

**Shared Care Protocol: Addition of a glucagon-like peptide-1 (GLP-1) analogues (exenatide or liraglutide) to patients already on insulin who have poorly controlled type 2 diabetes**

**All patients put on this combination must have been seen by a dietitian and made appropriate efforts to lose weight**

Approved by Hertfordshire Medicines Management Committee July 2012

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## **PART ONE**

### **Shared Care Responsibilities of Specialist, General Practitioner, Diabetes Specialist Nurse and Patient for the ADDITION of GLP-1 analogues in those with poorly controlled Type 2 Diabetes mellitus who are already on insulin**

The following guidelines provide information relating to the addition of GLP-1 analogues to insulin in adults with poorly controlled type 2 diabetes mellitus (T2DM) and outline responsibilities of the primary, community and secondary care teams and patients in this situation.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it and are able and willing to be accountable for the role set out in their list of responsibilities. The clinician who prescribes any medication legally assumes clinical responsibility for that drug and the consequences of its use regardless of whether the treatment has been initiated and/or advised by a specialist.

A copy of the shared care guideline (without the supporting information) should be given to the patient so that they have a record of the agreement.

#### **1) Diabetes Consultant Responsibilities**

The majority of patients will be seen in community diabetes clinics, with complex patients seen in the acute hospital setting.

- Select appropriate patients for treatment according to the inclusion and exclusion criteria (page 6).
- Apply the Hertfordshire criteria to decide whether any patients on insulin analogues should remain on them rather than being transferred onto human insulin<sup>1</sup>.
- Discuss the potential benefits and side effects of treatment with the patient.
- Explain to the patient that combination use may be outside the product license and if so record the patient's consent for off label use.
- Explain to the patient that treatment is intended to improve long term outcomes.
- Explain the continuation and stopping criteria to the patient, so that they are aware that treatment will be stopped if the continuation criteria are not met at 6 and 12 months, and are not maintained beyond that.
- Obtain patient's agreement that GLP-1 analogue treatment will be stopped if the continuation criteria are not met or maintained.
- Organise baseline blood tests (copied to the patient's GP).
- Transfer those who are currently on insulin analogues and who do not meet the criteria for continued analogue use in T2DM onto human insulin and stabilise them in conjunction with the Diabetes Specialist Nurse (DSN) before the addition of GLP-1 analogues.
- Document the value of a 3% and 10% weight loss and a 50% reduction of insulin dose in the patient record and include information in letter to GP.
- Communicate the above to both GP and patient.
- Provide a prescription for one months treatment if once weekly exenatide is used, and for one to two months for daily exenatide and liraglutide, until the patient's dose is stable.

- Enrol the patient into the Association of British Clinical Diabetologist's (ABCD) national audit and ensure that data is added to the national audit.
- Write immediately to the GP, using the template on page 9 asking the GP to reply to state whether they are willing to enter into a shared care agreement.
- Monitor patient's response to therapy and adjust other therapies such as insulin dose and doses of oral medication as needed in conjunction with the DSN.
- Decide on whether and when the dose of GLP-1 analogue should be increased in conjunction with the DSN.
- Communicate via letter to the GP when treatment is changed, so that the GP can adjust the quantities of items prescribed and/or the instructions on oral medications.
- Monitor patient in conjunction with the DSN.
- Be available to give advice to GP and ensure that clear backup arrangements exist for GPs to obtain advice and support.
- Decide when to stop therapy in accordance with the criteria on page 8.
- Report adverse events to the Medicines and Healthcare products Regulatory Agency (MHRA)/Commission on Human Medicines (CHM) and GP. Explain MHRA/CHM Yellow card reporting system to patient.

