ANTI-HYPERGLYCEMIC TYPE 2 DIABETES AGENTS: Drug Comparison Chart

DC'18 updated'20, ADA'23, ACP'18

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Generic/TRADE Pregnancy/Lactation → PL	Comments	Effects On: Hypo-glycemia	Effects On: PPG	Effects On: A1c %	Effects On: Wt	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Initial, Usual & Maximum Dose	$/100 d
Biguanide: site of action→adipose/muscle/liver; ↓ hepatic gluconeogenesis; ↑ insulin sensitivity; ↑ glucose utilization; ✓**T2DM** *(T2DM prevention; may use, but not officially indicated by Health Canada)*								
Metformin **GLUCOPHAGE**, **GLYCON**, g 500ᶜ, 850mg tab **GLUMETZA**, g ✗ ⊗ 500mg, 1000mg ER tab once daily dosing with food {ghost tab shell may be passed in stool after releasing drug **GLUMETZA** ✗ ⊗, **JANUMET XR** ☎ ✆}	**1st line for T2DM**. DC(A,1A), ADA(A), ACP (exception: insulin indicated 1st line ± metformin if metabolic decompensation) • Titrate ~q2-4 weeks to ↓ GI AEs (~85% of glycemic lowering effect reached at 1500mg/day) • Max effect ~2 weeks; peak: 3hr • Continue as other treatment added (e.g. insulin) ADA(A) • Other use: prevention of T2DM DC(A,1A),DPP, PCOS, pregnancy: gestational diabetes (insulin 1st line),DC,MIG continued/added to insulin in pre-existing T2DM.MiTy	Negligible risk with mono-therapy	↓	↓↓ 1-1.5	↓↓ 2.9kg /4yrs ADOPT Neutral DC **CVD outcome summary:** • **↓ mortality & myocardial infarction** in obese (>120% ideal body weight) **NNT=14**/10.7 yearsUKPDS-34 • Observational follow-up: ↓mortality **NNT=14**/1000 patient yrs & ↓MI **NNT=14**/1000 patient yrsUKPDS-80	**AE**:**Common: GI** (nausea/diarrhea), to avoid: **start low dose, titrate slowly, take with food, may divide large doses TID**; tolerance over ~1-2wks; reports of GI adverse events after many years of use (lowering dose may help to resolve) **Rare:** lactic acidosis 9/100 000 pt yrs Cochrane '10 (↑risk if eGFR <30mL/min), ↓Vit B12 absorption (anemia, peripheral neuropathy, treatment oral B12) **CI**: hx lactic acidosis, severe liver dx; Caution: eGFR 30-45mL/min (see dosing); **hold in acute illness if dehydrated** e.g. HF, AKI as ↑ risk for AE see SADMANS tool; lean, frail elderly ↓ muscle mass; hold day of surgery;ADA colonoscopy hold when NPO, if risk AKI **DI**: ↑Metformin: **EtOH**, dolutegravir (max metformin: 1000mg/d), cimetidine, TMP; contrast media (hold for 48hr after iodinated contrast media for imaging if eGFR<45mL/min);CAR 2012 insulin or sulfonylurea (↑ hypoglycemia); Metformin: ↓ Vit B12 & folate; &↓ TSH in treated hypothyroid patients **M**: SCr (baseline & then periodically), hemoglobin & B12 (periodically e.g. q1-2yrs) **Admin**: Take metformin ER e.g. **GLUMETZA, JANUMET XR** with food to ↑ bioavailability	**Initial**: **125-250-500mg po daily cc**, ↑ q2-4 weeks to minimize GI AEs **Usual**: 1000mg po BID **cc** ADOPT, GRADE background tx 1700mg cc am & 850mg cc pmUKPDS-34 **GLUMETZA**: 1000-2000mg ER po **cc** pm **Max**: 2550mg/d → 850mg TID (**usual** 1g BID) eGFR 30-45mL/min: ≤1000mg/d; eGFR <30mL/min: avoid (?ok-stable, eGFR ≥15mL/min:500mg/dLalau'18) **Dialysis:** discontinue (lactic acidosis risk)KDIGO **Adolescent**: 1st line ≥ 10 years old **Initial:** as per adult; **Max:** 2000mg/day **Prevent/Prediabetes**: (screen for CV risk factors) 850mg BID + lifestyleDPP	$11-13 $21 $21 $148-286g $21 $17
Sulfonylureas (SU): site of action→pancreas; insulin secretagogue; ↑ β cell insulin release; ✓ **T2DM**								
Gliclazide **DIAMICRON MR**, g 30, 60mgᶜ tab {ghost tab shell may be passed in stool after releasing drug} **DIAMICRON**, g ✗ ▼ 80mgᶜ tab	May be used 2nd line for T2DM (others preferred if CVD/CKD/HF); gliclazide preferred over glyburide b/c ↓ hypoglycemia, CV events and mortality. DC, ADA, Simpson'15 • Cost-effective 2nd line agent CADTH,WHO • Titrate ~q1-2wks slower if elderly (~75% of glycemic lowering effect reached at half of max dose) Plasma peak: 4-6h gliclazide; 2-3h glimepiride; 2-4h glyburide • Rapid BG lowering but poor durability, ~75% require combo tx • Lose efficacy over time as the pancreas produces less insulin • **Insulin initiation**: ↓dose 50% or dose AM if basal insulin; stop if prandial insulin Other use: 1st line HNF1A/4A-MODY,	Moderate risk (least with gliclazide)	↓	↓↓ 1-1.5	↑ 1.6kg /4 yrs ADOPT ↑ 1.5-2.5 kg DC **CVD outcome summary:** • Trials have shown microvascular benefitADVANCE, UKPDS-33 & similar, neutral CV outcomes when glimepiride compared to linagliptinCAROLINA • gliclazide, glimepiride, glyburide do not appear to cause CV harm but also haven't shown CV benefit	**AE**:**Common: hypoglycemia** (less than insulinUKPDS-33; most with glyburide > glimepiride > gliclazide preferred in elderly), **weight gain** (less than insulinUKPDS-33), GI 1-3%, sulfa