Appendix E: Antihyperglycemic Agents and Adjunctive Agents for Use in Type 2 Diabetes

Generic Name (Trade Name), Dosages	Adult Dose[1,2,3]	Cost/30 days (usual dose)	PharmaCare Coverage (definitions under resources)	Therapeutic Considerations
Biguanides				
Metformin (generic) 500, 850 mg tablets Glumetza: 500, 1000 mg SR tablets	Initial: 250 or 500 mg PO BID Usual: 1000 mg BID (Glumetza-daily dose) Max: 2550 mg/day.[1]	$6.50 (3x500 mg) $40 – Glumetza	Regular benefit Glumetza- no coverage	**Pro:** Usual first line drug for type 2 diabetes; low rates of hypoglycemia; weight neutral to modest weight loss (2-3 kg).[5,6] **Con:** GI side effects, Vitamin B12 deficiency. Use with caution / reduce dose if eGFR < 60 mL/min. **Contraindicated:** eGFR < 30 mL/min, hepatic or cardiac failure. **Effect:** lowers A1C 1.5%, decreases micro and macrovascular endpoints events.[7,8]
Insulin Secretagogues, Sulfonylureas				
Gliclazide (Diamicron®, Diamicron MR®, generic) 80 mg, 30 mg ER, 60 mg ER tablets	Initial: 80-160 mg PO daily Usual: 80-320 mg daily (≥160 mg divide BID) Diamicron MR. Initial: 30 mg PO daily at breakfast to a Max of 120 mg daily.	$6 (2x80 mg) $9 (2x30 mg ER)	Limited Coverage* (Requires Special Authority). Criteria: Treatment failure or intolerance to at least one other sulfonylurea drug at adequate doses. See Pharmacare website: gliclazide.	**Pro:** Extensive clinical experience. **Con:** Hypoglycemia variable based on drug (more with glyburide), dose, patient, modest weight gain[9,10,11] (2-3 kg). Use with caution / reduce dose if eGFR < 50 mL/min (glyburide), eGFR < 30 mL/min (glimepiride, gliclazide). **Not recommended:** eGFR < 30 mL/min (glyburide), eGFR < 15 (glimepiride, gliclazide). **Effect:** lowers A1C 1-2%.[12,13,14]
Glimepiride (Amaryl™, generic) 1, 2, 4 mg tablets	Initial: 1 mg PO daily Usual: 1-4 mg daily Max: 8mg daily	$16 (1x4 mg daily)	No Coverage	
Glyburide (Diabeta®, generic) 2.5, 5 mg tablets	Initial: 5 mg PO daily Usual: 2.5-20 mg (divide BID if >10 mg) Max: 20 mg daily	$2 (2x5 mg)	Regular Coverage	
Insulin Secretagogues, Meglitinides				
Repaglinide (GlucoNorm®) 0.5, 1, 2 mg tablets	Initial: 0.5mg (treatment-naïve) or 1 mg PO TID AC Max: 16 mg daily.[3]	$32 (4x2 mg)	No Coverage	**Pro:** No risk sulfa allergy, no dosage adjustment for decreased eGFR. **Con:** some hypoglycemia and weight gain, TID dosing. **Contraindicated:** pregnancy. **Effect:** lowers A1C 0.5-1%.[15,16,17]
Nateglinide (Starlix) 60, 120 mg tablets	Initial and maintenance: 60-120 mg PO TID AC.[3]	$55 (any dose TID)	No Coverage	

Generic Name (Trade Name), Dosages	Adult Dose[1,2,3]	Cost/30 days (usual dose)	PharmaCare Coverage (definitions under resources)	Therapeutic Considerations
Alpha-glucosidase inhibitor				
Acarbose (Glucobay®) 50, 100 mg tablets	Slowly titrate (every 1-2 weeks) from 50mg daily to 50 mg TID. Max 100 mg TID. AC meals.	$27 (3x50 mg)	No Coverage	**Pro:** low risk hypoglycemia, weight neutral to modest weight loss. **Con:** frequent GI side effects. Not recommended if eGFR < 25 mL/min. **Contraindicated:** IBS and IBD. **Note:** Must use glucose (dextrose) for hypoglycemia, not sucrose as complex sugars are ineffective.
Thiazolidinediones (TZDs)				
Pioglitazone (Actos®, generic) 15, 30 mg tablets	Initial: 15-30 mg PO daily Max: 45 mg daily	$29 (1x30 mg)	Limited Coverage* (Requires Special Authority). Criteria: part of a combination treatment for type 2 diabetes: 1. When insulin NPH is not an option **AND** 2. After inadequate glycemic control on maximum tolerated doses of dual therapy of metformin **AND** a sulfonylurea. See Pharmacare website: pioglitazone.	**Pro:** low risk of hypoglycemia, increase HDL. **Con:** weight gain (4-6 lbs, fluid retention contributes)[4], fluid retention, can precipitate heart failure, increased risk fractures, cardiovascular risk-benefit unclear. **Use with caution:** if eGFR < 30 mL/min. **Contraindicated:** pregnancy, metabolic bone disease, NYHA III/IV heart failure. **Effect:** Lowers A1C 1-1.5%. Pioglitazone may reduce cardiovascular harm.[18] Pioglitazone can cause significant fluid retention, particularly in heart failure. Contraindicated in active bladder cancer or history of bladder cancer. Risk of bladder cancer may increase with high dose and duration of use.
Rosiglitazone (Avandia®) 2, 4, 8 mg tablets *Use of rosiglitazone is not recommended.*	4 mg PO daily in 1-2 doses Max: 8 mg daily (4 mg if taking sulfonylurea)	$70 (1x4 mg)	No Coverage	Rosiglitazone can cause fluid retention, heart failure, and may be associated with an increased risk of cardiac ischemia.[19] Use of rosiglitazone is not recommended.

