GLP-1 agonists: Exenatide (Byetta® and Bydureon®), Liraglutide (Victoza®) Lixisenatide (Lyxumia®▼)

Introduction

GLP-1 agonists bind to, and activate the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppress glucagon secretion and slow gastric emptying. Treatment with exenatide, liraglutide or lixisenatide is associated with the prevention of weight gain and possible promotion of weight loss which can be beneficial in overweight patients.

They are given by subcutaneous injection for the treatment of type 2 diabetes mellitus.

Three GLP-1 agonists, exenatide (Bydureon®, liraglutide (Victoza®) and lixisenatide (Lyxumia®) are on the Barnsley Joint Formulary. The formulary was rationalised in August 2014 and twice daily exenatide (Byetta®) was removed. Twice daily exenatide may continue to be prescribed to patients who are already using it.

Lixisenatide is the newest of the GLP-1 agonists to be accepted onto the Barnsley Joint Formulary. Locally the following points have been noted:
- Lixisenatide is once daily administration
- With respect to GI side effects lixisenatide is better tolerated than exenatide
- Lixisenatide has a marked effect on post-prandial blood glucose
- Lixisenatide has a lower acquisition cost when compared to other GLP-1 receptor agonists that are available
- Lixisenatide probably offers less weight loss than exenatide or liraglutide

Responsibilities of the specialist* initiating treatment

*Specialist refers to either Consultant, Diabetes Specialist Nurse or a GP with specialist interest and training.

Summary
- To assess the suitability of the patient for treatment.
- To discuss the benefits and side effects of treatment with the patient/carer.
- To perform baseline tests (HbA1c and weight). Provide the GP with a starting weight and HbA1c.
- To prescribe until the patient is stabilised on GLP-1 agonist. Review the patient approximately 4 weeks after starting therapy. Continue prescribing and monitoring for a further 4 weeks. The GP can be asked to take on prescribing by week 7/8, provided the patient is stable.
- To train the patient/carer in administering the GLP-1 agonist injection.
- Adjust dose of sulfonylurea (if necessary) or basal insulin when a GLP-1 agonist is added and ensure this is completed before prescribing is transferred to primary care.
- To ask the GP whether they are willing to participate in shared care.
- To provide the GP with a summary of information relating to the individual patient to support the GP in undertaking reduced shared care (See Reduced Shared Care request form in Appendix A). To advise the GP of any dosage adjustments required, when to refer back, when and how to stop treatment (if appropriate) and when the patient will next be reviewed by the specialist.
- To monitor the patient for adverse events and report to the GP and where appropriate Commission on Human Medicines/MHRA (Yellow card scheme).
- To provide the GP with contact details in case of queries.
Baseline Tests
Baseline HbA1c and weight should be recorded prior to initiating a GLP-1 agonist

Routine Tests (if applicable)
Monitor the patient’s response to the treatment by measuring HbA1c and weight at 3 months and 6 months and, once stable, 6 monthly thereafter.

Daily blood glucose monitoring is not routinely required, however, blood glucose monitoring is necessary for patients initiating a GLP-1 agonist who are also taking a sulfonylurea or basal insulin where a dose adjustment of the sulfonylurea or insulin may be necessary.

Renal function should be monitored annually, or more frequently in patients whose renal function is approaching moderate impairment. Renal function should also be monitored prior to initiating concomitant medication that may affect renal function and periodically thereafter.

Disease monitoring
The patient will be reviewed by the Specialist if the need arises.

Responsibilities of other prescribers

Acceptance of Responsibility by the Primary Care Clinician
It is optional for GPs to participate in taking on responsibility for shared care for the patient. GPs will take on shared care only if they are willing and able.

Summary
- To reply to the request for shared care as soon as possible.
- To prescribe and adjust the dose as recommended by the specialist.
- To ensure there are no interactions with any other medications initiated in primary care.
- To monitor patient’s ongoing response to treatment, weight and HbA1c at 3 months, 6 months and 6 monthly thereafter.
- Advise the patient to seek prompt medical care should the patient experience unexplained persistent abdominal pain. Should pancreatitis be suspected, discontinue the GLP-1 agonist
- To refer back to the specialist where appropriate. For example:
  - Patient or general practitioner is not comfortable to continue with the existing regime due to either change in condition or drug side effects.
  - Blood glucose levels become unstable
  - The patient experiences any unmanageable side effects.
- Discontinue the drug as directed by the specialist if required.
- To identify adverse events if the patient presents with any signs and liaise with the hospital specialist where necessary. To report adverse events to the specialist and where appropriate the Commission on Human Medicines/MHRA (Yellow card scheme).
Reduced Shared Care Protocol—remains open to review in light of any new evidence

Amber with guidance (Amber-G) = To be initiated and titrated to a stable dose by a specialist prescriber with follow up prescribing by primary care. Once medical condition and drug dosage is stable, there is no specific requirement for ongoing monitoring.