skin reaction (rash/photosensitivity ~1%), headache, dizziness **Rare:** cardiac toxicity, SIADH, tooth discolouration with glyburide in peds Overdose: dextrose IV & possibly octreotide; watch for recurrence **CI**: severe renal (?30mL/min gliclazide, glimepiride, 60mL/min glyburide DC'18) or hepatic dysfunction Caution: G6PD deficiency, debilitated, ↑hypoglycemia (≥60yrs ↓dose, titrate slowly, gliclazide preferred by BEERS), **hold in acute illness if dehydrated** as ↑ AE risk see SADMANS, surgery (stop am of surgery and re-start when food intake is resumed), pre-colonoscopy (hold during clear, liquid prep & re-start post-procedure) **DI**:↑hypoglycemia risk: ranitidine, clarithromycin, **EtOH**, fluconazole, fluoxetine, TCAs, MAOIs, metronidazole, NSAIDs, quinolones, salicylates, sulfonamides, warfarin;glimepiride or glipizide (FDA) insulin (see left) ↓ SU effect: rifampin; BB can mask hypoglycemia symptoms (except sweating) **M**: SCr & LFTs (baseline & then periodically) **Administration**: Ensure consistent food intake & take with or before a meal. May dose in AM with 1st meal to prevent nocturnal hypoglycemia. D/C: Chlorpropamide **DIABINESE**; Tolbutamide **ORINASE**	**Initial**: 30mg **MR** or 40-80mg po daily in am cc **Usual**: 60mg **MR** daily or 80mg BID cc 30-120mg **MR** dailyADVANCE **Max**: 120mg **MR** daily or 160mg BID cc eGFR <30mL/minDC: **CI** **USA**: Gliclazide not available	$21 or $43 $17 or 75 $25 or 140
Glimepiride **AMARYL**, g ✗ ⊗ 1, 2, 4mgᶜ tab							**Initial**: 1-2mg po daily in am cc **Usual**: 1-4mg po daily in am ccCAROLINA (mean max dose ~5mg/day GRADE) **Max**: 8mg po daily cc Peds ≥8yrs: 1mg/day eGFR <30mL/minDC: **CI**	$145 $153 $276
GlyBURIDE **DIABETA**, g 2.5ᶜ, 5mgᶜ tab Gestational DM /pre-existing T2DM: glyburide 3rd lineDC **USA**: Glipizide **GLUCOTROL**							**Initial**: 1.25-2.5mg po daily cc **Usual**: 5mg daily-BID cc **Max**: 7.5mg-10mg BID cc eGFR <60DC: **CI** Peds >3 mo(s): 0.05-0.45$^{-1.5}$ mg/kg/day	$12-14 $17-23 $29-35
Dipeptidyl peptidase-4 (DPP4) inhibitors "gliptins": site of action→pancreas; glucose dependent ↑ insulin via ↓ incretin breakdown (↑GLP1, gastric inhibitory polypeptide [GIP]), ↓ glucagon; ✓**T2DM**								
Sitagliptin FDA'06 **JANUVIA**, g ☎ ✆ 25, 50, 100mg tab free base	May be used 2nd line for T2DM (others preferred if CVD/CKD/HF). DC, ADA • Option in elderly (well tolerated) • Plasma peak: sitagliptin 1-4hr; saxagliptin 0.5-1hr; linagliptin 1.5hr; alogliptin 1-2hr • Onset: ↓A1c ≥ 4 wks; no titration required • Drug Interactions: sitagliptin ~ alogliptin (least DIs) < linagliptin < saxagliptin (most DIs)	Negligible if mono-therapy	↓↓	↓ 0.5-0.7	-/↓ Neutral DC **CVD outcome summary:** • Mortality neutral & CVD neutral: sitagliptin,TECOS, GRADE saxagliptin,SAVOR-TIMI 53 linagliptin,CARMELINA & alogltipin;EXAMINE linagliptin vs glimepirideCAROLINA • ↑HF hospitalizations with saxagliptin **NNH=143**/2.1 yrs SAVOR-TIMI 53 & possibly alogliptin EXAMINE	**AE**:**Common:** well tolerated, ?headache, nausea, constipation/diarrhea **Rare:** hypoglycemia (reports with insulin, SUs may require ↓ insulin/SU dose), ?arthralgia (severe joint pain FDA), ?↑IBD, ↑LFTs/hepatotoxicity alogliptin, SJS, pancreatitis caution (most data with sitagliptin), pancreatic cancer, ↓lymphocyte, hypersensitivity, ?bullous pemphigoid 0.00042 cases/yr ?↑ ≥65yrs, CaucasianLee'20 **CI**: severe hepatic dysfunction & moderate dysfunction with saxagliptin Caution: HF: avoid saxagliptin (if tolerated ~1yr may continue subgroup, expert opinion) & possibly alogliptin, may use sitagliptin & linagliptin less trial data; pancreatitis history, severe renal, surgery (do not need to omit dose) **DI**: All: insulin, SUs (↑ hypoglycemia, for some may require ↓ dose); saxagliptin & linagliptin: CYP3A4 inducers (e.g. CBZ, phenytoin, rifampin) & CYP3A4 inhibitors esp saxagliptin (e.g. protease inhibitors, clarithromycin, ketoconazole); both PgP substrates GLP1 agonist: avoid combo; lacks efficacy data (& similar MOA, pancreatitis) & ↑$ **M**: SCr (baseline & then periodically), LFTs at baseline (esp alogliptin)	**Dose**: 100mg po dailyTECOS, GRADE eGFR 30-49mL/min: 50mg po daily eGFR <30mL/min, HD, PD-CKD: 25mg daily	$120g$378 $120g$378 $120g$378
Linagliptin FDA'11 **TRAJENTA** ☎ ▼ 5mg tab							**Dose**: 5mg po dailyCARMELINA no renal adjustment eGFR <15mL/min: use with caution DC	$319
SAXagliptin FDA'09 **ONGLYZA** ☎ ▼, (g ✗ ▼) 2.5, 5mg tab							**Dose**: 5mg po dailySAVOR-TIMI 53 eGFR <50mL/min: 2.5mg po daily eGFR <15mL/min: use alternative agent DC	$368$210g $314$185g
Alogliptin FDA'13 **NESINA** ✗ ⊗ 6.25, 12.5, 25mg tab							**Dose**: 25mg po dailyEXAMINE eGFR 30-50mL/min: 12.5mg po daily eGFR <30mL/min, HD: 6.25mg po daily	$289 $289 $289

