DORSET MEDICINES ADVISORY GROUP

SHARED CARE GUIDELINES FOR PRESCRIBING GLP-1 MIMETICS (EXENATIDE, LIRAGLUTIDE AND LIXISENATIDE) FOR PATIENTS WITH TYPE II DIABETES

INDICATION

Exenatide and liraglutide are licensed for the treatment of Type 2 diabetes mellitus in combination with other oral hypoglycaemic agents, in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. In addition the twice daily preparation of exenatide and once daily lixisenatide are licensed as adjunctive therapies to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.

- GLP-1 agonists (mimetics) should only be initiated by a suitably qualified HCP who has experience/training in the use of these drugs and has the ability and skills to discuss and offer other treatment options to a patients including insulin initiation. This suitably qualified HCP may be based in primary or secondary care.
- GLP-1 agonists should be used in line with the NICE guidelines, note that in an independent (not industry or NICE initiated) study only 27% of patients achieved the NICE requirements for continuation of treatment at 6 months. Current activity suggests (along with company data) that 95% of patients remain on it. It is important to ensure that there is a clear system in place to review patients at 6 months and act accordingly, hence the need for initiation by someone who can, on review, offer realistic alternative treatments.

Please note that this shared care guideline only covers the licensed indications at the time of approval and must be used in line with the guidance provided in the Summary of Product Characteristics (SPC) supplied by the manufacturers available online at:
www.medicines.org.uk/emc

Relevant NICE guidance
NICE Clinical Guideline no 87 – Type 2 diabetes, newer agents
NICE Technology Appraisal no.203 – Liraglutide for type 2 diabetes
NICE Technology Appraisal no.248 – Exenatide prolonged-release for type 2 diabetes
NICE Evidence Summary for new medicine: Type 2 diabetes - Lixisenatide

There is no formal NICE guidance on the use of lixisenatide but there is a new medicines summary, which says "*Local decision makers will need to consider the evidence for lixisenatide in type 2 diabetes alongside that for other GLP-1 mimetics, taking into account current NICE guidance, differences in individual patient factors and the acquisition costs of the different products*."

Exenatide, liraglutide and lixisenatide will be included in the update of the NICE clinical guideline for the management of type 2 diabetes. The publication date for this guideline is to be confirmed.

In line with relevant NICE guidance (as above), GLP-1 mimetics should be used in patients when control of blood glucose remains or becomes inadequate ($HbA_{1c} \geq 58$ mmol/mol (7.5%), or other higher level agreed with the individual), **and** the person has:

- a body mass index (BMI) ≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, **or**
- With a BMI < 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA_{1c} **and** a weight loss of at least 3% of initial body weight at 6 months).

Discuss the potential benefits and risks of treatment with a GLP-1 mimetic with the person to enable them to make an informed decision.

Specific NICE criteria for using individual GLP-1 mimetics in type 2 diabetes (in addition to those criteria above):

Drug and formulation	**Regime**	**Recommendation**
Exenatide (standard release)	Third line	Third-line therapy to first-line metformin and a second-line sulfonylurea
Exenatide (prolonged release)	Triple therapy	2mg once weekly, in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione
Liraglutide	Triple therapy	Liraglutide 1.2 mg daily in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione
Liraglutide	Dual therapy	Liraglutide 1.2 mg daily in combination with metformin or a sulphonylurea is recommended as an option, only if: • the person is intolerant of either metformin **or** a sulphonylurea, or treatment with metformin **or** a sulphonylurea is contraindicated, **and** • the person is intolerant of thiazolidinediones **and** dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.
Liraglutide	N/A	Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes.
Lixisenatide *(cheapest GLP-1 option as at October 2013)*	Dual or Triple therapy	In combination with oral antidiabetic drugs (e.g. metformin, pioglitazone, or a sulfonylurea) or basal insulin, or both. Lixisenatide should not be used in combination with both basal insulin and a sulfonylurea because of an increased risk of hypoglycaemia.

Local guidance supports the use of exenatide (daily) or lixisenatide in combination with basal insulin as a treatment option in type 2 diabetes, when initiated by a diabetes specialist. Exenatide (daily) and lixisenatide, in combination with basal insulin, has been

categorised as amber and suitable for shared care arrangements. The use of liraglutide, or exenatide prolonged release in combination with insulin is currently not supported as an amber shared care indication as they do not have marketing authorisation for this use.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of a GLP-1 mimetic can be shared between a specialist in diabetes care and the patient's general practitioner (GP). GPs are invited to participate.

If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the specialist initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The healthcare professional who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient.

- Patients will only be referred to the GP once the GP has agreed to each individual case
- Exenatide (including the prolonged release) and lixisenatide are "black triangle" drugs. The MHRA therefore asks that all suspected reactions (including those not considered to be serious) are reported through the Yellow Card Scheme.

Specialist Responsibilities	
1	To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	Where appropriate: ○ to initiate and stabilise treatment on the appropriate dose for the patient, i.e. ○ 5-10mcg of exenatide daily **or** ○ 0.6-1.2mg of liraglutide daily **or** ○ 10mcg lixisenatide daily **or** ○ 2mg of exenatide once weekly ○ obtain consent from the patient's GP to continue prescribing once treatment has been stabilised; ○ monitor the patient and their therapy at six monthly intervals. (HbA1c and weight), including discontinuation where the patient does not fulfil the NICE requirements.
3	Ensure that patients know what to do and who to contact if they experience symptoms of acute pancreatitis (persistent, severe abdominal pain; back pain may also be present).

Specialist Responsibilities	
4	To ensure that the patient (or carer) is trained and understands how to use the device that is prescribed for them and the dosage regimen.
5	To provide the GP with appropriate prescribing information and any additional information requested.
6	To be available for advice if the patient's condition changes.
7	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
8	To ensure the patient has given informed consent to their treatment.
9	To liaise with the GP on any suggested changes in prescribed therapy.

