TYPE 2 DIABETES – ORAL HYPOGLYCAEMIC AGENTS (1)

The North West London health and care partnership

NB: All information presented is in line with the Summaries of Product Characteristics (SPC) of each drug or the BNF.

BIGUANIDES (METFORMIN)

- *Decreases gluconeogenesis and increases peripheral utilisation of glucose. Improves insulin sensitivity.*

Preparation	Dose	Dose adjustments		
		Moderate renal impairment (eGFR= 30-44 mL/min/1.73 m^2)	Severe renal impairment (eGFR<30 mL/min/1.73 m^2)	Hepatic Impairment:
Metformin	500mg – 2g daily in divided doses, With or after a meal	Max daily dose, 1g	Contraindicated	Withdraw if tissue hypoxia likely.
Metformin modified-release	500mg - 2g once daily with evening meal If glycaemic control is not achieved, 1g twice daily should be considered.			

Contraindications:
- eGFR <30ml/min/1.73 m^2,
- any acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis),
- acute or chronic conditions that may alter renal function, hepatic insufficiency
- cardiac and/or respiratory failure which may likely cause tissue hypoxia

Pregnancy and breast-feeding: Can be used in pregnancy and breastfeeding

Cautions:
- Chronic stable heart failure (monitor cardiac and renal function)
- May cause Vitamin B12 malabsorption.
- Risk factors for lactic acidosis

Class side effects:
- GI side effects (e.g. diarrhoea, abdominal pain, nausea, taste disturbance and vomiting.)

Monitoring requirements:
- Monitor eGFR when initiating and if starting antihypertensive, diuretics and NSAIDs or other conditions that can acutely worsen renal function
- Withhold short term if dehydrated (including diarrhoea and vomiting), severe infection or shock (i.e. post-MI) and re-start once fully hydrated

Additional information:
- All people, irrespective of eGFR, should be educated on good sick day guidance (see page 16).
- Metformin MR is an option for people poorly tolerant on standard-release
- Based on clinical experience of increased side-effects, maximum dose for metformin immediate-release medicines in BNF Publications differs from product licence.
- Reduces cardiovascular disease in overweight or obese people

SULFONYLUREAS (GLICLAZIDE, GLIMEPIRIDE)

- *Stimulates insulin release from the pancreas.*

Preparation	Dose	Dose adjustments		
		Mild-moderate renal impairment	Severe renal impairment	Hepatic Impairment:
Gliclazide	Initially 40-80mg once daily, titrated until glycaemic control achieved before meals. Maximum daily dose: 160mg twice daily	Use with care in mild to moderate renal impairment.	Avoid	Avoid in severe hepatic insufficiency; use of insulin is recommended
Glimepiride	1mg once daily, titrated in steps of 1mg every 1-2 weeks to 4mg once daily if need be. Maximum 6mg once daily . Similar time daily, shortly before or with first main meal			

Contraindications:
- Presence of ketoacidosis
- Severe renal or hepatic insufficiency
- Gliclazide – Acute porphyrias, interaction with systemic and oromucosal miconazole

Pregnancy and breast-feeding: Avoid

Cautions:
- Elderly due to a possible age-related increased risk of hypoglycaemia
- People with G6PD deficiency
- Concomitant use of sulfonylureas and insulin should be avoided in people with severe renal impairment (<45mL/min/1.73m^2)

Class side effects:
- GI side effects (e.g. abdominal pain, nausea/vomiting , diarrhoea and constipation)
- Weight gain
- Please see individual drug monograph in the BNF for a complete side-effect profile

Monitoring requirements: Blood glucose (See page 23)

Additional information:
- Risk of hypoglycaemia when used with SGLT2i, DPP4i, pioglitazone and acarbose- consider reducing dose of sulfonylurea.
- ALL people should be told about recognition and management of hypoglycaemia when prescribed a sulfonylurea.

TYPE 2 DIABETES – ORAL HYPOGLYCAEMIC AGENTS (2)

The North West London health and care partnership

NB: All information presented is in line with the Summaries of Product Characteristics (SPC) of each drug or the BNF.