awaiting supply / : **Tirzepatide MOUNJARO**✗ ⊗: GIP+GLP1 agonist; 2.5,5,7.5,10,12.5,15mg per 0.5mL single-dose pen; 2.5mg subcut wkly, titrate after 4wks, max=15mg/wk. ↓A1c & ↑Wt loss vs semaglutide 1mg/wk.SURPASS-2 **AE**: GI **CI**: thyroid tumor.

/ : **Finerenone KERENDIA**✗ ⊗: MRA nonsteroidal; 10,20mg tab OD $400/100d ; in T2DM & albuminuric CKD, added to max tolerated ACEI/ARB, ↓renal composite **NNT=30** over 2.6yr.FIDELIO-DKD, FIGARO-DKD,EurHeartJ'22 **AE**:↑K+ **NNH=17** **CI**:strong CYP3A4 ⊖

ANTI-HYPERGLYCEMIC DIABETES AGENTS: Drug Comparison Chart DC'18 updated'20, ADA'23, ACP'18

M LeBras PharmD, T Trischuk PharmD, L Regier BSP © www.RxFiles.ca July 2023

Generic/TRADE	Comments	Effects On: Hypo-glycemia	PPG	A1c%	Wt	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Initial, Usual & Maximum Dose	$/100 d
Glucagon-like peptide-1 (GLP1) agonists: site of action→pancreas; glucose dependent ↑ insulin secretion (incretin mimetic); ↓glucagon; ↓ GI emptying; ✓**T2DM**; GLP1 agonist Practice Tool								
Liraglutide FDA'10 ❄ PL **VICTOZA** ✗ ⊗ 6mg/mL; 3mL pre-filled pen need to Rx needles **SAXENDA** ✗ ⊗ ✓ see pg 58 weight loss DC(A,1A)	May be used 2nd line for **T2DM**, **if CVD** may use liraglutide,A,1A dulaglutide,A,1A or semaglutide subcut,B,2 (or SGLT2i see below).DC *Note: 1st line if CVD / high risk CV or 2nd line (after SGLT2i) if CKD.ADA* • Plasma peak: lixisenatide ~2hr; liraglutide ~10hr; dulaglutide & semaglutide ~48hr • Onset: 4 wks, may titrate to max dose if not at glycemic target • Storage: in fridge ❄, but stable at room temperature: 56 days: semaglutide (subcut); 30 days: liraglutide; 14 days: dulagutide, lixisenatide • T2DM (insulin add-on) SUSTAIN-5 see Table 1 below. • Efficacy and safety established for combination therapy with GLP1 agonist and SGLT2 inhibitor. SUSTAIN-9, AWARD-10, DURATION-8 See Table 1 below. • T1DM (insulin add-on), limited evidence (↑hypoglycemia & ↑BG with ketosis) ADJUNCT • Other **po** ongoing eg danuglipron.	Negligible if mono-therapy	↓↓	↓↓ **1-1.5** sema: ↓↓ 1.5-2 SUSTAIN-7	↓↓ 1.5-3 kg sema: ↓↓ ~4kg/ 2 yrs SUSTAIN-6	**AE**:**Common: GI (N/V/D**, dyspepsia, ↓appetite); to avoid: **start low, titrate as per product monograph (slower if not tolerating), eat smaller, more frequent & low fat meals slowly**, consider HS dosing, possible ↓ nausea with once weekly agents, tolerance over few weeks, injection site reactions (rotate site each week: upper arm, abdomen, thigh), headache, dizziness, ↑HR & PR interval **Rare:** gallbladder disease (e.g. liraglutide **NNH=84**/3.8 yrs), thyroid C-cell tumor (liraglutide data from mice/rats), ?pancreatitis, ?pancreatic cancer, ?↑retinopathy with subcut semaglutide in patients with a history of diabetic retinopathy at baseline, AKI (case reports), long-term effects unknown SUSTAIN-6 **CI**: FDA black box warning: personal/family hx medullary thyroid carcinoma; multiple endocrine neoplasia syndrome type 2 Caution: gastric surgery hx GERD/gastroparesis, pancreatitis hx, unexplained/↓wt, cognitive/motor decline **DI**: All: insulin, can be insulin sparing (↓ insulin dose ~20-30% initially expert opinion) but watch ↑DKA risk due to poor glycemic control if insulin reduced or discontinued too quickly; SUs (↑ hypoglycemia; expert opinion: A1c ≤7.5%: stop SU, A1c 7.6-8.5%: ↓ SU dose by 50%, A1c >8.5% continue SU at current dose); ↓ gastric emptying (give agents ≥ 1 hr before if meds require rapid GI absorption e.g. antibiotics, oral contraceptives or narrow therapeutic index; cases of increased absorption of some meds e.g. levothyroxine, opioids) DPP4i: avoid combo; lacks efficacy data (& similar MOA, pancreatitis) & ↑cost DC'18 **M**: SCr (baseline & then periodically)	**Initial**: 0.6mg subcut daily, after ≥1 wk ↑1.2mg subcut daily; **Max**: 1.8mg/d VICTOZA LEADER, GRADE **Adolescent**: ≥10 years old CDN/FDA,ADA,ELLIPSE **If >3 missed doses**: restart at 0.6mg daily and titrate eGFR <15DC - 30mL/min<2.5% of LEADER populat.: **CI**	$270, 490 $710 /90 days
