	↑	
MF+ acarbose [39]	↓	-	↓	
TZD + acarbose	↓	↑	↑	
Insulin monotherapy	↓↓↓	↑↑↑	↑↑↑	•tight BG control but hypoglycemia/weight gain
Insulin + SU	↓↓↓	↑↑	↑↑	•may improve glycemic control over insulin alone; caution in elderly due to hypoglycemia
Insulin + MF (FINFAT STUDY [18])	**↓↓↓**	↑	↑	•**overcomes insulin resistance**; MF has positive effect on wt & lipids; preferred in obese patient; superior to insulin+SU; insulin sparing ~20-25%
Insulin+ pioglitazone or rosiglitazone*	↓↓ [40]	↑↑↑	↑↑↑	•**overcomes insulin resistance**; effective but more study needed (e.g. ↑ **risk of edema/HF** [41])
Insulin+ repaglinide	↓↓	↑↑	↑↑	•option to ↓ PPBG
Insulin + acarbose	↓↓	↑↑↑	↑↑↑	•recommended to ↓ PPBG when diet high in CHOs; may also ↓ weight & triglycerides

•some **3-drug regimens** useful for glycemic control but not well studied (e.g. Insulin+SU+MF)

BG= blood glucose **CHO**= carbohydrate **FPG**= fasting plasma glucose **HbA_{1C}** = glycosylated hemoglobin **HF**= heart failure **MF**= metformin **PPBG** = postprandial blood glucose **SE**= side effects **SU**= sulfonylurea **TZD**= pioglitazone & rosiglitazone **Wt**= weight *****official labeling: "not indicated"

Table 8: HYPOGLYCEMIC AGENTS - COMPARISON CHART[19,42,43,44,45,46,47,48]

Prepared by: Loren Regier, Sharon Downey, Brent Jensen–***www.sdh.sk.ca/RxFiles*** - **Oct/2001**