## **2) Diabetes Specialist Nurse (DSN) Responsibilities**

- Train patient how to use the GLP-1 analogue device.
- Provide telephone and face to face availability to:
  - discuss side effects with the patient
  - review blood glucose records
  - advise on increase of dose if patient is on daily exenatide or liraglutide.
- alter doses of the insulin and oral hypoglycaemic therapy, in consultation with the consultant, throughout insulin/GLP-1 combination therapy.
- inform the GP via fax when doses of oral hypoglycaemic drugs are changed, so that instructions and quantities on repeat prescription templates can be changed in the patient's record.
- inform the GP when the dose of daily exenatide or daily liraglutide has been increased, with enough time to allow the GP to issue a prescription for the correct product (exenatide) and the correct quantity (to give 1 months supply).

## **3) GP Responsibilities**

- Reply to the request for shared care as soon as possible (see reply slip page 10).
- Prescribe GLP-1 analogue and other diabetes medications as advised by consultant/DSN.
- Contact the consultant should any serious side effect occur.
- Adjust the instructions and quantities on prescriptions of GLP-1 analogue, insulin and oral hypoglycaemic agents as advised by the specialists.
- Stop treatment on the advice of the consultant, or immediately if an urgent need to stop treatment arises such as severe vomiting, anaphylactic reaction or angioneurotic oedema.
- Check for drug interactions before starting new medicines.
- Report adverse events to the specialist and MHRA/CHM.

#### 4) Patient's role

- Agree to the continuation and stopping criteria.
- Agree to changing from insulin analogue to human insulin prior to starting on GLP-1 analogue treatment where this is indicated.
- Administer the GLP-1 analogue as prescribed/agree to an informal carer administering the medication.
- Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
- Share any concerns in relation to treatment with GLP-1 analogue with the consultant, DSN or GP.
- Inform consultant and GP of any other medication being taken, including over-the-counter products.
- Monitor blood glucose levels as advised by the consultant and DSN and discuss the results with them as requested.
- Report any adverse effects or warning symptoms to the consultant, or GP whilst taking GLP-1 analogue and complete a yellow card for the MHRA/CHM.
- Have blood tests and attend for review as required to assess whether the treatment is effective and will be continued.
- Order prescriptions in good time, taking account of the practice's repeat prescribing policy.
- Seek urgent medical attention if diarrhoea and vomiting occur, or severe abdominal pain.
- Continue to follow advice regarding a healthy lifestyle in relation to exercise and diet.

## 5) Selection of patients

Consultant diabetologists will be responsible for selecting suitable patients, using the following inclusion and exclusion criteria:

### Inclusion Criteria

- Patient has seen a dietitian and demonstrated an attempt to lose weight over the previous 6 months.
- Age 40-70 inclusive at initiation.
- Patient is stable with no acute medical problems.
- Obese with a BMI > 35 kg/m<sup>2</sup>.
- Poor blood glucose control with a HbA1c ≥ 69 mmol/mol.
- On metformin (unless contraindicated) **and** sulphonylurea or gliptin or glitazone (unless contraindicated).
- Lipids optimally managed or patient on maximal tolerable treatment (refer to Hertfordshire Diabetes Clinical Guidelines <sup>(10)</sup>).
- Blood pressure optimally managed, or patient on maximal tolerable treatment.
- Patients have received and will continue to receive adequate lifestyle advice (diet, exercise, weight management, smoking cessation).
- Willing to accept that treatment with a GLP-1 analogue will be stopped if the continuation criteria are not met.
- Understands the rationale is to improve prognosis rather than to improve symptoms.
- Willing to consent to off label use of GLP-1 analogue where this applies.
- Willing to switch from insulin analogue to human insulin product (unless they are in a group who should not switch)<sup>1</sup>.

### Exclusion Criteria

- Inability to self-inject using the GLP-1 analogue system or without an informal carer who can administer injections.
- On-going gliptin treatment - gliptin will be stopped at initiation of GLP-1 analogue.
- Pregnancy/Breastfeeding.
- eGFR ≤ 30 ml/min/1.73m<sup>2</sup>.
- Conditions with an increased risk of vomiting:
  - Diabetic gastropathy with vomiting
  - Gastro-intestinal disease with delayed gastric emptying or recurrent vomiting
- Co-morbidities where there is no data to show that use is safe:
  - Heart Failure
  - Pulmonary hypertension
  - Advanced liver disease/cirrhosis
- Increased risk of pancreatitis:
  - History of pancreatitis
  - Known gall stones
  - Heavy alcohol intake

## 6) Choice of product

Liraglutide and once weekly exenatide are only licensed in those with normal renal function, so should not be used in those with an eGFR <60 ml/min/1.73m<sup>2</sup>.