THIAZOLIDINEDIONES (PIOGLITAZONE)

- *Reduces peripheral insulin resistance, leading to a reduction of blood-glucose concentration.*

Preparation	Dose	Dose adjustments	
		Renal Impairment	Hepatic Impairment:
Pioglitazone	Initially 15–30 mg once daily, adjusted according to response up to 45 mg once daily with or without food. Elderly - initiate with lowest possible dose and increase gradually.	No dose adjustment is necessary	Should not be used in people with hepatic impairment (Therapy with pioglitazone should not be initiated if the ALT is > 2.5 times the upper limit of normal or with any other evidence of liver disease.)

Contraindications:
- Cardiac failure / Hx of cardiac failure (NYHA stages I to IV)
- hepatic impairment
- diabetic ketoacidosis
- current bladder cancer or a history of bladder cancer
- uninvestigated macroscopic haematuria

Pregnancy and breast-feeding: Avoid

Cautions: Potentiates the hypoglycaemic effects of insulin and sulfonylureas (see page 32/65)

Side effects:
- Bone fracture (particularly in women);
- Increased risk of infection;
- numbness;
- visual impairment;
- weight increased

Monitoring requirements:
Review treatment after 3–6 months and regularly thereafter
- Liver function tests prior to commencing therapy, and periodically thereafter
- Whilst on pioglitazone, if ALT levels are increased to 3 times upper limit of normal, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued
- Weight

Additional information:
- Important safety information – Please see hyperlinks for more detailed advice
- MHRA/CHM advice: Pioglitazone cardiovascular safety (December 2007 and January 2011)
  - People should be informed on the signs and symptoms of DKA, discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed
- Pioglitazone: risk of bladder cancer (July 2011)
  - Pioglitazone should not be used in people with active bladder cancer or a past history of bladder cancer, or in those who have uninvestigated macroscopic haematuria.
- Weight gain which may be due to fat accumulation, and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure, therefore weight should be closely monitored.

DPP-4 INHIBITORS: DIPEPTIDYLPEPTIDASE-4 INHIBITORS (SITAGLIPTIN, SAXAGLIPTIN, LINAGLIPTIN, VILDAGLIPTIN, ALOGLIPTIN)

- *Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.*

Preparation	Dose	Dose adjustments		
		Moderate renal impairment (eGFR= mL/min/1.73 m²)	Severe renal impairment (eGFR= mL/min/1.73 m²)	Hepatic Impairment:
Alogliptin*	25 mg once daily	eGFR 30–50: 12.5 mg once daily	eGFR <30: 6.25 mg once daily; Use with caution	No dose adjustment necessary if mild/moderate impairment. Use with caution Therapeutic experience in severe hepatic impairment is limited and therefore use is not recommended by manufacturer.
Linagliptin	5 mg once daily	N/A		
Sitagliptin	100 mg once daily	eGFR 30–45: 50 mg once daily	eGFR <30: 25 mg once daily	
Saxagliptin	5 mg once daily	eGFR <45: 2.5mg once daily		
Vildagliptin	50 mg twice daily ***50 mg once daily*** *in the morning when used in* ***combination with a sulfonylurea***	eGFR <50: 50 mg once daily		Should not be used in people with hepatic impairment

Contraindications:
- Ketoacidosis

Pregnancy and breast-feeding: Avoid

Cautions:
- Potentiates the hypoglycaemic effects of insulin and sulfonylureas (see page 32/65)
- People with a history of pancreatitis.

Class side effects:
- Headache/dizziness
- Please see individual drug monograph in the BNF for a complete side-effect profile

Monitoring requirements:
- Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain)
- Vildagliptin associated with liver toxicity; seek medical attention if nausea, vomiting, abdominal pain, fatigue, and dark urine develops. Monitor liver enzymes 3 month interval for first year, periodically after.

Additional information:
*Alogliptin not licensed for monotherapy

TYPE 2 DIABETES – ORAL HYPOGLYCAEMIC AGENTS (3)

The North West London health and care partnership

NB: All information presented is in line with the Summaries of Product Characteristics (SPC) of each drug or the BNF.