NAME /DOSAGE FORMS	KINETICS	EFFECTS ON: FPG	PPBG	HbA1c	LDL	HDL	TGs	Wt	DRUG INTERACTION	COMMENTS	INITIAL & (Max.) DOSE	USUAL DOSE RANGE	$ / 30 Days
SULFONYLUREAS (SU) – stimulate insulin release from β cell; increase peripheral glucose utilization (↑ #/sensitivity of insulin receptors?); reduce hepatic gluconeogenesis													
Chlorpropamide DIABINESE (100, 250mg scored tab)	P = 6-8h D =24-**72h**	chlorpropamide not recommended due to ↑BP & ↑ retinopathy (UKPDS-33)							**Numerous:** ◆ ↑ Hypoglycemic effect with: **EtOH**, NSAIDs,salicylates, sulfonamides, MAOIs, cimetidine. ◆ β-Blockers may mask hypoglycemia ◆ Disulfiram rx. with EtOH, mostly with chlorpropamide ◆ rifampin ↓ effect	Does not correct impaired 1st phase insulin response; many (~75%) require 2nd agent for adequate control (e.g. + metformin or TZD); ~ 1st choice option for **lean** patient	100mg od (500mg od)	100mg po od 250mg po od	10.00 **9.00**
Gliclazide ✘ DIAMICRON 80mg tab DIAMICRON MR 30mg	P = 4-6h D=10-**24h**	↓	↓	↓↓	-	-	-	↑↑		**Hypoglycemia**: most with chlorpropamide & glyburide (see note below); **least** with **tolbutamide & gliclazide**[49] Caution in elderly (hypoglycemia risk) & obese (wt gain). **Require consistent food intake** to avoid problems with hypoglycemia (↑risk: elderly, debilitated, malnourished) **SE: Wt gain,** headache, dizziness, sulfa skin reactions (rash/photosensitivity ~1%), GI side effects in 1-3%; concerns with cardiac toxicity and hyperinsulinemia. Reduce dose if hypoglycemia or renal/hepatic dysfx **Dose titration q1-2 weeks**	40mg (160mg bid) 30mg (120mg od)	80mg po bid 60mg MR po od	**25.00** **25.00**
Glyburide DIABETA (2.5, 5mg scored tab)	O=15-60min P= 2-4h D =12-**24h**	Total Wt gain with glyburide >4kg vs >6kg insulin (UKPDS-33)									1.25-2.5mg od (10mg bid)	5mg po od 5mg po bid 10mg po bid	8.00 **9.00** 11.00
Tolbutamide ORINASE (500mg scored tab)	P = 3h D =6-**12h**	**Glimepiride** AMARYL ✘ (1,2,4mg scored tablets) 1mg od(4);2mg od($);4mg od($)									250mg od (1000mg tid)	500mg po bid 500mg po tid	9.00 **11.00**
BIGUANIDES – increase insulin sensitivity and cellular glucose uptake & utilization; reduce hepatic glucose production; ↓ morbidity & mortality in obese patients (UKPDS-34)													
Metformin (MF) GLUCOPHAGE (500, 850mg tab)	P = 3h D = 8-12h	↓	↓	↓↓	↓ **+'ve effect on lipids & weight**	↑	↓	-/↓	◆ **EtOH** and cimetidine ↑ effect ◆ contrast media (long-term ↓ B_{12} & folate absorption) {**Caution if CrCl ≤ 60ml/min**}	**Does not by itself cause hypoglycemia** Possible **wt loss** vs wt gain; **⇨ DOC for OBESE !** **SE**: To avoid **GI** SEs, **start low & titrate up q2-4wk** Anemia 6-8:100 (due to B12 malabsorption) Avoid if **severe renal dysfx/CHF** or hepatic disease (lactic acidosis 1:10,000)[8]. +SU, TZD, Ins., CMBA **Elderly**: dose reduction required (see Table 2).[8] UKPDS: 1700mg po am, 850mg po pm TID dosing option for larger doses to ↓ GI intolerance (dyspepsia, nausea & diarrhea)	**250-500mg od** (850mg tid)	500mg po bid 500mg po tid 850mg po bid	11.00 **13.00** **17.00** 22.00
α GLUCOSIDASE INHIBITORS – inhibit α-glucosidases in brush border of small intestine; prevent hydrolysis & delay digestion of carbohydrates (Tx hypoglycemia with glucose/Insta-gluc)													
Acarbose PRANDASE (50,100mg scored tab)	**Meal-time dosing**; may take several weeks for max. effect	acarbose minimally absorbed; monitor 2hr PPBG							◆ ↓ digoxin effect ◆ Cholestyramine & cathartics ↑ effect ◆ amylase & pancreatic enzymes ↓ effect ◆↓ Fe^{++}? (**sucrose** not absorbed)	**Does not by itself cause hypoglycemia** ↑ Liver enzymes = 3% with acarbose; monitor. (Caution as may accumulate in chronic renal failure.) **SE: GI intolerance**: **flatulence** >41%, **diarrhea** >28%, Maximal effect takes weeks; ↑ **dose q4-8wks** **ROLE**: useful in pts with ↑ **PPBG**; + SU, MF; (+Ins.?)	**25mg od** (100mg tid)	50mg po tid 100mg po tid	31.00 **41.00**
Miglitol (not yet available in Can.) ✘ GLYSET (25,50,100mg tab)		↓ miglitol well absorbed		↓↓	↓	-	-	-/↓	-/↓		25mg od (100mg tid)	25mg po tid 50mg po tid	n/a **n/a**
THIAZOLIDINEDIONES (TZDs) or "GLITAZONES" – insulin sensitizers: ↓ hepatic output of glucose & ↑ peripheral insulin uptake; ~ 4+ weeks before effect (adjust dose at ~3 months)													
Pioglitazone ACTOS (15, 30, 45 mg tab)	**Delayed action**… Onset ~3wks	↓	↓	↓	-	↑	↓	-/↑	◆ Cholestyramine ↓ absorption ~70% ◆Hepatic CYP 2C8 ◆ rosiglit. has no effect on CYP3A4 ◆ ↓ effect of oral contraceptives?	More effective in obese or hyperinsulinemia patients **Does not by itself cause hypoglycemia**; resumption of ovulation in anovulatory premenopausal women **SE: Edema 4.8%** (**HF**;HTN); **Wt gain;** 1% mild anemia (due to hemodilution?);monitor **liver fx** (**ALT**) **q2mo** in **1st yr**; pioglitazone may have more +ve lipid effects[50,51] **ROLE**: + MF,SU; (possibly alone or + Ins. but ↑HF risk)	15mg od (45mg/day)	15mg po od 30mg po od 45mg po od	92.00 **92.00** 92.00
Rosiglitazone AVANDIA (2, 4, 8mg tab)	**Max effect in 8-16 wks**	↓	↓	↓	52 -/↑	-/↑	-/↓	-/↑			4mg od (4mg bid) bid dose ~more effective (53)	4mg po od 4mg po bid 8mg po od	92.00 183.00 **106.00**
CARBAMOYL BENZOIC ACID DERIVATIVES (CMBAs) – short-acting insulin secretagogue; bind to β cell to stimulate insulin release at different site than SUs; (adjust dose at ~7days)													
Repaglinide GLUCONORM (0.5, 1, 2mg tab)	O = **<10min** P=60-90min D = ~**2-4h**	↓	↓↓	↓↓	-	-	-	-/↑	◆ CYP3A4 inhibitors ↑ effect: azole antifungals & erythromycin ◆CYP3A4 inducers ↓ effect: barbs, carbamaz & rifampin	Restores 1st phase insulin release - (↓ PPBG) **Rapid, short duration** ⇒ ↓ risk of hypoglycemia vs SUs ∴option in **elderly**; greater **flexibility** with food intake If stopping other hypoglycemic agents, begin next day and watch for hypoglycemia **ROLE**: alone or + MF, TZD, or Ins. **Flexibility with food intake: skip dose if skip meal; take extra dose if add meal**	0.5mg tid if no previous drug tx or if HbA_{1c} <8%; (4mg qid)	0.5mg po tid 1mg po tid 2mg po tid 4mg po tid	34.00 **35.00** 36.00 65.00

