

Factsheet

LIRAGLUTIDE 1.2mg (Victoza®) and DULAGLUTIDE[▼] (Trulicity®) Treatment of Type 2 Diabetes Mellitus

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FACTSHEET TO FACILITATE PRESCRIBING

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Factsheet – LIRAGLUTIDE 1.2mg (Victoza®) and DULAGLUTIDE ▼ (Trulicity®)

Type 2 Diabetes Mellitus

As per local formulary agreement, liraglutide 1.2mg or dulaglutide should only be initiated under the direction of a specialist in diabetes.

Checklist and actions for GP:

- Ensure documented communication has been received from the diabetes specialist with an indication for use (see 'Indication') and evidence that the specialist has counselled the patients on liraglutide/ dulaglutide
- Ensure that the patients meets the criteria for treatment
- Conduct necessary monitoring (see 'Clinical Monitoring')
- Prescribe the drug treatment as described below. The term "as directed" should not be used.
- Refer patients back to the diabetes specialist if the patient:
 - Is intolerant of side effects
 - Is non- adherent with medicines, or this is suspected
 - Does not achieve an adequate response at 6 months (see 'Continuation criteria')

Indication

Triple therapy with metformin and sulphonylurea

Liraglutide 1.2 mg and dulaglutide 1.5 mg will be initiated in triple therapy regimens in those who fail to have optimal glycaemic control despite fully titrated triple oral therapy. They will only be used when control of blood glucose remains or becomes inadequate (HbA1c \geq 58mmol/mol or other higher level agreed with the individual) and **either** of the following criteria are met:

- Body mass index (BMI) \geq 35 kg/m² in those of European descent with appropriate adjustment for other ethnicities (\geq 32 kg/m² for South Asian, Chinese, African Black and African-Caribbean) and specific psychological or medical problems associated with high body weight
- BMI < 35 kg/m² and
 - therapy with insulin would have significant occupational implications (e.g. Class 2 driver, working at heights), OR
 - weight loss would benefit other significant obesity-related comorbidities (including sleep apnoea, non-alcoholic fatty liver disease [NAFLD], CKD secondary to obesity, musculoskeletal issues due to obesity)

Dual therapy with metformin, or triple therapy with metformin and pioglitazone

The use of liraglutide 1.2 mg or dulaglutide 1.5 mg in combinations with oral medications which do not include a sulphonylurea may occasionally be advised by Specialists in Diabetes (e.g. if the patient is at serious risk from the consequences of hypoglycaemia or unable to tolerate a sulphonylurea). The eligibility criteria are identical to described under 'Triple therapy with metformin and sulphonylurea'

In combination with insulin

Liraglutide 1.2 mg and dulaglutide 1.5 mg may be used in combination with insulin in the following circumstances:

- Control of blood glucose remains or becomes inadequate ($\text{HbA1c} \geq 58\text{mmol/mol}$, or other higher level agreed with the individual) for patients prescribed maximum tolerated basal insulin \pm OADs and
 - insulin escalation (switching to biphasic or adding a bolus insulin) would have significant occupational implications (e.g. Class 2 driver, working at heights), OR
 - weight loss would benefit other significant obesity-related comorbidities (including sleep apnoea, non-alcoholic fatty liver disease [NAFLD], CKD secondary to obesity, musculoskeletal issues due to obesity)
- Control of blood glucose becomes inadequate ($\text{HbA1c} \geq 58\text{mmol/mol}$, or other higher level agreed with the individual) for patients prescribed GLP-1RA + MET + SU.

Patients who would have fulfilled the criteria for GLP-1RA agonist therapy but who were commenced on insulin treatment should be considered for co-administration of insulin and GLP-1RA therapy with the potential to wean off insulin if possible.

Continuation criteria

NICE recommends that liraglutide and dulaglutide should only be continued if the patient has a beneficial metabolic response within 6 months, defined as:

- Reduction of at least 11mmol/mol (1%) in HbA1c, **and**
- Weight loss of at least 3% of initial body weight

In exceptional circumstances, the requirement to achieve 3% weight loss may be waived if a reduction of at least 11mmol/mol (1%) in HbA1c has been achieved. These circumstances include patients in whom insulin (or insulin intensification) is the only alternative treatment, and in whom insulin (or insulin intensification) would have significant occupational implications.