SGLT-2 INHIBITORS: SODIUM GLUCOSE CO-TRANSPORTER 2 AGENTS (CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN, ERTUGLIFLOZIN)

- *Inhibit sodium-glucose co-transporter 2 (SGLT-2) in the proximal renal tubule to reduce glucose reabsorption and increase urinary glucose excretion.*

Preparation	Dose	Dose adjustments			
		Initiating in eGFR <60 mL/min/1.73 m^2:	If taking as current treatment- eGFR <60 mL/min/1.73 m^2:	Moderate-severe Renal Impairment (eGFR= mL/min/1.73 m^2):	Hepatic Impairment:
Canagliflozin	100 mg once daily Increased if tolerated to 300 mg once daily if required Preferably before breakfast	100mg once daily	Reduce dose to 100 mg once daily	If eGFR<30: Do not initiate; Can be continued until dialysis or renal transplantation if urinary albumin/creatinine ratio > 300 mg/g	No dose adjustment necessary if mild/moderate impairment. Therapeutic experience in severe hepatic impairment is limited and therefore use is not recommended by manufacturer.
Empagliflozin	10 mg once daily, Increased up to 25 mg once daily, If necessary with or without food. *Initiation not recommended in adult ≥85 years*	Avoid initiation	Reduce dose to 10 mg once daily	If eGFR persistently <45: Discontinue/Avoid	
Ertugliflozin	5 mg once daily Increased to 15 mg once daily if necessary and if tolerated Dose to be taken in the morning.		10 mg once daily Increase monitoring of renal function		
Dapagliflozin	10 mg once daily With or without food		10 mg once daily Monitor renal function at least 2-4 times a year		Initial dose 5 mg daily in severe hepatic impairment, can increase to 10mg according to response/tolerability

Contraindications:
- Diabetic ketoacidosis

Pregnancy and breast-feeding:
Avoid—toxicity in animal studies

Monitoring requirements:
- Renal function - before treatment and at least annually thereafter, and before initiation of drugs that may reduce renal function and periodically thereafter.
- Volume status and electrolytes

Cautions:
- People at risk of hypotension/hypovolaemia) (e.g. Elderly, dehydration)
- Please see specific drug monograph in the BNF for complete cautions
- Potentiates the hypoglycaemic effects of insulin and sulfonylureas (see page 32/65)

Class side effects:
- Increased risk of UTI
- Polydipsia
- urinary disorders
- Please see individual drug monograph in the BNF for a complete side-effect profile

Additional information:
- **Important safety information – Please see hyperlinks for more detailed advice:**
  - MHRA/CHM advice (updated April 2016): SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis (DKA)
    - People should be informed on the signs and symptoms of DKA, discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed
  - MHRA/CHM advice (MHRA/CHM advice March 2017): SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)
    - SGLT2i's may increase the risk of lower-limb amputation (mainly toes) . All people taking an SGLT2i should be counselled on good preventive foot care. Review if lower limb complications develop (e.g. skin ulcer, osteomyelitis, or gangrene). Monitor people with risk factors for amputation, signs and symptoms of water or salt loss.
  - MHRA/CHM advice: SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) (February 2019)
    - if Fournier's gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement as required)
  - MHRA/CHM advice: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness (March 2020)
    - SGLT2 inhibitor treatment should be interrupted in people who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine. Treatment may be restarted when the ketone values are normal and the person's condition has stabilised.

SGLT2 inhibitors: safe prescribing guidance

INTRODUCTION

- In a number of drug trials various members of the SGLT-2i class have been shown to have cardio renal protective effects over and above their glycaemic effectiveness. Data on these cardio renal effects is emerging rapidly and this may be reflected in changes to the licensing arrangements for individual members of this class
- This guidance is only designed to be used for the prescription of SGLT-2i inhibitors within each individual drug's current licence (see slide 36)
- The prime purpose of this guideline is to ensure that, where an SGLT-2i is prescribed in a patient with type II diabetes for cardiorenal protection, it is undertaken safely. This can be achieved by ensuring that these agents are only prescribed for the appropriate patients and that the appropriate information is given to patients to ensure safety.