Those with an eGFR between 30 and 59 ml/min/1.73m<sup>2</sup> should have twice daily exenatide.

## 7) Dosage and Administration

GLP-1 analogues are given by injection.

Where there are two doses available for a product, the lower dose will be used initially. The aim will be to increase to the higher dose, and maintain the patient on that dose, unless they are unable to tolerate the dose due to side effects.

Starting with a lower dose reduces the likelihood of the patient developing side effects severe enough for the patient to stop treatment.

Three GLP-1 analogue products are currently available:

| Generic Name | Brand     | Frequency   | Dose            | Interval for dose increase | Comments   |
|--------------|-----------|-------------|-----------------|----------------------------|--|
| Exenatide    | Byetta®   | bd          | 5-10 micrograms | 4 weeks                    | Licensed for use with basal insulin with or without metformin/pioglitazone |
| Exenatide    | Bydureon® | Once weekly | 2mg             | N/A                        | Not licensed for use with insulin  |
| Liraglutide  | Victoza®  | od          | 0.6–1.2 mg      | 2-4 weeks                  | Not licensed for use when added to insulin                                 |
|              |           |             | 1.8mg           |                            | Dose will NOT be used as NICE does NOT advise use of this dose             |

## 8) Monitoring

### Baseline data

- 1) HbA1c
- 2) Weight, Height & BMI: 3% and 10% weight reduction calculated and recorded
- 3) Insulin requirements: 50% dose reduction calculated and recorded
- 4) Doses of oral hypoglycaemic agents
- 5) Renal function (to determine whether GLP-1 analogues can be used at all and if so which products are indicated)
- 6) Lipids
- 7) Blood pressure

### Ongoing 3 monthly reviews

As for baseline data, although blood tests may not be organised at every clinic visit.

## 9) Stopping criteria (at any point)

- 1) Patient choice
- 2) Drug intolerance
- 3) Occurrence of any of the exclusion criteria
- 4) Failure to meet the continuation criteria
- 5) Failure to attend for blood tests and clinical reviews

## 10) Stopping criteria at 6 months

Treatment with a GLP-1 analogue should be stopped if the HbA1c has not fallen by at least 5mmol/mol and there is no weight loss or change in insulin dose.

## 11) Continuation criteria at 12 months

Improvement in HbA1c  $\geq$  11mmol/mol AND weight reduction  $\geq$  3%

OR

Improvement in HbA1c  $\geq$  11mmol/mol AND insulin dose reduction  $\geq$  50%

OR

Improvement in HbA1c  $\geq$  5mmol/mol AND weight reduction  $\geq$  10%

## 12) Stopping criteria beyond 12 months

GLP-1 analogues will be withdrawn if the HbA1c, weight or insulin dose deteriorates to a point where the patient would not have met the 12 month continuation criteria.

## 13) Contact Numbers

Outside normal working hours the patient should contact the Out of Hours GP Service, who will receive a copy of this Shared Care Guideline.

In hours the patient should contact their GP for urgent problems, and their consultant for non-urgent problems.