Dulaglutide FDA'14 PL **TRULICITY** ✗ ⊗ ❄ 0.75mg/0.5mL & 1.5mg/0.5mL single use pre-filled pen							**Initial**: 0.75mg subcut once wkly; if additional control required titrate to 1.5mg once wkly **Max**: 1.5mg subcut once weekly 🇺🇸: 4.5mg/wk, ↓1.6kg & ↓A1c 0.24% vs 1.5mg/wk AWARD11 eGFR <15mL/min: caution DC **Adolescent**: ≥10 yrs & BMI >85th off-label,AWARD-PEDS	$754 $754 /12 wks
Semaglutide CDN'18; FDA'17 **OZEMPIC** ☎▼ ❄ 1.34mg/mL Pre-filled pens SUSTAIN 1-8 PL 1.5mL(2mg), 3mL(4mg) 3mL (8mg)USA **RYBELSUS** ✗ ⊗ CDN/FDA'19 3mg, 7mg, 14mg tablet PIONEER 1-10 (investigational 25,50mg tab Wt loss) **WEGOVY** ✗ ⊗❄ 2.4mg/0.75mL ✓ see pg 58 weight loss chart	**CVD/CKD outcome summary:** • **↓ mortality**: liraglutide **NNT=71**/3.8 yrs LEADER, GRADE exploratory ↓ mortality with oral semaglutide PIONEER-6 • **↓ MACE**: liraglutide LEADER semaglutide, SUSTAIN-6 Abiglutide, HARMONY & dulaglutide REWIND in patients with established CVD • MACE neutral: lixisenatide, ELIXA exenatide extended release EXSCEL & semaglutide PO PIONEER-6 • **?CKD** benefit liraglutide, dulaglutide, semaglutide; ongoing semaglutide FLOW						**Initial**: 0.25mg subcut once wkly, titrate at 4 wks to 0.5mg then 1mg once wkly if required SUSTAIN-6 **Max**: 1-2mg subcut once weekly OZEMPIC eGFR <30mL/min: caution<4% of SUSTAIN-6 populat. **Initial**: 3mg **po** daily **30 min ac** with ≤120mL H20, after 30 days ↑7mg daily PIONEER-6 **Max**: 14mg daily eGFR <30mL/min: caution excluded PIONEER-6	$366 $683 $680-1300 /12 wks $806 /100 days
Lixisenatide FDA'16 PL **ADLYXINE** CAN ☎▼ ❄ 0.05mg/mL, 0.1mg/mL; 3mL pre-filled pen **EU**: **LYXUMIA** ❄ **USA** 🇺🇸: **ADLYXIN** ❄							**Initial**: 10mcg subcut daily **ac**, after ≥2 wks ↑20mcg subcut daily ac **Max**: 20mcg subcut daily ac eGFR <30mL/minDC: **CI** D/C: Exenatide BYETTA, BYDUREON, Abiglutide HARMONY, EPERZAN CAN & TANZEUM FDA	$392 $734 /90 days
Sodium-glucose co-transporter-2 (SGLT2) inhibitors "flozins": site of action→kidney; ↑urinary glucose excretion via ↓ glucose resorption (inhibits SGLT2 at proximal tubule). Other: BP lowering may play role in benefit.								
Empagliflozin FDA'14 (empa) PL **JARDIANCE** ☎ ▼ 10, 25mg tab ✓T2DM, HF (±T2DM)	May be used **2nd line for T2DM**, if eGFR>30 &:DC -**CVD**: empa,A,1A cana,B,2 (or GLP1) -**HFrEF**: dapagliflozin,A,1A empa;A,1 -**CKD**: cana,A,1A dapa,A,1 empa EMPA-Kidney *Note: 1st line if CVD / high risk CV, HFrEF or HFpEF, or CKD.ADA*	Negligible if mono-therapy	↓↓	↓ 0.5-0.8	↓↓ 2-3 kg	**AE**:**Common:** ↑urinary frequency/volume (take in am), ↑thirst, nausea, hypovolemia/AKI (↑SCr, BUN,↓eGFR ~5mL/min; caution if SCr ↑>30%), but some data suggests neutral or even decreased risk of AKI CMAJ'20, Menne'19 see SADMANS, ↓BP ~5/2mmHg (postural hypotension), dizziness, infection (↑3x genital mycotic, esp ♀; ?UTIs), diabetic ketoacidosis euglycemic or mild ↑BG; Health CDN **↑ DKA risk**: acute serious illness follow "SADMANS", low CHO intake/fasting, sudden ↓ insulin dose, surgery hold 3 days prior (FDA), prev episode, ↑EtOH, T1DM, elderly **Rare:** ?acute pancreatitis,HC Fournier's gangrene FDA (urgent medical attention if severe pain, tenderness, swelling in genital area & fever/malaise), ? erythrocytosis (case report),CMAJ'20 electrolyte abnormalities Canagliflozin: ↑fracture HR=1.3 CANVAS (but neutral vs GLP1 agonists in low risk pts Fralick'19; observational trial meta-analysis