Appendix C

Performed Controlled Acts and Procedures

Table 1: List of Medications (Insulin) Implemented under this Directive with Detailed Indications/Contraindications

Insulin Type	Onset	Peak/ Duration	Indications for Adjustment	Therapeutic Considerations
Rapid-Acting • Lispro (Humalog) • Aspart (Novorapid) • Glulisine (Apidra) • Lispro 200 (Humalog 200) • Aspart (Fiasp)	2-15 minutes	1-2 hours/ 3-5 hours	• 2 hr post-meal and/or pre-meal blood sugars (lunch, dinner) are either elevated or hypoglycemia occurs	• Patient's should eat within 0-15minutes after injection • In certain circumstances injecting shortly after eating is appropriate e.g. GI disturbance resulting in early satiety, vomiting etc. • For Patient's on MDI (multiple daily injections) using a rapid-acting insulin it is recommended that they self-monitor blood glucose (SMBG) at least QID for safe titration of doses • Humalog 200 must only be used in the pre-filled pen. It must not be drawn up in a syringe • Fiasp is best injected 2 minutes before and up to 20 minutes after a meal. It may not be best in people with delayed gastric emptying & has not been studied in pregnancy
Short-Acting • Humulin R • Novolin Toronto	30 minutes	2-3 hrs/6.5 hours	• Pre-meal blood sugars (lunch, supper) and/or bedtime are elevated or hypoglycemia occurs	• Patient's should inject insulin 30 minutes prior to eating • For Patient's on MDI (multiple daily injections) using a short-acting insulin it is recommended that they SMBG at least QID for safe titration of doses
Intermediate-Acting • Humulin N • Novolin NPH	1-3 hours	5-8 hours/up to 18hours	• Increase evening dose if high fasting blood sugar (if rebound hyperglycemia has been eliminated) • Decrease dose if hypoglycemia (recommend CBG testing in the night to rule out nocturnal hypoglycemia)	• Must be adequately re-suspended before injecting • Higher risk of hypoglycemia compared to long-acting insulin • Recommended for Patient's to SMBG OD-BID for safe titration of doses

			• Increase or decrease morning dose if 5-8 hour pre-meal blood sugars are out of target	
Pre-Mix Analogues • NovoMix 30 • Humalog Mix 25 • Humalog Mix 50 **Regular Insulin** • Novolin 30/70, 40/60, 50/50 • Humulin 30/70	10-15 minutes 30-60 minutes	Contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin: see above for information about peak actions based on insulin contained	• Increase/ decrease morning dose if lunch/supper readings are out of target • Increase/decrease evening dose if HS or fasting sugars are out of target • Recommend CBG testing in the night to rule out nocturnal hypoglycemia	• Must be adequately re-suspended before injecting • Patient's should eat within 0-15 min after injecting Mix 30, Mix 25 or Mix 50 • Patient's should inject 30/70, 40/60 or 50/50 30 minutes prior to eating • Recommended for Patients to SMBG at least BID (AC breakfast and dinner) for safe titration of doses
Long-Acting • Detemir (Levemir) • Glargine (Lantus, Basaglar) • Glargine 300 (Toujeo) • Degludec (Tresiba) U-100, U-200	90 minutes	No peak/16-24hrs No peak/up to 24 hrs No peak/ up to 30hrs No peak/up to 42h	• Increase/decrease dose if fasting or pre-supper sugars (if injecting in the morning) are out of target	• Do not mix with other insulin in the same syringe • Recommended for patient's to SMBG at least OD (FBG or AC meals) for safe titration of dose • Toujeo can be stored for 42 days at room temperature • Toujeo and Tresiba U-200 must only be used in the pre-filled pen. They must not be drawn up in a syringe • Degludec can be stored for 8 weeks at room temperature • Use a 1:1 conversion using total daily dose when switching from intermediate or long-acting insulin to Tresiba • Use a 1:1 conversion using total daily dose when switching from long-acting insulin to Toujeo or 80% of total daily intermediate dose