| Clinician   | Trust | Hospital   | Contact number  |
|---|-------|--|---|
| Dr. Ken Darzy<br>Dr. Peter Winocour<br>Dr. Ben Zalin<br>Dr. Felicity Kaplan<br>Dr Samer el Sabbagh<br>Dr Stella George<br>DSN | ENHT  | QEII<br>QEII<br>Lister<br>Lister<br>Lister/QEII<br>Lister QEII | QE2: 01707 365093<br>Lister: 01438 314333   |
| Dr Colin Johnston<br>Dr Chantal Kong<br>Dr Arla Ogilvie<br>Dr Michael Clements<br>Dr Julia Ostberg<br>DSN                     | WHHT  | HHH<br>HHH<br>WGH<br>WGH<br>WGH                                | HHH: 01442 287083<br>WGH: 01923 217696  |
| Community DSNs  | HCT   | Potters Bar<br>Community<br>Hospital                           | Barnet Road<br>Potters Bar<br>Hertfordshire<br>EN6 2RY<br>Tel: 01707 621152<br>Fax: 01707 621178<br>Email: <a href="mailto:Hertscommunitydiabetes@nhs.net">Hertscommunitydiabetes@nhs.net</a> |

## Specialist letter to GP requesting GLP-1 analogue added to insulin shared care arrangements

Dear GP Name

Re patient details

This patient meets the criteria for the addition of a GLP-1 analogue to their existing diabetes therapy, which includes insulin. I am writing to ask you to prescribe the GLP-1 analogue under a shared care arrangement. The full shared care guideline can be found at <http://www.hertfordshire.nhs.uk/pharmacy/index.php/local-decisions-about-medicines/6-hmmc>.

Delete as appropriate: The patient is on human insulin / The patient is on an insulin analogue because they meet one or more of the following criteria:

|  |  |
|--|--|
|  | Documented history of significant nocturnal hypoglycaemia on human insulin that has not recurred with insulin analogue |
|  | Pre-existing insulin analogue treatment and holder of Group 2 vehicle driving licence                                  |

| Data                                | Baseline Patient Value            | Improvements Required at 12 months    |
|-------------------------------------|-----------------------------------|---------------------------------------|
| BMI $\geq$ 35 kg/m <sup>2</sup>     | Weight: kg BMI: kg/m <sup>2</sup> | 3% / 10% weight loss = / kg           |
| Daily insulin dose                  | units                             | 50% baseline dose =                   |
| HbA1c $\geq$ 69mmol/mol             | mmol/mol                          | 11 / 5mmol/mol reduction = / mmol/mol |
| eGFR > 30 ml/min/1.73m <sup>2</sup> | ml/min/1.73m <sup>2</sup>         | Not applicable                        |

I have explained that the use of GLP-1 analogues in combination with insulin may be outside the product licence and where appropriate the patient has consented to the off-label use of the medication. I have discussed stopping and continuation criteria with the patient. At 12 months the continuation criteria for this patient will be a change that meets or exceeds one of the following:

- 1) A reduction of HbA1c to \_\_\_\_\_ mmol/mol ( $\geq$ 11mmol/mol reduction) or less AND a weight of \_\_\_\_\_ kg ( $\geq$ 3% reduction) or less.
- 2) A reduction of HbA1c to \_\_\_\_\_ mmol/mol ( $\geq$ 11mmol/mol reduction) or less AND daily insulin dosage reduction to \_\_\_\_\_ units ( $\geq$ 50% reduction) or less.
- 3) A reduction of HbA1c to \_\_\_\_\_ mmol/mol ( $\geq$ 5mmol/mol reduction) or less AND a weight of \_\_\_\_\_ kg ( $\geq$ 10%reduction) or less.

The treatment I have started is:

Exenatide 5 micrograms bd which will increase to exenatide 10 micrograms bd from the first prescription from you (licensed as adjunctive therapy to basal insulin).

Liraglutide 0.6 mg once daily, increased to 1.2 mg once daily after 2-4 weeks, depending on the level of side effects ('off-label' use when added to patients taking insulin).

Exenatide 2 mg once weekly ('off-label' use when combined with insulin).

The patient will be reviewed by phone by the Diabetes Specialist Nurse (DSN)..... (insert name) who will inform you in writing if the dose cannot be increased because of side effects. The DSN will also review the patient's home blood glucose monitoring results to decide whether their insulin/oral hypoglycaemic drug doses need reducing. You will be notified in writing when doses change so that you can amend the quantities and doses of medication on the patient's repeat prescription record.