CAUTIONS

- **Frail elderly**
- **Potential for pregnancy**
- **SGLT-2i should NOT be prescribed to people with type 1 diabetes *unless* under the direction of a diabetologist**
- **SGLT-2i should not be prescribed to people with type 2 diabetes at increased risk of *euglycaemic diabetic ketosis* – *see below*****
- **Always offer advice on *sick day guidance* when introducing these agents and reiterate at every opportunity i.e. stop perioperatively or if restricted food intake or dehydration.**
- **Reiterate that if on an SGLT-2i, very low carbohydrate diets (or ketogenic diets) carry an increased risk of ketosis.**
- **In people with reasonable glycaemic control and risk of hypoglycaemia, consider reducing other hypoglycaemic agents when introducing SGLT-2i.**
- **In people on diuretics, consider reducing the dose.**
- **Give advice to seek medical attention (via GP, urgent care centre or pharmacy) should they develop symptoms of a genital infection.**
- **Caution is advised if the person has active peripheral vascular disease including active arterial ulceration or claudication.**

** TYPE 2 DIABETIC PEOPLE AT INCREASED RISK OF EUGLYCAEMIC DIABETIC KETOSIS

- **Those who rapidly progressed to requiring insulin (within 1 year of diagnosis)**
- **Past history of diabetic ketoacidosis (DKA)**
- **History of pancreatic disease – including alcoholic pancreatitis as a cause of their pancreatitis**
- **BMI<27**
- **The possibility of Latent Autoimmune Diabetes in Adults**

TYPE 2 DIABETES – ORAL HYPOGLYCAEMIC AGENTS (4)

NB: All information presented is in line with the Summaries of Product Characteristics (SPC) of each drug or the BNF.

ALPHA GLUCOSIDASE INHIBITORS (ACARBOSE)

- *Acarbose, an inhibitor of intestinal alpha glucosidases, delays the digestion and absorption of starch and sucrose; it has a small but significant effect in lowering blood glucose.*

Preparation	Dose	Dose adjustments	
		Renal Impairment	Hepatic Impairment:
Acarbose	Initially 50 mg daily, Titrated up to maximum of 200 mg 3 times a day, if required. Before food	As Acarbose has not been studied in people with severe renal impairment, it should not be used in people with a creatinine clearance <25 ml/min/1.73m²	Contraindicated in people with hepatic impairment

Contraindications:
- Hepatic impairment
- Hernia;
- inflammatory bowel disease;
- predisposition to partial intestinal obstruction;
- previous abdominal surgery

Pregnancy and breast-feeding:
Avoid

Cautionary use in:
- Potentiates the hypoglycaemic effects of insulin and sulfonylureas (see page 32/65), hypoglycaemic episodes may be treated with oral glucose, but not with sucrose.

Side effects:
- Abdominal pain
- Diarrhoea
- Flatulence

Monitoring requirements:
- It is recommended that liver enzyme monitoring is considered during the first 6 to 12 months of treatment. If elevated transaminases are observed, withdrawal of therapy may be warranted, particularly if the elevations persists. In such circumstances, people should be monitored at weekly intervals until normal values are established.

Additional information:
- For use in people inadequately controlled by diet alone, or by diet with oral anti-diabetic drugs.
- Poorer anti-hyperglycaemic effect than many other antidiabetic drugs.
- Low incidence of hypoglycaemia.

MEGLITINIDES (REPAGLINIDE)

- *Stimulates insulin secretion.*

Preparation	Dose	Dose adjustments	
		Renal Impairment	Hepatic Impairment:
Repaglinide	Initially 500 micrograms (max. per dose 4 mg), adjusted according to response at intervals of 1–2 weeks. Maximum daily dose: 16 mg per day in divided doses. *Initiation not recommended in adults ≥75 years* To be taken within 30 minutes before main meals	Use with caution in renal impairment	Avoid in severe liver disease

Contraindications:
- Ketoacidosis
- Concomitant use of gemfibrozil

Pregnancy and breast-feeding:
Avoid

Cautionary use in:
- Debilitated people;
- Malnourished people

Side effects:
- Abdominal pain;
- diarrhoea;
- hypoglycaemia

Monitoring requirements:
- It is recommended that liver enzyme monitoring is considered during the first 6 to 12 months of treatment

Additional information:
- Licensed as monotherapy, or in combination with metformin, when metformin alone inadequate.
- Rapid onset of action and short duration of action.
- Substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery.