GLP-1 Receptor Agonists

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Incretins

- Incretins are hormones produced by the intestinal mucosa in response to oral intake of nutrients → enhance glucose-stimulated insulin secretion (incretin effect)
- Glucose-dependent insulinotropic polypeptide (GIP)
- Glucagon-like peptide 1 (GLP-1) more effective in stimulating insulin release
- Incretin effect reduced in people with type 2 diabetes → impaired capacity to secrete insulin

GLP-1 Receptor Agonists

Pharmacological Effects

- GLP-1 receptor agonists stimulate GLP-1 receptors → increased insulin secretion in response to oral glucose
- Decreased glucagon concentrations
- Slowed gastric emptying
- Increased satiety
- Decreased free fatty acid concentrations

GLP-1RAs: multifactorial effects beyond glycaemic control

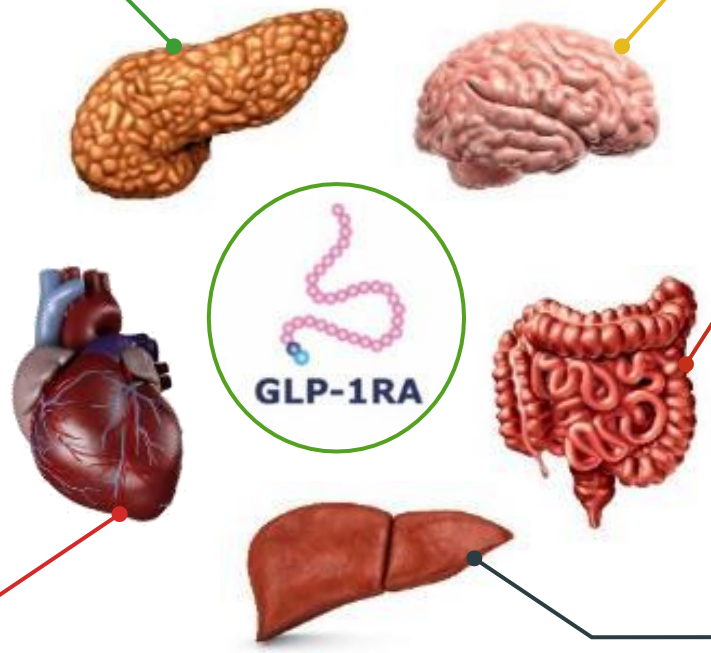
DATA ORIGINATING FROM HUMAN AND NON-HUMAN (i.e. ANIMAL AND IN-VITRO) STUDIES

Pancreas

- ↑ Beta-cell function[1*]
- ↓ Beta-cell death[1]
- ↑ Insulin production[1*]
- ↓ Glucagon secretion[1]

Brain

- ↓ Body weight[5*]
- ↓ Food intake[6]
- ↓ Appetite[7,8]



Incretin system

Replacement of deficient GLP-1 response[9]

- ↓ Glucose production[10]
- ↑ Insulin sensitivity[10]
- ↓ Conversion carbohydrate to fat[10]
- ↓ Accumulation of lipids[10]
- ↓ Retention of lipids[11]

Heart

- ↓ Cardiovascular risk[2]
- ↓ Fatty acid metabolism[3]
- ↑ Cardiac function[3]
- ↓ Systolic blood pressure[3]
- ↓ Inflammation[4]
- ↓ Plaque progression[4]

Liver

*Data from non-human studies. GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Campbell JE, DJ Drucker. *Cell Metab* 2013;17:819-837; 2. Marso SP et al. *N Engl J Med* 2016;375:311-322; 3. Ryan D, Acosta A. *Obesity* 2015;23:1119-1129; 4. Hogan AE et al. *Diabetologia* 2014;57:781-784; 5. Baggio LL, Drucker DJ. *J Clin Invest* 2014;124:4223-4226; 6. Bagger JI et al. *Clin Endocrinol Metab* 2015;100:4541-4552; 7. Flint A et al. *J Clin Invest* 1998;101:515-520; 8. Blundell J et al. Presented at the 76th Scientific Sessions of the American Diabetes Association. June 10-14, 2016. New Orleans, Louisiana, USA: Oral Presentation 23-OR; 9. Tong J, D'Alessio D. *Diabetes* 2014;63:407-409; 10. Armstrong MJ et al. *J Hepatol* 2016;64:399-408; 11. Armstrong MJ et al. *Lancet* 2016;387:679-90.