Please return the reply slip as soon as possible to indicate whether you are willing to enter into a shared care agreement,

Yours sincerely

Diabetes Consultant

**GP Reply Slip - GLP-1 analogue added to insulin shared care arrangements**

To Name & address of Diabetes Consultant

Re Patient details

I will be able to prescribe a GLP-1 analogue

I will not prescribe a GLP-1 analogue for this patient because

Signature

Date

GP Details

## **PART TWO: SUPPORTING INFORMATION**

### **1. Background**

Patients with type 2 diabetes are at risk of macrovascular and microvascular complications. Evidence has shown that an improvement in blood glucose control, as shown by a reduction in HbA1c levels, is associated with a reduction in microvascular complications (2,3,4).

Evidence from ACCORD<sup>(2)</sup>, UKPDS<sup>(3)</sup> and ADVANCE<sup>(4)</sup> suggests that intensive blood glucose control reduced composite endpoints for microvascular outcomes, but the impact on patient oriented outcomes such as renal failure or dialysis or blindness is uncertain. The ACCORD study found that intensive blood glucose control improved visual acuity.

A meta-analysis of large randomised trials (CONTROL) showed that more intensive blood glucose control (average difference between intensive and standard care groups 9mmol/mol (0.9%)) showed some reduction in cardiovascular (CV) outcomes, mainly by a reduced risk of myocardial infarction (MI). The number needed to treat (NNT) to prevent one CV event is 119 (compared with NNT for blood pressure reduction of 34, and management of cholesterol of 44), hence the need to ensure that these patients have optimally managed blood pressure and cholesterol prior to adding in GLP-1 analogues for which we do not have evidence of patient oriented outcomes.

Data from the national audit of GLP-1 analogue use by the ABCD has shown that it can take longer than 6 months for the benefits of GLP-1 analogue therapy on disease oriented outcomes such as weight, HbA1c and dose of insulin to be realised compared with those who are not already on insulin.

Previous studies have shown that very intensive blood glucose control worsens outcomes, and accordingly the aim is to reduce patient's HbA1c to about 58mmol/mol (7.5%) when blood-glucose-lowering therapy is altered beyond metformin monotherapy.

The main benefit expected from use of the addition of GLP-1 analogues to insulin in T2DM is that a reduction in HbA1c will lead to a reduction in microvascular events as seen in the ACCORD study where a reduction of 9mmol/mol (0.9%) sustained for 5 years was needed. Loss of weight may also reduce the dose of insulin required, which may in itself promote weight loss, and reduce the costs of treatment. A loss of weight may improve lipid profiles and blood pressure and so lead to a reduction in macrovascular events as well as leading to an improvement in HbA1c.

A published review has estimated the benefits of an overweight or obese patient losing 10% of their weight include a fall of about 10 mm Hg in BP in hypertensive patients and a 20% fall in all cause mortality<sup>(12)</sup>.

### **2. Licensed indications & NICE & HMMC Guidance**

GLP-1 analogues are licensed for use in patients with T2DM<sup>(12)</sup>. NICE has approved the use of exenatide and liraglutide as triple therapy as an alternative to insulin in those with a BMI of > 35 kg/m<sup>2</sup> (adjusted downwards for those of non-European ethnicity) and with a HbA1c of 8.5% (69mmol/mol) or more. Treatment should only be continued beyond 6 months in those who have had a reduction of 3% in their weight and 11mmol/mol (1%) in their HbA1c at 6 months<sup>(7)</sup>.

NICE does not advocate the routine use of insulin analogues in those with T2DM. There are limited circumstances where patients with T2DM should have insulin analogues rather than

human insulin<sup>(1)</sup>. In all other cases, patients should be switched to, and stabilised on human insulin therapy before a GLP-1 analogue is added.

**The addition of insulin to patients on GLP-1 analogues has not been considered by HMMC, is not approved for use in Hertfordshire and is not covered by this shared care guideline.**

### 3. Contraindications

Hypersensitivity to the active ingredients and excipients.