Generic Name (Trade Name), Dosages	Adult Dose[1,2,3]	Cost/30 days (usual dose)	PharmaCare Coverage (definitions under resources)	Therapeutic Considerations
Dipeptidyl Peptidase-4 Inhibitors (DPP4Is)				
Sitagliptin (Januvia™) 25, 50, 100 mg Tabs	100 mg PO daily	$96 (all doses)	No Coverage	**Pro:** weight neutral. **Con:** rare reports of pancreatitis, emerging concerns about HF (saxagliptin), modest lowering effect on A1C, may cause severe joint pain. Dosage reduction required if eGFR < 50 mL/min (sitagliptin, saxagliptin). **Contraindicated:** pregnancy, hepatic failure, previous lactic acidosis. **Effect:** Lowers A1C 0.75%.[20] Trials up to 3 years in length show no cardiovascular disease benefit over placebo.[20-22]
Saxagliptin (Onglyza™) 2.5, 5mg tablets	5 mg PO daily	$77 – 2.5 mg $92 – 5 mg	Limited Coverage* (Requires Special Authority). Criteria: part of a combination treatment for type 2 diabetes: 1. When insulin NPH is not an option **AND** 2. After inadequate glycemic control on maximum tolerated doses of dual therapy of metformin **AND** a sulfonylurea. See Pharmacare website: saxagliptin.	
Linagliptin (Trajenta) 5 mg tablets	5 mg PO daily	$73	Limited Coverage* (Requires Special Authority). Criteria: As saxagliptin above See Pharmacare website: linagliptin	
Alogliptin (Nesina) 6.25 mg, 12.5 mg, 25 mg	25 mg daily	$85 (1x25 mg)	No Coverage	
Glucagon-Like-Peptide 1 (GLP-1) Agonists				
Albiglutide (Eperzan)	30mg SC once weekly, may increase to 50 mg SC once weekly after 4 weeks if needed.	Not available in BC as of 2015/09/28	Not available in BC as of 2015/09/28	**Pro:** modest weight loss (up to 2-3 kg)[23], low hypoglycemia. **Con:** GI side effects, rare reports of pancreatitis, increased heart rate, injectable. Use with caution / not recommended if eGFR < 50 mL/min. **Contraindicated:** pregnancy, history of pancreatitis, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. **Effect:** lowers A1C 1%. [24]
liraglutide (Victoza®) pre-filled pen (0.6 mg/0.1 ml) Pack size: 2x3 ml, 3x3 ml (3 ml=15 doses of 1.2 mg/ml)	Initial: 0.6 mg SC once daily x 1 week Increase to 1.2-1.8 mg SC once daily (1.8 is more expensive, similar A1C effect)	$175 (1.2 mg)	No Coverage	
Exenatide (Byetta) Pre-filled pen. 5 mcg/0.02 ml Pack size: 1.2 ml (60 doses of 5 mcg/dose) and 2.4 ml (60 doses of 10 mcg/dose)	Initial: 5 mcg SC BID within 60-minute period before the two main meals of the day, at least 6 hours apart. Increase to 10 mcg BID as tolerated	$150 (all doses)	No Coverage	