Table 1 Notes:

- The implementer will adhere to the indications and contraindications outlined in Table 1
- The implementer is responsible for teaching patient safe injection technique according to FIT 2011 guidelines. Implementer is also responsible for recommending needle length appropriate to patient.
- A prescription is required from the primary health care provider and/or endocrinologist prior to insulin initiation
- Most patients new to insulin are started on 10 units HS of a basal insulin, or 0.1-0.2 units per kg/d for patients < 50 kg. Alternatively, they can be started on a premixed insulin at 5 – 10 U twice daily before breakfast and before supper or started on Basal + Bolus insulin with initial total daily dose of 0.3 – 0.5 units per kg/d (40% of this as basal and 20% of this a bolus with each meal). However individual considerations need to be assessed i.e. patient's who are hypoglycemic unaware or have a fear of insulin-induced hypoglycemia can be initiated on a smaller dose etc.
- Evidence-based recommendations are to adjust insulin by 1-2u q 3-4 days or by 1u per day. Under certain circumstances patients may need insulin adjustment greater or less than 5-10% of total daily dose i.e. extreme hyperglycemia, medications and/or lifestyle factors that can increase/decrease glycemic levels
- Glargine 300 and Degludec should be titrated q3-4 days by 2-3 units
- Implementer should determine a communication plan with the patient for further insulin adjustment
- Implementer will instruct a patient starting insulin around hypoglycemia treatment, driving instructions and instruct family/caregivers on using a glucagon kit when applicable i.e. type 1 diabetes and high risk for hypoglycemia
- In the case of high CBG readings and low CBG readings, always correct for hypoglycemia first
- Patients should be instructed as to how to adjust insulin during times of illness, travel and physical activity following current best practice guidelines
- Allergic reactions are rare but can occur with a few patients. Reactions may be local (i.e. rash/weal at site) or systemic (i.e. shortness of breath, wheezing or severe weakness). Implementer should instruct Patient to hold insulin and get in contact with primary care provider a.s.a.p. and/or proceed to the nearest emergency department
- Patient should be instructed to store unopened insulin vials/cartridges in the refrigerator, store open insulin vials/cartridges at room temperature, not expose insulin to heat or direct sunlight, not freeze insulin, and to use by expiration date
- The primary care provider or endocrinologist must be available to provide consultation as required
- Primary care provider and/or endocrinologist should be consulted in the following circumstances:
    - Recurrent or severe hypoglycemia with no apparent cause
    - Glycemic control is not improving or is deteriorating despite adjustments made to insulin or other component of the treatment plan

- Total daily dose exceeds what is generally expected for age/body type
- Patient shows signs and symptoms of Diabetic Ketoacidosis (DKA), dehydration or other serious problems *send to the Emergency Department immediately
- Recurring/persistent vomiting/diarrhea
- Disordered eating pattern resulting in calorie restriction
- Significant error in dose or timing of insulin administered by person or caregiver
- Situations requiring prolonged fasting i.e. for religious or medical reasons
- Change in brand or type of insulin
- Change in frequency of injections i.e. BID to TID
- For patients with additional complex medical or endocrine disorders which may influence insulin requirements or patient safety
- In all situations that are beyond the implementer's scope of practice and/or competency level

Table 2: Non-Insulin Antihyperglycemic agents: List of Medications Implemented under this Directive with Detailed Indications/Contraindications