$ Retail *Cost to Consumer* based on acquisition cost, markup & dispensing fee in Sk; Lowest generic price used where available. ✎ = Exception Drug Status in SK ✘ = Non-formulary in SK; '+' denotes combination options **BP**= blood pressure **DOC**= drug of choice **dysfx**= dysfunction **EtOH**= alcohol **FPG**= fasting plasma glucose **GI**= gastrointestinal **HbA_{1C}** = glycosolated Hemoglobin A_{1C} (reflects glycemic control over prior 8-10 weeks) **HDL**= high density lipoprotein **HF**= heart failure **Ins.**= Insulin **KINETICS**: **O**= onset **P**= peak **D**= duration; **LDL**= low density lipoprotein **PPBG**= postprandial blood glucose **SE**= side effects **Wt**= weight

*** Drugs that may cause hyperglycemia** and loss of diabetic control: corticosteroids, diuretics (high-dose thiazides), estrogens, phenothiazines, phenytoin, sympathomimetics (decongestants) & thyroid products. Beta-blockers minimal risk of altering glucose control but may alter/mask hypoglycemic response. **Pregnancy:** Encourage diet, moderate exercise; Avoid oral hypoglycemics; Add insulin as needed if FBG >5.3 & 2hr PPBG >8.9.

Hypoglycemia risk -UKPDS: risk of **≥1 MAJOR** hypoglycemic events/yr (ITT): chlorpropamide=1%, glyburide=1.4%, insulin 1.8%; risk of **ANY** hypoglycemic event/yr chlorprop.= 16%, glyburide=21%, insulin 28%.

Oral agents +/- insulin: with progression of Type 2 diabetic disease, combination therapy with oral agents &/or addition of insulin to the regimen may eventually be required.

PPBG may better reflect risk of cardiovascular disease and all-cause mortality than FBG[10]; FBG and HbA_{1c} are greater predictors of microvascular complications.

◆ Also consider: ASA, ACE Inhibitor, control of lipids/ hypertension, diet/exercise & DC smoking!

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