General Practitioner Responsibilities	
1	Initially, to refer the patient for specialist advice.
2	Where appropriate to continue to prescribe exenatide, liraglutide, lixisenatide or prolonged release exenatide as part of a shared care arrangement.
3	To ensure that patients are routinely monitored to ensure use remains within the NICE guidance.
4	To deal with general health issues of the patient.
5	Monitor concordance with therapy

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate GP and other follow up appointments
3	Share any concerns in relation to treatment
4	Use written and other information on the medication.
5	Seek help urgently if suspected side effects, or otherwise unwell.

SUPPORTING INFORMATION

Dosage and Administration

Recommended doses in adults with type 2 diabetes:

Drug & formulation	Dose	Comments
Lixisenatide *(cheapest GLP-1 option as at October 2013)*	Initially 10 micrograms once daily within 1 hour before the first meal of the day or the evening meal for 14 days, increased to 20 micrograms once daily thereafter	If a dose is missed, inject within 1 hour before the next meal—do not administer after a meal. Some oral medications should be taken at least 1 hour before or 4 hours after lixisenatide
Exenatide standard release	5 micrograms per dose administered twice a day for at least one month and then	Doses higher than 10 micrograms twice a day are not recommended. Exenatide can be

Drug & formulation	Dose	Comments
	increased to 10 micrograms twice a day.	administered at any time within the 60 minutes before the morning and evening meal; it should not be administered after a meal.
Liraglutide	The starting dose of liraglutide is 0.6 mg daily. After at least one week, the dose should be increased to 1.2 mg.	Increasing the dose above 1.2mg is not recommended within NICE TA 203.
Exenatide prolonged release	2mg once weekly (on the same day each week) by subcutaneous injection.	Exenatide prolonged release can be administered at any time of the day, with or without meals.

Monitoring

- HbA1c and weight - 6 monthly.
- The dose of exenatide, liraglutide, lixisenatide or exenatide prolonged release does not need to be adjusted on a daily basis using self monitored glycaemia. Blood glucose self monitoring may be needed if the GLP-1 mimetic drug is used in combination with a sulphonylurea, in order to adjust the sulphonylurea dose.
- Patients switching from exenatide twice daily to exenatide weekly may experience transient elevations in blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy.

Contraindications

Exenatide, liraglutide and lixisenatide are contraindicated in:

- patients with a known hypersensitivity to the drug or any of the excipients
- the treatment of diabetic ketoacidosis
- pregnancy and if breast-feeding (see below and SPC for individual products):
    - Exenatide prolonged release should be discontinued at least three months before a planned pregnancy.
    - Lixisenatide should not be used in women of childbearing potential who are not using contraception.
- Liraglutide is contra-indicated in inflammatory bowel disease and diabetic gastro-paresis, exenatide and lixisenatide are contra-indicated in patients with any severe gastro-intestinal disease.

Caution

- Use of glucagon-like peptide-1 (GLP-1) receptor agonists has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, the GLP-1 agonist should be discontinued; if acute pancreatitis is confirmed, it should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Special Warnings

- Exenatide, liraglutide, lixisenatide or exenatide prolonged release are not recommended for use in patients with end stage renal disease or severe renal impairment. Refer to individual summary of product characteristics (SPC) for use in mild or moderate renal impairment.
- In addition refer to individual drug's SPC for details of use in severe G-I disease, congestive heart failure and hepatic impairment
- The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicinal products. Lixisenatide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, require careful clinical monitoring or have a narrow therapeutic ratio. For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, or substances sensitive to stomach degradation such as antibiotics, patients should be advised to take those medicinal products at least 1 hour before or 4 hours after lixisenatide injection.

Side Effects

The most common adverse effects are nausea, vomiting, diarrhoea and hypoglycaemia. In addition there are reports of decreased appetite, headache, dizziness and rarely pancreatitis with exenatide. Post marketing anaphylactic reaction has been reported (very rarely).**The summary of product characteristics should be consulted for full information with respect to adverse effects and drug interactions for each drug.**

Drug Interactions

The slowing of gastric emptying may reduce the extent and rate of orally administered medicinal products, refer to the individual drug's SPC for more details.

N.B. it is recommended that the GLP-1 agonists used daily are stopped 24 hours prior to surgery.

The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug Costs*

Drug and formulation	Cost
Lixisenatide *(cheapest GLP-1 option as at October 2013)*	Starter pack: 1 x 10mcg pen and 1 x 20mcg pen = £54.04 20mcg, 2 x 3ml pre-filled pens = £54.04 10mcg, 1 x 3ml pre-filled pen = £27.07
Exenatide (standard release)	5mcg, 60-dose pre-filled pen = £68.24 10mcg, 60-dose pre-filled pen = £68.24
Liraglutide 6mg/ml solution for injection	2x3ml pre-filled pens = £78.48 3x3ml pre-filled pens = £117.72
Exenatide prolonged release	2mg powder and solvent for prolonged-release suspension for injection = £73.36

**Prices taken from Dictionary of Medicines and Devices, October 2013*

References

1. Byetta® (Lilly) Summary of Product Characteristics. April 2013
2. Victoza® (Novo Nordisk) Summary of Product Characteristics. March 2013
3. Bydureon® (Lilly) Summary of Product Characteristics. August 2013
4. Lyxumia® (Sanofi) Summary of Product Characteristics. February 2013
5. BNF online at www.bnf.org

Other information

An audit of patient orientated outcomes with GLP-1 mimetics is to be presented to the CCG's medicines optimisation group in 2014.

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