Antihyperglycemic Agent	Indications for Adjustment	Contraindications/Precautions
Alpha-Glucosidase Inhibitor **<u>Acarbose (Glucobay, Prandase)</u>** *Initial Dose:* 25-50 mg daily *Average Dose (Max dose):* 50-100 mg tid (300 mg) *Special Instructions:* Take with first bite of meal *Onset/peak/duration:* 1h/2h/4-6h *Expected HbA1C reduction:* 0.6% *ODB Coverage:* limited use	• Gastrointestinal (GI) side effects • Inadequate blood glucose control • Very low frequency of hypoglycemia unless combined with a sulfonylurea • Initiate therapy with 25mg OD-BID and titrate slowly by 25mg/day every 2-4 weeks as tolerated • Maximum effectiveness with at 50mg TID; higher doses associated with increased adverse events	• Not recommended as initial therapy in people with severe hyperglycemia (AIC $\geq$8.5%) • Gastrointestinal side effects in approx. 30% of Patient's i.e. cramps, diarrhea, abdominal distension, flatulence (effects usually decrease with continued use but there is a high discontinuation rate based on GI side effects) • Treat hypoglycemia with Dextrose tablets, milk or honey as Acarbose interferes with glucose absorption • Contraindicated in Patient's with DKA, inflammatory bowel disease, intestinal ulcers, cirrhosis, partial intestinal blockage or predisposed to blockage • Renal dosing: discontinue use if creatinine clearance (CrCl) <25ml/min or eGFR <30 mL/min • In patients with known liver impairment or liver disease, liver enzymes should be monitored prior to start of Acarbose, and monitored on a regular basis within the first year • Case reports of reduction in absorption of digoxin and increased absorption of warfarin Maximum doses based on weight <132 lbs: 50mg TID; >132 lbs: 100mg TID
Biguanides **<u>Metformin (Glucophage)</u>** *Initial Dose:* 250-500 mg daily *Average Dose (Max dose):* 500-1000 mg bid or 850 mg tid (2550 mg) *Special Instructions:* Take with meals to reduce GI side effects *Onset/peak/duration:* 1-2h/6h/6-12h *Expected HbA1C reduction:*	• Initiate Glucophage 500mg twice daily or 850mg OD • Initiate Glumetza 500mg once or twice daily • GI side effects in 20-30% of Patient's (Glumetza associated with fewer GI side effects than short-acting Metformin). Side effects can be reduced by slow titration (500mg/day every 2	• Contraindicated in people with a history of lactic acidosis, severe hepatic dysfunction, severe infection/dehydration, trauma or cardiorespiratory insufficiency, surgery or alcohol abuse • Reduced dose recommended if CrCl/eGFR <60 ml/min and contraindicated if CrCl/eGFR <30 ml/min • 5-10% of people are unable to tolerate due to substantial GI side effects (upset stomach, nausea, diarrhea, anorexia, metallic taste) • Metformin should be stopped during acute illness (severe infections, trauma, surgery) and the recovery phase afterwards. Should also be