Liraglutide 1.2 mg and dulaglutide are not licensed for weight loss; therefore patients who fail to achieve a reduction in HbA1c of at least 11mmol/mol (1%) should discontinue treatment.

Dose and Administration

Liraglutide 1.2 mg (for use in individuals 18 years and older)

To reduce the incidence of gastro-intestinal adverse effects, the starting dose is liraglutide 0.6 mg subcutaneously daily. After at least one week, if tolerated the dose should be increased to 1.2 mg (liraglutide 1.8 mg will NOT be prescribed as it is not considered cost-effective in NCL).

- Liraglutide is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that liraglutide is injected around the same time of the day, when the most convenient time of the day has been chosen.

Dulaglutide 1.5 mg (for use in individuals 18 years and older)

The recommended dose for dose for dulaglutide when used in combination with other glucose-lowering medicinal products including insulin, is 1.5 mg once weekly by subcutaneous injection. For potentially vulnerable patients, such as patients > 75 years, 0.75 mg once weekly can be considered.

- Dulaglutide is injected subcutaneously in the abdomen, thigh or upper arm. The dose can be administered at any time of day, with or without meals. If a dose is missed, it should be administered as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days (72 hours), the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule. The day of weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days (72 hours) before.

When liraglutide or dulaglutide is added to sulfonylurea therapy or basal insulin, a reduction in the dose of sulfonylurea or basal insulin should be considered to reduce the risk of hypoglycaemia. See 'Clinical Monitoring' section.

Adverse Effects

Liraglutide

The most frequently reported adverse effects are listed below:

- Gastrointestinal disorders
 - Nausea and diarrhoea are very common, whereas vomiting, constipation, abdominal pain, and dyspepsia are common.
 - At the beginning of liraglutide therapy, these gastrointestinal adverse reactions may occur more frequently and usually diminish within a few days or weeks on continued treatment.
 - Short-term use of antiemetic treatment may be considered.
 - Escalation of dose from 0.6 mg to 1.2 mg should not be carried out until the symptoms have resolved.
 - If symptoms occur on dose escalation to 1.2 mg consider temporary reduction in dosage followed by rechallenge at 1.2 mg. If liraglutide 1.2 mg cannot be tolerated liraglutide therapy should be discontinued (the 0.6 mg dose should not be continued long-term as unlikely to be cost-effective)
- Headache – common and are usually self-limiting
- Nasopharyngitis – common and are usually self-limiting
- Hypoglycaemia
 - Hypoglycaemia is common and very common when liraglutide is used in combination with a sulphonylurea or insulin.
 - Major hypoglycaemia has primarily been observed when combined with a sulphonylurea or insulin.
 - If this occurs consider reduction in dosage of sulphonylurea or insulin.
- Injection site reactions – if severe, consider cessation of treatment with liraglutide
- Acute pancreatitis
 - A few cases (<0.2%) of acute pancreatitis have been reported during long term clinical trials with liraglutide. A causal relationship between liraglutide and pancreatitis can neither be established nor excluded. In the event of pancreatitis or suspected pancreatitis liraglutide must be discontinued. In pancreatitis is confirmed further treatment with liraglutide is not recommended.
- Thyroid neoplasms, increased blood calcitonin and goitres are the most frequently thyroid adverse events and were reported in 0.5%, 1% and 0.8% of patients respectively.