### 4. Side Effects

In trials, the most common adverse effects were gastrointestinal events, including nausea, vomiting and diarrhoea.

**Adverse Drug Reactions reported post-marketing:**

**Immune system disorders:** Anaphylactic reaction, very rarely.

**Metabolism and nutritional disorders:** Dehydration, generally associated with nausea, vomiting and/or diarrhoea, some reports associated with elevation of serum creatinine.

**Nervous system disorders:** Dysgeusia, somnolence.

**Gastro-intestinal disorders:** Eructation, constipation, flatulence, pancreatitis.

**Skin and subcutaneous tissue disorders:** Macular rash, papular rash, pruritis, urticaria, angioneurotic oedema.

### 5. Drug Interactions

GLP-1 analogues do not directly cause hypoglycaemia: however, as glycaemic control improves, the hypoglycaemic effects of insulin and oral hypoglycaemic drugs may increase and their dose may need to be adjusted.

Increases in INR have been reported with concomitant warfarin and exenatide, and the SPC for liraglutide advises more frequent testing of INR when used with warfarin on initiation of treatment.

See the BNF <http://www.medicinescomplete.com/mc/bnf/current/> or summary of product characteristics at <http://www.medicines.org.uk/EMC/default.aspx> for more information.

### 6. Cost

**Estimated average annual treatment cost per patient (from NICE TA 248)**

| Drug name                   | Dose  | Frequency   | Drug cost        | Cost per dose | Annual drug cost | Consumables | Self-monitoring of blood glucose | Total cost   |
|-----------------------------|-------|-------------|------------------|---------------|------------------|-------------|----------------------------------|--------------|
| Liraglutide                 | 1.2mg | once daily  | £39 for 15 doses | £3            | £955             | £44         | £51                              | <b>£1050</b> |
| Exenatide                   | 10mg  | twice daily | £68 for 60 doses | £1            | £830             | £88         | £51                              | <b>£969</b>  |
| Prolonged-release exenatide | 2mg   | once weekly | £73 for 4 doses  | £18           | £954             | 0           | £51                              | <b>£1005</b> |

## 7. References

- 1 NHS Hertfordshire Patient selection criteria for human insulin vs insulin analogues in Type 2 Diabetes mellitus (T2DM) July 2012.
- 2 ACCORD study <http://www.nejm.org/doi/full/10.1056/NEJMoa0802743>
- 3 UKPDS study [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(98\)07019-6/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(98)07019-6/abstract)
- 4 ADVANCE study [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(98\)07019-6/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(98)07019-6/abstract)
- 5 NPCi MeReC Rapid Review - Does intensive blood glucose control reduce microvascular outcomes in type 2 diabetes? Results from ACCORD (October 2010) <http://www.npc.nhs.uk/rapidreview/?p=1956>
- 6 NPCi MeReC Rapid Review - CONTROL blood glucose in type 2 diabetes — but individualise care (April 2011) <http://www.npc.nhs.uk/rapidreview/?p=2726>
- 7 NICE Clinical Guideline 87 2010 Type 2 diabetes: Newer agents <http://www.nice.org.uk/cg87>
- 8 NICE Clinical Guideline 66 2008 Type 2 diabetes <http://guidance.nice.org.uk/CG66>
- 9 HMMC decision November 2011
- 10 Hertfordshire Diabetes Clinical Guidelines July 2010 <http://www.hertfordshire.nhs.uk/resource-centre/pharmacy-and-medicines-management/clinical-guidelines.html>
- 11 BNF <http://www.medicinescomplete.com/mc/bnf/current/>
- 12 Electronic Medicines Compendium <http://www.medicines.org.uk/EMC/default.aspx>
- 13 NICE TA248: Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes, February 2012 <http://guidance.nice.org.uk/TA248>
- 14 NPC Therapeutics, other therapeutics, Obesity - Key slides <http://www.npc.nhs.uk/therapeutics/other/obesity/index.php>