1-1.5% *ODB Coverage:* Yes **<u>Glumetza (Metformin HCL ER)</u>** *Initial Dose:* 500 mg daily (ideally with dinner) *Average Dose (Max dose):* 1000-2000 mg daily (2500 mg) *Onset/peak/duration:* 1-2h/4-8h/17.6-19.8h *Expected HbA1C reduction:* 1-1.5% *ODB Coverage:* No	weeks and taking medication with meals • Decrease in FBG levels seen within 3-5 days; maximal effect in 1-2 weeks • 80-85% of glucose lowering effect is seen with 1500mg/day • Maximum effective dose is 2000mg/day • Renal insufficiency • Hypoglycemia (rare as monotherapy) • Blood glucose remains above target	put on hold in patients with severe dehydration (i.e., vomiting and unable to keep down fluids) • Should do baseline liver function tests (LFT's) • Higher doses (above 2000mg/day) associated with increased risk of adverse events with no additive effect • Hold for 48 hours if undergoing radiologic studies with administration of iodinated contrast material (hold on day of procedure until 2-3 days after) • Not recommended in the elderly (over 80yrs) unless CrCl/eGFR is >60 mL/min due to decreased muscle mass • Recommend conservative dosing in the elderly • Lactic acidosis is rare 0.03/1000 patients and 0.015 fatal cases/1000 patients; more likely to occur in patients with renal insufficiency, alcohol or liver disease. Hold dose in hypoxic states, shock, severe infection or septicemia • Measurements of serum vitamin B12 are advisable at least every 1 to 2 years in patients on long-term treatment (Product Monograph – Health Canada)
Insulin Secretagogues **Sulfonylureas:** **<u>Diamicron (Gliclazide)</u>** *Initial Dose:* 40-80 mg daily or bid with meals *Average Dose (Max dose):* 80-160 mg bid (320 mg) *Onset/peak/duration:* 1-2h/4-6h/10-14h *Expected HbA1C reduction:* 0.8% *ODB Coverage:* Yes **<u>Diamicron MR (Gliclazide MR)</u>** *Initial Dose:* 30 mg daily with first meal *Average Dose (Max dose):* 30-120 mg daily (120 mg)	• Frequent hypoglycemia (decrease or discontinue if hypoglycemia persists 1-2 times per week) • Inadequate blood glucose control (blood glucose remains above target consistently) • Dose should be started low and titrated every 1-2 weeks until glycemic targets are met	• Associated with weight gain (unless dietary modifications are made) • Associated with hypoglycaemia; annual rate of any hypoglycaemia is 20%. Major hypoglycemic events occur in 1-2 % of individuals • Consider using other class(es) of oral antihyperglycemic agents first in patients at high risk of hypoglycemia i.e. the elderly • Requires lower dose and slower titration in patients with hepatic/renal impairment and the elderly • Increased risk for hypoglycemia with insulin • Glyburide not recommended with eGFR <30 mL/min, and should be used with caution in eGFR 30-45 mL/min. • Gliclazide and Glimepiride are contraindicated in severe renal impairment (CrCl eGFR<15 ml/min). Lower dose should be used if eGFR <30 mL/min • Sulfonylureas should be put on hold in patients with severe dehydration (i.e. vomiting and unable to keep down fluids)

Onset/peak/duration: 1-2h/6-12/>24h *Expected HbA1C reduction:* 0.8% *ODB Coverage:* Yes **<u>Diabeta (Glyburide)</u>** *Initial Dose:* 2.5 mg – 5.0 mg daily or bid with meals *Average Dose (Max dose):* 5-10 mg bid with meals (20 mg) *Special Instructions:* Take 30min prior to meal) *Onset/peak/duration:* 1-2h/4-6h/10-14h *Expected HbA1C reduction:* 0.8% *ODB Coverage:* Yes **<u>Amaryl (Glimepiride)</u>** *Initial Dose:* 1 mg daily with first meal *Average Dose (Max dose):* 1-4 mg daily (8 mg) *Onset/peak/duration:* 20min/2-4h/24h *Expected HbA1C reduction:* 0.8% *ODB Coverage:* No	See above.	See above.
Insulin Secretagogues **Non-Sulfonylureas:** **Meglatinides** **<u>Gluconorm (Repaglinide)</u>** *Initial Dose:* 0.5-1mg tid with meals *Average Dose (Max dose):* 0.5-4 mg tid (16 mg)	• Frequent hypoglycemia (decrease or discontinue if hypoglycemia persists 1-2 times per week) • Less hypoglycemia compared to sulfonylurea's and are ideal for patients with irregular meal times	• Less likely to cause weight gain and hypoglycemia than sulfonylureas • Safe to use in renal impairment and mild hepatic impairment but requires slower dose titration • In the elderly Repaglinide should be initiated at 0.5mg TID and titrate dose slowly (especially with CrCl 20-39mL/min) • Preferred for use in elderly individuals with erratic eating patterns