suggests no association, however limited by length of trials Hidayat et al '19), ↑amputation HR=2 CANVAS (toes, ~30% above foot), but neutral in CREDENCE & FDA warning removed'20, BMJ'20; risk ↑: ≥65yr with CVD, PAD **CI**: severe hepatic/**dialysis**; Caution: ↓BP e.g. SBP<95/hypovolemia, **surgery/colonoscopy (hold** 24-72-96hr prior & start when tolerating po), **acute illness (hold if dehydrated)**, elderly, cachexic, ↑amputation risk canagliflozin (e.g. peripheral artery disease, neuropathy, diabetic foot ulcers) **DI**: All: diuretics (↓BP/hypovolemia; may require ↓dose); BP meds (↓BP); insulin & SUs (↑hypoglycemia, may require ↓dose); NSAIDs (AKI hypovolemia) dapagliflozin: pioglitozone (? bladder CA); ↓canagliflozin: UGT inducers (CBZ, rifampin, phenytoin, St. John's Wort; may ↑300mg/d, avoid eGFR <60) **M**: volume status (blood pressure, electrolytes); renal function (SCr, K+: baseline & within 2-4 weeks of initiation, then periodically ↓eGFR ~5ml/min normal), blood ketones if symptoms of DKA (e.g. vomiting, difficulty breathing, confusion)	**Initial/Usual**: 10mg po daily am EMPA-REG (CV outcome data similar between 10mg &25mg) **Max**: 25mg po daily am EMPA-REG eGFR <30mL/min: **CI** eGFR <20mL/min EMPEROR (HF) FDA, HC: **CI** eGFR <20mL/min EMPA-KIDNEY: **CI** **Adolescent:** ≥10 yrs FDA'23	$323 $323
Dapagliflozin FDA'14 (dapa) PL **FORXIGA** CAN ☎ ▼ **USA** 🇺🇸: **FARXIGA** FDA 5, 10mg tab (g ✗ ⊗) ✓T2DM, HFrEF (±T2DM), CKD (±T2DM) FDA also ✓HfpEF May 2023	• May titrate if not at glycemic target, but additional ↓ in blood glucose minimal • Plasma peak: 1-3hr; max ↓A1c ~3-6 months • Efficacy & safety for combo GLP1 agonist & SGLT2 inhibitor therapy SUSTAIN-9, AWARD-10, DURATION-8 • T1DM (insulin add-on, CDN: off-label; EMA: sotagliflozin), limited evidence (↓A1c, Wt & ↑ketosis) DEPICT-1, inTANDEM3 Empagliflozin ☎ ▼: inadequate glycemic control with metformin & established CVD (SK: only "flozin" with CVD coverage: HF not included) Dapagliflozin ☎ ▼: NYHA II-III HFrEF added to standard care (SK: only "flozin" with HF coverage)	**CVD/CKD outcome summary:** • **↓ mortality**: empagliflozin **NNT=38**/3.1 yrs, EMPA-REG dapagliflozin **NNT=44**/1.5 yrs DAPA-HF & **NNT=48**/2.4 yrs DAPA-CKD • **↓ MACE**: empagliflozin EMPA-REG & canagliflozin CANVAS in pts with established CVD • Neutral MACE: dapagliflozin, DECLARE but lower risk population • **↓ CKD**: canagliflozin, CREDENCE dapagliflozin, DAPA-CKD empagliflozin EMPA-KIDNEY • **↓ HF**: dapagliflozin, DAPA-HF, DELIVER empagliflozin, EMPEROR-Reduced, EMPEROR-Preserved only 2° HF outcome with canagliflozin				**Initial**: 5mg po daily am **Max**: 10mg po daily am DECLARE, DERIVE, DAPA-HF eGFR <45mL/min (T2DM) FDA, HC: avoid use for glycemic control eGFR <30mL/min DAPA-HF: **CI** eGFR <25mL/min DAPA-CKD (most >30): **CI** initiation FDA, HC **Adolescent:** ≥10 yrs off-label, Lancet Diabetes Endocrinology 2022	$323 $323 (g $90)
Canagliflozin FDA'13 (cana) PL **INVOKANA** ☎ ✆ 100, 300mg tab ✓T2DM, diabetic CKD **USA** 🇺🇸: bexagliflozin BRENZAVVY 2023 20mg tab OD sotagliflozin INPEFA 2023 200-400mg tab OD Investigational: **exagliflozin, ipragliflozin** JAPAN D/C: **ertugliflozin** STEGLATRO'20 CDN, 🇺🇸							**Initial**: 100mg po daily am **Max**: 300mg/d CANVAS eGFR <60mL/min + UGT inducer: avoid eGFR 30-60: 100mg/day (DC 45-60 no dose change) eGFR <30mL/min CANVAS, CREDENCE, HC: **CI** **SGLT2i Renal Dosing** see page 48 • Thresholds ↓ based on new data & expert • **Key: ensure nephrology referral** if eGFR <45 & esp if <30 expert opinion • DC: **SGLT2i CI** eGFR <15; **KDIGO**: initiate if eGFR ≥20 & continue until dialysis KDIGO'22 **All SGLT2i CI in dialysis** DC,KDIGO	$340 $340