Dulaglutide

The most frequently reported adverse effects are listed below:

- Gastrointestinal disorders
 - Nausea, diarrhoea, vomiting and abdominal pain are very common, whereas dyspepsia, constipation, flatulence, abdominal distension, GORD, eructation are common.
 - Short-term use of antiemetic treatment may be considered.
 - If dulaglutide 1.5 mg cannot be tolerated consider trial at dose of 0.75 mg followed by escalation to 1.5 mg when symptoms resolve (0.75 mg dose should not be continued long-term as unlikely to be effective).
- Hypoglycaemia
 - Hypoglycaemia is very common when used in combination with prandial insulin, metformin or metformin with sulphonylurea. If this occurs consider reduction in the dosage of insulin or sulphonylurea.
- Fatigue, sinus tachycardia and first degree atrioventricular block are common

- Acute pancreatitis
 - Acute pancreatitis is rare. In the event of pancreatitis or suspected pancreatitis dulaglutide must be discontinued. If pancreatitis is confirmed further treatment with dulaglutide is not recommended.
- Injection site reactions are uncommon – if severe, consider cessation of treatment with dulaglutide
- Dulaglutide is a black triangle drug and as such is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions using the [Yellow Card Scheme](#).

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Special Warnings and Precautions for Use

Liraglutide

- Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Avoid in patients with inflammatory bowel disease and diabetic gastroparesis.
- Use with caution in patients with congestive heart failure New York Heart Association (NYHA) class I-II and avoid in those with congestive heart failure NYHA class III-IV[†].
- Not recommended for use in patients with severe renal impairment (creatinine clearance below 30ml/min) including patients with end stage renal disease[†].
- Not recommend for use in patients with mild, moderate or severe hepatic impairment[†].
- Avoid in pregnancy and lactation.

Dulaglutide

- Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Avoid in patients with severe gastrointestinal disease including severe gastroparesis.
- Should not presently be used in patients with congestive heart failure due to lack of clinical experience[†].
- Not recommended for use in patients with severe renal impairment (eGFR [by CKD-EPI] < 30ml/min/1.73M2)) including patients with end stage renal disease[†].
- No dosage adjustment is required in patients with hepatic impairment.
- Avoid in pregnancy and lactation.

[†] Treatment may be recommended by Specialists in Diabetes however care should only transfer if the GP is in agreement to take clinical and prescribing responsibility.

For a full list of cautions and contraindications, refer to the Summary of Product Characteristics of the individual products.

Drug Interactions

- A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded.
 - Warfarin: Upon initiation of liraglutide treatment in patients on warfarin, more frequent monitoring of INR (International Normalised Ratio) is recommended, whereas with dulaglutide no warfarin dose adjustment is necessary.
- Liraglutide has a very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 and plasma protein binding.

For a full list of drug interactions, refer to the Summary of Product Characteristics as there are differences between liraglutide and dulaglutide

Clinical Monitoring

- The HbA1c, U&E and weight, should be reassessed at 3 months and then 6 months. Thereafter to repeat 6 to 12 monthly according to clinical response (if Hb1Ac is higher than the Personalised HbA1c target, HbA1c should be rechecked every 3 months)
- Self-monitoring of blood glucose is not needed in order to adjust the dose of these GLP-1RAs. However, when initiating treatment in combination with a sulphonylurea, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea.
 - Also consider whether the patient prescribed sulphonylurea and/or insulin should be self-monitoring in accordance with DVLA guidelines
- Use of GLP-1 RAs have been associated with the risk of pancreatitis (incidence of 0.19% with liraglutide and 0.07% for dulaglutide). Patients should be monitored for signs of acute pancreatitis (e.g. persistent, severe abdominal pain) and if suspected the GLP-1RA should be stopped. This should be reported to the MHRA via the Yellow Card scheme as detailed under “General Practitioner Responsibilities.”
- Patients with pre-existing thyroid disorders may be at risk of thyroid disorders such as increased blood calcitonin, goitre and thyroid neoplasm. Such patients should be monitored clinically. There is no need to routinely monitor calcitonin levels, thyroid function or perform thyroid USS. If pre-existing thyroid disorders worsen or new thyroid disorders develop while on treatment they should be investigated in the normal way.
- Liraglutide and dulaglutide are contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.
- Do not initiate liraglutide or dulaglutide in patients with a history of pancreatitis or if they have untreated risk factors for pancreatitis (e.g. severe hypertriglyceridaemia, gallstones or alcohol excess).

References

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