Special Instructions: take 1-30min before meals *Onset/peak/duration:* 30min/1h/4-5h *Expected HbA1C reduction:* 0.7% *ODB Coverage:* Exceptional Access Program (EAP)	• Inadequate blood glucose control (blood glucose remains above target consistently) • Doses should be titrated weekly as required to obtain glycemic targets	• The concomitant use of Repaglinide and Clopidigrel (Plavix) is contraindicated as it may lead to a significant decrease in blood glucose levels due to a drug-drug interaction
Thiazolidinediones (TZD's) **<u>Actos (Pioglitazone)</u>** *Initial Dose:* 15 mg daily *Average Dose (Max dose):* 15-45 mg daily (45 mg) *Onset/peak/duration:* 30min/2-4h/4 weeks *Expected HbA1C reduction:* 0.8% *ODB Coverage:* EAP **<u>Avandia (Rosiglitazone)</u>** *Initial Dose:* 4 mg daily *Average Dose (Max dose):* 2-8 mg daily (8 mg) *Onset/peak/duration:* 30-60min/1-2h/4 weeks *Expected HbA1C reduction:* 0.8% *ODB Coverage:* EAP	• Edema • Shortness of breath • Discontinue TZD if insulin is initiated • Titrate every 2-4 weeks • Full BG-lowering effect seen within 6-12 weeks • Discontinue if ALT >3 X upper limit of normal	• Should do baseline LFT's prior to initiation, every 2 months for the first year and then periodically • May induce edema, fluid retention (recommended to monitor weight) • Pioglitazone may increase risk of bladder cancer and is not recommended for use with Patient's who have or have had bladder cancer, are at high risk, have blood or a red color in their urine. Patient's taking pioglitazone should be assessed regularly for potential symptoms of bladder cancer i.e. blood or red color in urine, painful urinate etc. • Can cause weight gain (subcutaneous fat + fluid retention) 1.5-4.84kg but decrease in visceral and hepatic fat. Weight gain is generally dose dependent • Associated with increased risk for bone loss and fractures in women 55yrs or older (0.78 per 100) • Used in combination with insulin may increase risk of edema and CHF. The combination of a TZD plus insulin is currently not an approved treatment in Canada • Rosiglitazone is no longer approved for use alone to treat DM2 except when Metformin use is contraindicated or not tolerated and all other oral agents have been tried alone or together and targets are not reached • Rosiglitazone is not indicated for triple therapy and is only indicated in combination with Metformin or a sulfonylurea • Pioglitazone is no longer approved for use with Metformin and a sulfonylurea • Can be used safely in mild to severe renal impairment

		• Contraindicated for people with CHF New York Heart Association (NYHA) Class I to IV cardiac status; evidence of left ventricular dysfunction or serious hepatic impairment (ALT 2.5 X upper limit of normal) • Prior to prescribing Avandia practitioners must 1) document the individual's eligibility to meet the above criteria; 2) counsel the individuals on the risks and benefits of Avandia, including the CV risks; and 3) obtain the person's written informed consent to take the drug
DPP4 Inhibitors **<u>Sitagliptin (Januvia)</u>** *Initial Dose:* 100 mg daily qam with/without food *Average Dose (Max dose):* 100 mg daily (100 mg) *Onset/peak/duration:* Rapidly absorbed/1-4h/24h *Expected HbA1C reduction:* approx. 0.7% *ODB Coverage:* Yes **<u>Saxagliptin (Onglyza)</u>** *Initial Dose:* 5 mg daily with/without food *Average Dose (Max dose):* 5 mg daily (5 mg) *Onset/peak/duration:* Rapidly absorbed/2.5h/26.9h *Expected HbA1C reduction:* approx. 0.7% *ODB Coverage:* Yes **<u>Linagliptin (Trajenta)</u>** *Initial Dose:* 5 mg daily with/without food *Average Dose (Max dose):* 5 mg daily (5 mg) *Onset/peak/duration:* Rapidly absorbed/1.5h/24h	• Nasopharyngitis, cough and headache (rare cases) • Severe joint pain (rare cases), usually within 1 month of initiation • Inadequate glucose control • Increased risk for hypoglycemia if combined with a sulfonylurea • Discontinue if suspicion of pancreatitis i.e. severe ongoing stomach or back pain with/without vomiting	• Linagliptin can be used in renal insufficiency (eGFR <15 ml/min and dialysis) • Saxagliptin dose should be decreased to 2.5 mg od if eGFR <50 mL/min, and discontinued if eGFR <15 mL/min. It should not be used in patients on dialysis (assess renal function prior to treatment and periodically after) • Sitagliptin dose should be decreased to 50 mg od if eGFR is 30-49 mL/min, and decreased further to 25 mg od if eGFR <30 mL/min (assess renal function prior to treatment and periodically after) • Alogliptin dose should be decreased to 12.5 mg if eGFR is 30-60 mL/minute, 6.25 mg od if eGFR is 15-30 mL/minute and can be used at 6.25mg of in ESRD with hemodialysis (has not been studied with peritoneal dialysis) • Use in caution in the elderly (as per renal guidelines) • Safety profile has not been studied and is unclear in individual's who are immunocompromised e.g. lymphocyte abnormalities, HIV, or people who have undergone organ transplant • Approved for use with Metformin and a sulfonylurea • Approved for use with insulin except for Linagliptin • Linagliptin , Sitagliptin and Alogliptin are not recommended in severe hepatic insufficiency and Saxagliptin is not recommended in moderate to severe hepatic impairment (monitor hepatic function before initiating treatment and periodically after) • Not recommended if history of pancreatitis • Caution if history of alcoholism, high triglycerides (higher risk for pancreatitis) • Not recommended for people with heart failure

Expected HbA1C reduction: approx. 0.7% *ODB Coverage:* Yes **<u>Alogliptin (Nesina)</u>** *Initial Dose:* 25 mg daily with/without food *Average Dose (Max dose):* 25 mg daily (5 mg) *Onset/peak/duration:* Rapidly absorbed/1-2h/approx. 24h *Expected HbA1C reduction:* approx. 0.7% *ODB Coverage:* No		
GLP–1 Receptor Agonist **<u>Liraglutide (Victoza)</u>** *Initial Dose:* 0.6 mg SC daily *Average Dose (Max dose):* 1.2-1.8 mg SC daily (1.8 mg) *Expected HbA1C reduction:* 1-1.5% ODB Coverage: No **<u>Exenatide (Byetta)</u>** *Initial Dose:* 5 mcg (1.2 mL)SC bid *Average Dose (Max dose):* 5-10 mcg (1.2 mL–2.4 mL) bid (20 mcg) *Special Instructions:* inject <60minutes before two meals (breakfast and dinner) *Onset/peak/duration:* Rapid onset/2.1h/10h *Expected HbA1C reduction:* 1.3-1.5% ODB Coverage: No **<u>Dulaglutide (Trulicity)</u>**	• Liraglutide to be increased to ideal therapeutic dose of 1.2mg OD after 1 week as tolerated. Can further increase to 1.8mg OD if needed based on response after 1 week at 1.2mg • Dulaglutide to be increased to ideal therapeutic dose of 1.5mg q 1week after 1 week as tolerated. • Exenatide should be titrated up to 10ug BID after 1 month if tolerating well • Increased risk of hypoglycemia if used with sulfonylurea (assess need to decrease sulfonylurea dose by 50%)	• Common adverse effects are nausea (10.7-18.6%), diarrhea (8.3-14.9%), headache (5.4-12.4%), vomiting (5.4-7.4%) and dyspepsia (2.1-7.0%) • Symptoms usually improve over time • Should be stored in the refrigerator and unused medication discarded after 30 days • Increase in heart rate/ PR interval prolongation • Liraglutide is only approved for use with Metformin and/or a sulfonylurea in Canada • Exenatide is approved for use with Metformin and/or a sulfonylurea and with insulin Glargine • Use with prandial insulin has not been studied and cannot be recommended • Rare cases of pancreatitis have been reported. Should be discontinued in the presence of persistent severe abdominal pain and vomiting • Contraindicated with type 1 diabetes, DKA, personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome • May slow absorption of medications; caution with medications that require rapid absorption (acetaminophen, pain medications)