Available GLP-1 Receptor Agonists

Generic name	Brand name
Exenatide (twice-daily injection)	Byetta
Exenatide extended release (once-weekly injection)	Bydureon
Liraglutide (once-daily injection)	Victoza
Lixisenatide (once-daily injection)	Lixumia
Dulaglutide (once-weekly injection)	Trulicity
Semaglutide (once weekly injection)	Ozempic
Semaglutide (by mouth once daily)	Rybelsus

Clinical Effects of GLP-1 Receptor Agonists in Type 2 Diabetes

- HbA1c reduction by ~0.8–1.6%
- Body weight reduction by ~1–3 kg over 6 months
- Blood pressure reduction
- Lipid lowering effect
- Reduced cardiovascular risk

Contraindications

- Ketoacidosis
- Acute pancreatitis
- Severe renal impairment
- Severe hepatic impairment
- Severe gastrointestinal disease (diabetic gastroparesis, inflammatory bowel disease)

Cautions

- History of pancreatitis
- Renal impairment
- Hepatic impairment
- History of medullary thyroid cancer or multiple endocrine neoplasia (MEN) type 2 disease (for liraglutide)
- Retinopathy (semaglutide)

Adverse effects

- Acute pancreatitis (rare)
- Mainly gastrointestinal — decreased appetite, altered taste, usually mild and transient nausea, vomiting, dyspepsia, burping, gastro-oesophageal reflux, constipation, diarrhoea, gallbladder disorders (liraglutide).
- Headache, dizziness, drowsiness, alopecia, hyperhidrosis
- Renal impairment (exenatide, liraglutide)
- Atrioventricular block, sinus tachycardia, delayed gastric emptying (dulaglutide).
- Skin reactions including rash, angioedema, urticaria, and pruritus
- Increased risk of hypoglycaemia when used with sulfonylureas

NICE National Institute for Health and Care Excellence

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard–release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified–release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - *metformin and an SGLT-2i*[b]
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - *metformin, pioglitazone[a] or an SU, and an SGLT-2i*[b]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:
- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- have a BMI lower than 35 kg/m^2, and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
  - an SGLT-2i[b] instead of a DPP-4i if an SU or pioglitazone[a] is not appropriate
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i, SGLT-2i or pioglitazone **or** 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy[e] with:
  - a DPP-4i and pioglitazone[a]
  - a DPP-4i and an SU
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or** would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem **or** blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- *An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option*[b].

Abbreviations: [DPP-4i]Dipeptidyl peptidase-4 inhibitor, [GLP-1]Glucagon-like peptide-1, [SGLT-2i]Sodium–glucose cotransporter 2 inhibitors, [SU]Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. See NICE technology appraisal guidance 288 & 418, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin, respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions, as options in triple therapy regimens and in combination with insulin. All three are also options as monotherapies in adults in whom metformin is contraindicated or not tolerated. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

Dulaglutide

- Higher doses of Dulaglutide now available (3.0 mg and 4.5 mg) for additional glucose control and body weight reduction
- Starting dose 1.5 mg weekly and increased if necessary to 3 mg once weekly after at least 4 weeks, then increased if necessary to 4.5 mg once weekly after another 4 weeks

Oral Semaglutide (Rybelsus)

Rybelsus® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in combination with other medicinal products for the treatment of diabetes

SmPC, Summary of Product Characteristics
Rybelsus® Summary of Product Characteristics, Novo Nordisk

Once-daily administration of semaglutide tablets

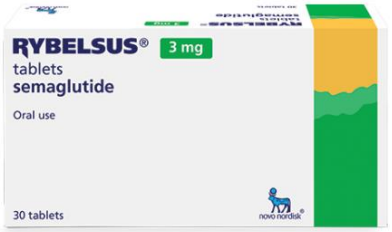
Starting dose

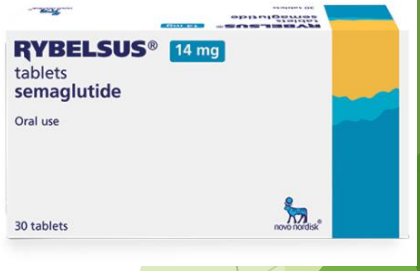
3 mg — Start with 3 mg once daily for 1 month