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Generic/TRADE	Comments	Effects On: Hypo-glycemia	PPG	A1c %	Wt	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Initial, Usual & Maximum Dose	$/100 d
Thiazolidinediones (TZDs) "glitazones": site of action→adipose/muscle/ liver; ↑ insulin sensitivity, ↓ hepatic gluconeogenesis, ↑ peripheral insulin uptake; ✓ **T2DM** *(Rosiglitazone: only if failure with others)*								
Pioglitazone FDA'99 PL ACTOS, g ☎ ▼ 15, 30, 45mg tab	May be used 2nd line for T2DM (others preferred if CVD/CKD/HF).DC, ADA • Titrate q4-8wks • Max effect: 6-12 wks • Plasma peak: 2 hours • No renal dosing but caution as may lead to fluid retention • ↑↑ weight: Pioglitazone- 3.6 kg/3 yrsPROACTIVE Rosiglitazone- 4.8 kg/4 yrsADOPT	Negligible if mono-therapy	↓	↓ 1.0	↑↑ 2.5-5 kg	**AE**: **Common: edema (~5%), HF**, ↑**Wt**, fracture (♀ **NNH~30**/3.5 yrs), anemia (1%, ?hemodilution) **Rare:**↑AST, macular edema; Pio: ?bladder CA; Rosi: ?↑MI **CI**: HF (NYHA III-IVUS & I-IICDN), severe liver dx; Pioglitazone: bladder cancer Rosiglitazone: ↑MI FDAFDA Caution: hypertension, osteoporosis, fractures, falls, elderly, macular edema, ↑ ovulation in anovulatory premenopause ♀, surgery (may continue) **DI**:↑TZDs: CYP2C8 inhibitor (e.g. gemfibrozil, trimethoprim), insulins↑Wt, edema, HF; ↓TZDs: CYP2C8 inducer (e.g. rifampicin); Pioglitazone: dapagliflozin ?↑ bladder CA **M**: LFTs & SCr (baseline, then periodically) **CVD outcome summary:** • Pioglitazone: ?CVD benefitIRIS ↓MACE **NNT=50**/2.9 yrs but 1° endpoint **NS**;PROACTIVE ↑HF **NNH=50**/2.9 yrsPROACTIVE • Rosiglitazone: ↑?MI,RECORD ↑HF **NNH=69**/5.5 yrsRECORD	**Initial**: 15mg po daily **Usual**: 30mg-45mgPROACTIVE, IRIS po daily **Max**: 45mg po daily eGFR <60mL/min: caution DC	$78 $106-154 $154
Rosiglitazone FDA'99 PL AVANDIA, g ☎ ⊗ 2, 4, 8mg tab (CDN: restricted access; **USA**: D/C; EU: D/C'10)							**Initial**: 4mg po daily **Usual**: 4mg po daily-BIDADOPT **Max**: 8mg po dailyDREAM, RECORD eGFR <60mL/min: caution DC	$192 $354 $262
Meglitinides: site of action→pancreas; ***short-acting*** insulin secretagogue; ↑ β cell insulin release (binds to a different site than SUs); ✓ **T2DM**								
Repaglinide PL GLUCONORM, g 0.5, 1, 2mg tab Nateglinide **STARLIX** D/C '15	May be used 2nd line for T2DM (others preferred if CVD/CKD/HF).DC, ADA • Consider use if irregular eating • Titrate ~ every 1-2 weeks • Plasma Peak: 1-1.5h (↓PPG) • Other uses: ?HNF1A/4A-MODY	Moderate risk	↓	↓↓ 1-1.5	-/↑ (~1kg)	**AE**: **Common:** hypoglycemia (less than SU), headache **Rare:** skin reaction **CI**: severe hepatic dx, gemfibrozil, clopidogrel CDN; Caution: pre-colonoscopy, surgery (stop am of surgery and re-start when food intake is resumed) **DI**: ↑ repaglinide: CYP3A4 inhibitor (e.g. azoles, clari-/ery-thromycin, ciproflox, PI HIV meds, cyclosporine) & CYP2C8 inhibitor (e.g. clopidogrel, gemfibrozil, TMP); ↓ repaglinide: CYP3A4 inducer (e.g. CBZ, rifampin) **M**: SCr & LFTs (baseline & then periodically) **Admin**: Take ≤30 minutes prior to meal. **Flexibility with food** → if meal skipped, skip dose; if meal added, add dose **CVD outcome summary:** • Limited data	**Initial**: A1c <8%: 0.5mg po **TID** ac; A1c ≥8%: 1-2mg po **TID** ac **Usual**: 1-2-4mg po **TID** ac **Max**: 12mg/d eGFR <30mL/min: caution Note: If unable to eat regular meals during **acute illness, hold until able to eat regularly** see SADMANS tool	$37 $39 $39-68 $68
α - Glucosidase Inhibitors: site of action→ gut; inhibits intestinal α-glucosidases preventing hydrolysis & delaying carbohydrate digestion; ✓ **T2DM**								
Acarbose PL GLUCOBAY, g (previously PRANDASE) 50, 100mg ᶜ tab **USA**: PRECOSE	Role limited in T2DM.ADA ?preventionSTOP-NIDDM • Titrate ~q4-8 weeks • Plasma Peak: 1-1.5hr (↓PPG) • Requires TID dosing	Negligible	↓↓	↓ 0.5-0.8	-/↓	**AE**: **Common: GI (diarrhea** 30%; **flatulence** 74%, tolerance over time), ↑LFTs **Rare:** hypoglycemia (treat with glucose tabs/honey/milk; sucrose not absorbed) **CI**: chronic GI disease (e.g. IBS), severe hepatic disease **DI**: ↓ absorption of other meds (Fe++); enzymes (amylase/pancreatic) ↓ acarbose **M**: SCr & LFTs (baseline & then periodically) **Admin**: With first bite of main meals • IFG-↓MACE: **NNT=40**/3.3 yrs, effect did not persist;STOP-NIDDM not in Chinese with IGT & CVDACE	**Initial**: 25mg po daily cc **Usual**: 50mgACE -100mg po **TID** cc **Max**: 100mg po **TID** ccSTOP-NIDDM eGFR <25-30mL/min: **CI** Note: if meal is skipped, skip dose	$18 $54-72 $72