Initial Dose: *0.75mg* (0.5 mL) SC qweekly *Average Dose (Max dose):* 1.5mg(1.5mg) *Special Instructions:* can be taken with or without meals *Onset/peak/duration:24 hrs/48hrs/120hrs* *Expected HbA1C reduction:* 1.1% *ODB Coverage:* No		• Liraglutide not recommended for moderate to severe renal impairment (eGFR <50 mL/min) • Exenatide dose should be decreased to 5 mcg bid if eGFR 30-59 mL/min, and discontinued if eGFR <30 mL/min • Assess renal function prior to treatment and periodically thereafter • Caution in patients with recent MI, unstable angina, CHF, IBS or gastroparesis (no studies) • Exenatide should not be taken after meals or if dose was missed • Dulaglutide can be used with Metformin, with Metofrmin & a Sulfonylurea, with mealtime insulin. • Dulaglutide has not been studied in combination with a basal insulin • Dulaglutide's day of weekly administration can be changed if necessary, as long as the last dose was at least 3 days before
SGLT2 Inhibitors **<u>Canagliflozin (Invokana)</u>** *Initial Dose:* 100 mg daily qam ideally before meal *Average Dose (Max dose):* *300mg daily (300mg)* *Onset/peak/duration:* Rapidly absorbed/1-2 hrs/approx. 24 hrs *Expected HbA1C reduction:* 0.77-1% * up to 2.56% with HbA1C >10% *ODB Coverage:* Yes **<u>Dapagliflozin (Forxiga)</u>** *Initial Dose:* 5 mg daily with/without food *Average Dose (Max dose):* 10 mg daily (10 mg) *Onset/peak/duration:* Rapidly absorbed/2h/approx. 24 hrs *Expected HbA1C reduction:* 0.7-0.99% * up to 2.04% with HbA1C >9% *ODB Coverage:* No	• Start Canagliflozin at 100mg and increase to 300mg if well tolerated and eGFR >60 mL/min • Start Dapagliflozin at 5mg od and increase to 10mg od if well tolerated and eGFR >60 mL/min • Start Empagliflozin at 10mg od and increase to 25mg od if well tolerated and eGFR >60 mL/min • Canaglifozin and Empagliflozin should be discontinued when eGFR is <45 mL/min as it would not be effective in these patients and adverse reactions are more severe • Dapagliflozin should be discontinued when eGFR is <60 mL/min • Increased risk for hypoglycaemia if combined with sulfonylurea or insulin (may need to adjust diabetes medications)	• Indicated as monotherapy in patients with type 2 diabetes for whom Metformin is inappropriate due to contraindications or intolerance • Indicated in combination therapy with Metformin, sulfonylureas or insulin (with or without Metformin) • Invokana and Forxiga are indicated in combination with Januvia • Common adverse effects are increased serum potassium >5.4 mEq/ml (12-27%) and >6.5 mEq/ml (2%), genital mycotic infections (7-11% in women and 3-4% in men), urinary tract infections (4-6%), nasophyringitis (6-7%), polyuria (3-5%) • Renal function should be assessed prior to initiation of and regularly after with more frequent monitoring for patients taking Canagliflozin or Empagliflozin with eGFR 45-60 mL/min • Should not be initiated in patients with an eGFR <60 mL/min or <45 mL/min for Empagliflozin • Monitor serum potassium levels periodically after initiating in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions • May increase the risk for ketoacidosis. Patients experiencing signs and symptoms of ketoacidosis (e.g., difficulty breathing, nausea, vomiting, abdominal pain, confusion, unusual fatigue or sleepiness) should be evaluated and SGLT2 inhibitor should be discontinued if acidosis is confirmed • LDL levels should be monitored due to dose dependent increases in LDL-C seen with therapy