Maintenance doses

7 mg — Increase dose to 7 mg once daily for at least 1 month

14 mg — Based on individual needs, may increase dose to 14 mg once daily

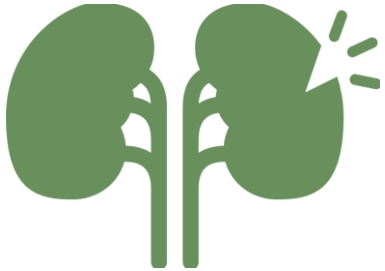




- Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of semaglutide
- Taking two 7 mg tablets to achieve the effect of a 14 mg dose has not been studied and is therefore not recommended
- Store in the original blister package in order to protect from light and moisture.
- This medicinal product does not require any special temperature storage conditions

Rybelsus® Summary of Product Characteristics, Novo Nordisk.

No dose adjustment for specific populations

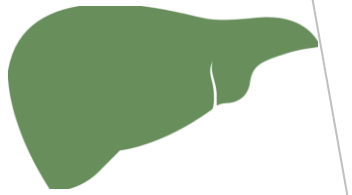


Renal Impairment

- No dosage adjustment for mild, moderate, or severe renal impairment
- Experience with the use of Rybelsus® in patients with severe renal impairment is limited
- Use is not recommended in end-stage renal disease

Elderly

- No dose adjustment is required based on age
- Therapeutic experience in patients ≥75 years of age is limited



Hepatic Impairment

- No dose adjustment is required for patients with hepatic impairment
- Experience with the use of Rybelsus® in patients with severe hepatic impairment is limited
- Caution should be exercised when treating these patients with Rybelsus®

Rybelsus® Summary of Product Characteristics, Novo Nordisk.

Optimising oral semaglutide exposure

Take on an **empty stomach** upon waking, with a **sip of water** (no more than 120 mL)

Wait at least **30 minutes** before eating, drinking, or taking any other oral medication

Taken whole and **not** to be **split, crushed** or **chewed**

Rybelsus® Summary of Product Characteristics, Novo Nordisk.

Other precautions with Rybelsus®

Treatment response

- Compliance with the dosing regimen is required for optimal effect of semaglutide. Absorption of semaglutide is highly variable and may be minimal (2-4% patients will not have any exposure)

Diabetic retinopathy complications

- In patients with diabetic retinopathy treated with insulin and s.c. semaglutide, an increased risk of developing diabetic retinopathy complications has been observed, a risk that cannot be excluded for orally administered semaglutide
- Caution should be exercised when using oral semaglutide in patients with diabetic retinopathy. These patients should be monitored closely and treated according to clinical guidelines

Interactions with levothyroxine

- Total exposure (AUC) of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single dose of levothyroxine
- Monitoring of thyroid parameters should be considered when treating patients with semaglutide at the same time as levothyroxine

Sodium content

- This medicinal product contains 23 mg sodium per tablet, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult

AUC Area Under Curve, subcutaneous; SmPC, Summary of Product Characteristics. Rybelsus® Summary of Product Characteristics, Novo Nordisk

Liraglutide for managing overweight and obesity

NICE TA664 December 2020 Saxenda for managing overweight and obesity alongside a reduced-calorie diet and increased physical activity in adults, only if:

- BMI at least 35 kg/m2 (or at least 32.5 kg/m2 for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population) and
- non-diabetic hyperglycaemia (defined as a haemoglobin A1c level of 42 mmol/mol to 47 mmol/mol [6.0% to 6.4%] or a fasting plasma glucose level of 5.5 mmol/litre to 6.9 mmol/litre) and
- high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia

Liraglutide for managing overweight and obesity

- Prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service
- Initially 0.6 mg daily, increased in steps of 0.6 mg at intervals of at least 1 week. Max dose 3 mg per day
- Contraindications: elderly 75 years or over (limited information), obesity secondary to endocrinological or eating disorder. Avoid in severe hepatic impairment, eGFR less than 30 ml/minute
- Should be discontinued if at least 5% body weight not been lost after 12 weeks on the full dose (3 mg per day)
- Treatment for all patients will stop after two years