Table 1: Fixed Dose Combination Products (consider if patient is stabilized on multiple single ingredient tablets or injectables)	Usual Dose	$/100d
Metformin/**Linagliptin: JENTADUETO** 500/2.5mg, 850/2.5mg, 1000/2.5mg tab ☎ ▼; **JENTADUETO XR** 2.5/1000mg, 5/1000mg XR tab	1 tab po BID cc	$328
Metformin/**Sitagliptin:JANUMET**, g 500/50mg, 850/50mg, 1000/50mg tab ☎; **JANUMET XR**, g 500/50mg ☎, 1000/50mg ☎, 1000/100mg tab ☎	1 tab po BID cc; 1-2 tab po daily cc	$225g;$130-225g
Metformin/**SAXagliptin: KOMBOGLYZE** 500/2.5mg, 850/2.5mg, 1000/2.5mg tab ☎ ▼; **KOMBIGLYZE XR** 2.5/1000mg, 5/500mg, 5/1000mg	1 tab po BID cc	$320
Metformin/**Alogliptin: KAZANO** 500/12.5mg, 850/12.5mg, 1000/12.5mg tab ✗ ⊗	1 tab po BID cc	$309
Metformin/**Empagliflozin: SYNJARDY** 500, 850, 1000mg /// 5, 12.5mg tab ☎ ▼ ≥10 yrsFDA'23; **SYNJARDY XR** 5/10/12.5/25//1000mg	1 tab po BID cc	$326
Metformin/**Canagliflozin: INVOKAMET** 500, 850, 1000mg /// 50, 150mg tab ✗ ⊗; **INVOKAMET XR** 50//500/1000mg; 150//500/1000mg	1 tab po BID cc	$410
Metformin/**Dapagliflozin: XIGDUO** 850, 1000mg // 5mg tab ☎ ▼; **XIGDUO XR**	1 tab po BID cc	$307
Linagliptin/Empagliflozin: GLYXAMBI 5/10, 5/25 tab ✗ ⊗	1 tab po daily	$567
Insulin degludec 100units/mL & **Liraglutide** 3.6mg/mL: **XULTOPHY 100/3.6** ✗ ⊗ *(↑dose by 2 units every 3-4 days; room temp for 21 days, max insulin dose 50 units/d; may start at low dose to decrease GLP1 GI AEs)*	16units/0.58mg-50units/1.8mg **subcut** daily	$1110
Insulin glargine 100units/mL & **Lixisenatide** 33mcg/mL: **SOLIQUA 100/33** ☎ ▼ *(titrate by 2-4 units every week; room temp for 28 days, max insulin dose would be 60 units/day; may start at low dose to decrease GLP1 GI AEs)*	15units/5mcg-60units/20mcg **subcut** daily	$684
Alogliptin/Pioglitazone: OSENI 12.5/30mg, 12.5/45mg; 25/15mg, 25/30mg, 25/45mg tab	1 tab po daily	**Not available in Canada**
Metformin/**Pioglitazone: ACTOPLUS MET** 500/15mg, 850/15mg tab & **ACTOPLUS MET XR**	1 tab po bid cc	
Metformin/**Repaglinide: PRANDIMET** 500/1mg, 500/2mg tab	1 tab po TID-QID	
Glimepiride/Pioglitazone: DUETACT 2/30mg, 4/30mg tab	1 tab po daily	
SAXagliptin/Dapagliflozin: QTERN 5/10mg tab	1 tab po daily	
Metformin/**SAXagliptin/Dapagliflozin: QTERNMET XR** 1000/2.5/2.5mg, 1000/2.5/5mg, 1000/5/5mg, 1000/5/10mg XR tab	1 tab po daily	
Metformin/**Linagliptin/Empagliflozin: TRIJARDY XR** 1000/2.5/5mg, 1000/5/10mg, 1000/2.5/12.5mg, 1000/5/25mg XR tab	1 tab po daily	