Empagliflozin (Jardiance) *Initial Dose:* 10 mg daily with/without food *Average Dose (Max dose):* 25 mg daily (25 mg) *Onset/peak/duration:* Rapidly absorbed/1.5h/approx. 24 hrs *Expected HbA1C reduction:* 0.7-0.99% * up to 2.04% with HbA1C >9% *ODB Coverage:* Yes		• Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer • Dapagliflozin is not recommended in combination with pioglitazone (Actos) • Dapagliflozin and Canagliflozin tablets contain lactose • May cause symptomatic hypotension due to intravascular volume depletion especially in patients with renal impairment (eGFR <60 mL/min), elderly, patients on other antihypertensives, or those with low systolic blood pressure. Assess volume status prior to initiation in patients at risk of hypotension and correct if depleted; monitor for signs and symptoms of hypotension after initiation • Not recommended for use with patients on loop diuretics • Can be used in mild-moderate hepatic impairment • Elderly patients (≥65 years) may have an increased risk of symptoms related to intravascular volume depletion (e.g., hypotension, orthostatic hypotension, dizziness, syncope, and dehydration) during therapy, especially with higher doses; elderly patients ≥75 years may experience a more pronounced risk. HbA1c reductions may be less in patients >65 years compared to younger patients. • Patients should be educated about the increased risk for genital mycotic infections and/or urinary tract infections • Patents should be advised about the possible side effect of increased urination and encouraged to drink sugar-free liquids during the day to avoid dehydration
Combination Medications **Janumet (Januvia and Metformin)** *Initial Dose:* 50/500mg bid *Average Dose (Max dose):* 50/1000mg bid (50/1000mg bid) *Special Instructions:* Take with meals to reduce GI side effects *ODB Coverage:* Yes **Janumet XR (Januvia and Glumetza)**	• See the indications for medications included in combination tablet • Initiate at higher doses (not initial dose) if already taking Metformin at higher doses and tolerating well	• See contraindications/precautions for medications included in combination tablet

Initial Dose: 50/1000mg daily ideally with dinner *Average Dose (Max dose):* 50/2000mg od (50/2000mg od) *Special Instructions:* Take with meal to reduce GI side effects *ODB Coverage:* Yes **Jentadueto (Trajenta and Metformin)** *Initial Dose:* 2.5/500mg bid *Average Dose (Max dose):* 2.5/1000mg bid (2.5/1000mg bid) *Special Instructions:* Take with meals to reduce GI side effects *ODB Coverage:* Yes **Komboglyze (Onglyza and Metformin)** *Initial Dose:* 2.5/500mg bid *Average Dose (Max dose):* 2.5/1000mg bid (2.5/1000mg bid) *Special Instructions:* Take with meals to reduce GI side effects *ODB Coverage:* Yes **Kazano (Nesina and Metformin)** *Initial Dose:* 12.5/500mg bid *Average Dose (Max dose):* 12.5/1000mg bid (12.5/1000mg bid) *Special Instructions:* Take with meals to reduce GI side effects *ODB Coverage:* No **Xigduo (Forxiga and Metformin)** *Initial Dose:* 5/850mg bid		

Average Dose (Max dose): 5/1000mg bid (5/1000mg bid) *Special Instructions:* Take with meals to reduce GI side effects *ODB Coverage:* No **<u>Invokamet (Invokana and Metformin)</u>** *Initial Dose:* 50/500mg bid *Average Dose (Max dose):* 150/1000mg bid (150/1000mg bid) *Special Instructions:* Take with meals to reduce GI side effects *ODB Coverage:* No **<u>Synjardy (Jardiance and Metformin)</u>** *Initial Dose:* 5/500mg bid *Average Dose (Max dose):* 12.5/1000mg bid (12.5/1000mg bid) *Special Instructions:* Take with meals to reduce GI side effects *ODB Coverage:* No **See dosing information for medications included in combination tablet for more information**		