Generic Name (Trade Name), Dosages	Adult Dose[1,2,3]	Cost/30 days (usual dose)	PharmaCare Coverage (definitions under resources)	Therapeutic Considerations
Sodium-Glucose Cotransporter 2 Inhibitors				
Canagliflozin (Invokana) 100, 300 mg tablets	100 mg PO daily prior to first meal. May increase to a maximum of 300 mg daily. Use only 100 mg dose if eGFR 45-60 mL/min.	$84 (all doses)	Under Review	**Pro:** weight loss (2-3 kg), low rates of hypoglycemia, blood pressure lowering (unknown clinical significance). **Con:** decreased bone mineral density and increased risk of bone fractures (canagliflozin), reports of euglycemic diabetic ketoacidosis, volume depletion (more in age > 65 years), genital mycotic infections, UTI, increased LDL, glucose lowering is independent of beta cell function and insulin sensitivity. **Contraindicated:** pregnancy, eGFR < 45 mL/min (< 60 mL/min if dapagliflozin), renal disease, dialysis, bladder cancer imbalance (dapagliflozin). **Effect:** lowers A1C 0.5 – 0.7%.[25,26] limited by filtered load of glucose, osmotic diuresis and kidney function.
Dapagliflozin (Forxiga) 5, 10 mg tablets	Initial: 5 mg once daily; may increase to 10 mg once daily	$84 (all doses)	Under Review	
Empagliflozin (Jardiance) 10, 25 mg tablets	10 mg once daily; may increase to 25 mg once daily	Under review	Under Review	
Combinations				
Rosiglitazone plus metformin (Avandamet™) 2/500, 2/1000, 4/500, 4/1000 mg tablets *Rosiglitazone not recommended*	2 mg/500 mg PO BID with meals, max 8 mg/1000 mg BID	$52 (4 mg/500 mg)	No Coverage	See individual drug components. Rosiglitazone not recommended.
Sitagliptin plus metformin (Janumet™) 50 mg/500, 50/1000 mg tablets	50 mg/500 mg PO BID, Max: 50 mg/1000 mg BID	$104 (all doses)	No Coverage	
Alogliptin-metformin (Kazano) 12.5/500 mg, 12.5/850 mg 12.5 mg/1000 mg	One tablet BID	$89 (all doses)	No Coverage	
Linagliptin plus metformin (Jentadueto) 2.5/500 mg, 2.5/850 mg, 2.5/1000 mg Tablets	Max: 2.5 mg/1000 mg BID	$77 (all doses)	Limited Coverage* (Requires Special Authority). Criteria: As saxagliptin and linagliptin above.	
Saxagliptin plus metformin (Komboglyze) 2.5/500 mg, 2.5/850 mg, 2.5/1000 mg Tablets	Max: 2.5 mg/1000 mg BID	$82 (all doses)		

Abbreviations: AC=before meals; A1C=glycosylated hemoglobin; BID= twice a day; BC=British Columbia; eGFR= estimated glomerular filtration rate; ER= extended release; GI=gastrointestinal; HDL= high density lipoprotein; IBD= inflammatory bowel disease; IBS= Irritable bowel syndrome; LDL = low density lipoprotein; mg=milligram; NPH= Neutral protamine hagedorn (e.g., Humulin N); NYHA= New York Heart Association Functional Classification; PO=orally; SC=subcutaneous; TID= three times a day; URTI=upper respiratory tract infection; UTI=urinary tract infection

- Limited Coverage Criteria are current as per Pharmacare 2014/12/01 and are subject to change. Refer to Pharmacare website for updated criteria.
- Pricing is approximate as per PharmaNet 2014/08/26 and does not include dispensing fee and retail markup.
- For information on the current costs, please visit BC PharmaCare Formulary Search, website: pcbl.hlth.gov.bc.ca/pharmacare/benefitslookup/

PharmaCare Coverage Definitions:

Regular coverage: also known as regular benefit; does not require Special Authority; patients may receive full coverage*

Partial coverage: Some types of regular benefits are only partially covered* because they are included in the Low Cost Alternative (LCA) program or Reference Drug Program (RDP) as follows: LCA: When multiple medications contain the same active ingredient (usually generic products), patients receive full coverage* for the drug with the lowest average PharmaCare claimed price. The remaining products get partial coverage. RDP: When a number of products contain different active ingredients but are in the same therapeutic class, patients receive full coverage* for the drug that is medically effective and most cost-effective. This drug is designated as the Reference Drug. Remaining products get partial coverage.

Special Authority: requires Special Authority for coverage. Patients may receive full or partial coverage* depending on LCA or RDP status. These drugs are not normally regarded as first-line therapies or there are drugs for which a more cost-effective alternative exists. Pharmacare coverage period is indefinite, 3rd party payers may require re-confirmation.

No coverage: does not fit any of the above categories

* coverage is subject to drug price limits set by PharmaCare and to the patient's PharmaCare plan rules and deductibles. See www.health.gov.bc.ca/pharmacare/ for further information.

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