Post-op management: ensure antihyperglcemic medications are restarted as appropriate e.g. eating meals, etc.

Discontinued: Metformin/Rosiglitazone: '17 **AVANDAMET** 500/1mg & 500, 1000mg // 2mg, 4mg; Metformin/Ertugliflozin:'20 **SEGLUROMET** 500, 1000mg // 2.5, 7.5mg tab; Sitagliptin/Ertugliflozin:'20 **STEGLUJAN** 100/5mg, 100/15mg tab.

ANTI-HYPERGLYCEMIC TYPE 2 DIABETES AGENTS: Drug Comparison Chart, Online Extras

Complete ABBREVIATIONS: =↓ dose for renal dysfunction =↓ dose for hepatic dysfunction ç=scored tab $=total cost in SK ☎=Exception Drug Status (EDS) in SK ✗=Non-formulary in SK ✆=prior approval for non-insured health benefits for First Nations (NIHB) ⊗=not covered by NIHB ▼=Covered by NIHB & ONLY for those drugs which have SK Formulary restrictions such as EDS or non-formulary status ✓=Health Canada Indication ❄=refrigerate ♀=female **1º**=primary **A1c**=glycosylated hemoglobin **ac**=before meals **ACP**=American College of Physicians **ADA**=American Diabetes Association **AE / AE(s)**=adverse effect(s) **AFP**=American Family Physcians **AKI**=acute kidney injury **am**=morning **AST**=asparate aminotransferase **BB**=beta blocker **BID**=twice daily **BG**=blood glucose **BP**=blood pressure **CA**=cancer **cc**=with food **CDN**=Canadian **CHO**=carbohydrate **CI**=contraindicated **CKD**=chronic kidney disease **CV**=cardiovascular **CVD**=cardiovascular disease **D**=diarrhea **D/C**=discontinued **DC**=Diabetes Canada **DI**=drug interaction **DKA**=diabetic ketoacidosis **DM**=diabetes mellitus **DPP4**=dipeptidyl peptidase-4 **dx**=disease/diagnosis **eGFR**=estimated glomerular filtration rate **EMA**=European Medicines Agency **ER**=extended release **EtOH**=alcohol **EU**=Europe **FDA**=US Food and Drug Administration **Fe^{++}**=iron **Fx**=function **g**= generic **GERD**=gastroesophageal reflux disease **GI**=gastrointestinal **GIP**=glucose-dependent insulinotropic polypeptide **GLP1**=glucagon-like peptide-1 **HA**=headache **HD**= hemodialysis **HF**=heart failure **HNF1**=Homeobox A (gene mutation) **hr**(s)=hour(s) **HS**=bedtime **hx**=history **IBD**=inflammatory bowel disease **IBS**=irritable bowel syndrome **IFG**=impaired fasting glucose **IGT**=impaired glucose tolerance **kg**=kilogram **LFT**=liver function test **MACE**=major adverse cardiovascular events **MAOI**=monoamine oxidase inhibitor **MI**=myocardial infarction **MODY**=Maturity-onset diabetes of the young **MRA**=mineralocorticoid receptor antagonist **N**=nausea **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-significant **po**=oral **PPG**=postprandial blood glucose **PCOS**= polycystic ovary syndrome **PD-CKD**=peritoneal dialysis for chronic kidney disease **pm**=evening **po**=by mouth **REMS**=risk evaluation and mitigation strategy **subcut**=subcutaneous **SGLT2i**=sodium-glucose cotransporter-2 inhibitor **SU**=sulfonylurea **SGLT2**=sodium-glucose cotransporter-2 **SIADH**=syndrome of inappropriate antidiuretic hormone secretion **SJS**=Stevens-Johnson Syndrome **SK**=Saskatchewan **T1DM**=type 1 diabetes mellitus **T2DM**=type 2 diabetes mellitus **TID**=three times daily **TZD**=thiazolidinediones **URTI**=upper respiratory tract infection **US**=United States **UTI**=urinary tract infection **V**=vomiting **wk(s)**=week(s) **Wt**=weight **XR**=extended-release **yr(s)**=year(s)

ACEI=angiotensin converting enzyme inhibitor **ACR=**albumin: creatinine ratio **ARB=**angiotensin II receptor blocker **BB=**beta blocker **BMD=**bone mineral density **BMI=**body mass index **CVA=**cerebrovascular accident **d=**day **dysfx=**dysfunction **EDS=**exception drug status **ESRD=**end-stage renal disease **HC=**Health Canada **HF-pef/HF-ref=**heart failure preserved/reduced injection **HIV=**human immunodeficiency virus **HR=**heart rate or hazard ratio **IFG=**impaired fasting glucose **LFT=**liver function test **mo(s)=**month(s) **NIHB=**non-insured health benefits for First Nations **NPH=**neutral protamine Hagedorn **NPO=**nothing by mouth **NSAIDs=**non-steroidal anti-inflammatory drug **OD=**daily **PAD=**peripheral artery disease **peds=**pediatric **PPBG=**postprandial (2hr) blood glucose **Pt=**patient **QID=**four times per day **SCr=**serum creatinine **SKH=**Saskatchewan Health **TCA=**tricyclic antidepressant **TIA=**transient ischemic attack **tx=**treatment **vs=**versus

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Online Extras:

Discontinued Agents, select:

Exenatide FDA'05 PL **BYETTA** ✗ ⊗ ❄ 250mcg/mL; 1.2mL, 2.4mL pre-filled pen **BYDUREON** ✗ ⊗ ❄ long-acting release (LAR) single use pen (powder	• Plasma peak: **BYETTA** ~2hr; **BYDUREON** 2wks & at ~6-7 wks • Store in fridge ❄, stable at room temperature: 30 days: exenatide	**Doses for prefilled pens** **Exenatide BYETTA:** 1.2mL — 60 doses x 5mcg 2.4mL — 60 doses x 10mcg Others: one pen = one weekly dose (e.g. **BYDUREON**)	**BYETTA** 5mcg subcut BID ac, prior to main meals (≥6hr apart); **Max**: 10mcg subcut BID ac **BYDUREON**: 2mg subcut once weekly (must reconstitute) **Adolescent**: ≥10yr old eGFR <50mL/min: caution; <30mL/min: **CI**	$520 $520 $710 /90 days
Tolbutamide PL **ORINASE, g** 500mg$^{\varsigma}$ tab	• Plasma peak: 3-4 hours		**Initial**: 250mg po daily in am cc **Usual**: 500mg po BID-TID cc **Max**: 1000mg po TID cc	$17 $47 $85