**GLP-1 agonists – Drug summary** *(Please see the full Summary of Product Characteristics for more information. Available at [www.medicines.org.uk/emc](http://www.medicines.org.uk/emc))*

<table>
<thead>
<tr>
<th>GLP-1 agonist</th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication / Licensing information</strong></td>
<td>Treatment of type 2 Diabetes in combination with other anti-diabetic drugs. Byetta® is also licensed as an Adjunct to basal insulin with or without metformin and/or pioglitazone in adults with type 2 Diabetes who have not previously achieved adequate glycaemic control.</td>
<td>Treatment of type 2 Diabetes in combination with other anti-diabetic drugs including oral antidiabetic drugs as well as basal insulin</td>
<td>Treatment of type 2 diabetes mellitus in combination with oral antidiabetic drugs or basal insulin, or both, when adequate glycaemic control has not been achieved</td>
</tr>
<tr>
<td><strong>Relevant NICE guidance</strong></td>
<td>NICE Clinical Guideline CG87  NICE guidance states a GLP-1 agonist can be used as third-line adjunctive therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate on maximally tolerated doses (HbA1c ≥ 7.5%, or other higher level agreed with the individual), and the person has:  - a body mass index (BMI) ≥ 35.0 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or  - a BMI &lt; 35.0 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities  Only continue GLP-1 agonist if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months).</td>
<td>NICE Technology Appraisal TA248  Bydureon® has the same place in therapy as the twice daily preparation Byetta®</td>
<td>NICE Technology Appraisal TA203  Triple therapy regime as CG87 above but liraglutide + metformin + sulfonylurea or thiazolidinedione  <strong>Dual therapy</strong> regime if treatment with metformin or a sulfonylurea is contraindicated or not tolerated and treatment with pioglitazone or a dipeptidylpeptidase-4 inhibitor is contraindicated or not tolerated. Only continue if a beneficial metabolic response has been shown (defined as a reduction of at least 1% / 11mmols/mol in HbA1c at 6 months).</td>
</tr>
</tbody>
</table>
Reduced Shared Care Protocol—remains open to review in light of any new evidence

**Amber with guidance (Amber-G)** = To be initiated and titrated to a stable dose by a specialist prescriber with follow up prescribing by primary care. Once medical condition and drug dosage is stable, there is no specific requirement for ongoing monitoring.

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Lixisenatide</th>
</tr>
</thead>
</table>
| **Dosing information** | • Administered by subcutaneous injection in the thigh, abdomen, or upper arm.  
• Dose of concomitant insulin or drugs that stimulate insulin secretion should be reviewed and reduced if necessary  
• Blood glucose self-monitoring may be necessary to adjust the dose of sulfonylurea when GLP-1 agonist is initiated | • Adults over 18 years: initially 0.6mg once daily, increased after at least 1 week to 1.2mg once daily. **NICE guidance does not** recommend the higher dose of 1.8mg once daily.  
• Liraglutide should be administered at the same time each day. | • Adult over 18 years – 10micrograms once daily within one hour before the first meal of the day or the evening meal for 14 days, increased to 20micrograms once daily thereafter. |
| **Byetta®** | • Initial dose 5 microgrammes bd, for at least one month. The dose can be increased to 10 microgrammes bd if necessary.  
• Dose should be administered within 1 hour before 2 main meals (at least 6 hours apart). Exenatide should **NOT** be administered after a meal. If an injection is missed, the treatment should be continued with the next scheduled dose. | | |
| **Bydureon®** | • Administer on same day each week. This can be changed if necessary as long as the next dose is administered at least 24 hours later. It can be administered at any time of day, with or without meals.  
• The recommended dose is 2 mg exenatide once weekly.  
• Appropriate training is recommended for administering the product. Reconstitution is needed prior to administering.  
• If a dose is missed, it should be administered as soon as practical. Patients can resume their once weekly dosing schedule. Two injections should not be given on the same day. | | |

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GLP-1 agonist Shared care Guideline (Amber-G)

Date Prepared: July 2014  
Review Date: July 2016
Reduced Shared Care Protocol – remains open to review in light of any new evidence

**Amber with guidance (Amber-G)** = To be initiated and titrated to a stable dose by a specialist prescriber with follow up prescribing by primary care. Once medical condition and drug dosage is stable, there is no specific requirement for ongoing monitoring.

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<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse drug reactions</strong></td>
<td>• Most common side effects are: nausea, vomiting, diarrhoea, constipation, abdominal pain, dyspepsia – these reactions are mostly mild and transient. Nausea may be minimised by stopping eating before satiety.  &lt;br&gt;• Headache and dizziness.  &lt;br&gt;• Hypoglycaemia has been reported in patients also taking a sulfonylurea and/or basal insulin  &lt;br&gt;• Decreased appetite  &lt;br&gt;• Injection site reactions  &lt;br&gt;• Anaphylactic reaction  &lt;br&gt;Rare or very rare (&gt;1 in 100 to &gt;1 in 1000): acute pancreatitis. GLP-1 agonists should be avoided in patients considered to be at high risk of pancreatitis e.g. gallstones, severe hypertriglyceridaemia, or alcohol use. Patients suspected to have pancreatitis should have the GLP-1 agonist discontinued, be admitted to hospital and the diabetes team should be informed.  &lt;br&gt;Excessive sweating, feeling jittery, asthenia have also been reported for exenatide  &lt;br&gt;Nasopharyngitis.  &lt;br&gt;Upper respiratory tract infection, cystitis</td>
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<tr>
<td><strong>Renal impairment</strong></td>
<td>No dosage adjustment is needed in patients with mild renal impairment (both Byetta® and Bydureon®)  &lt;br&gt;In patients with moderate impairment (eGFR 30-50ml/minute/1.73m²) care should be taken if increasing the dose from 5mcg to 10mcg (Byetta®). Bydureon® is not recommended in patients with moderate renal impairment  &lt;br&gt;Avoid both Byetta® and Bydureon® in patients with end stage renal disease or those with severe renal impairment (eGFR &lt;30ml/minute/1.73m²)</td>
<td>Liraglutide is not recommended in patients with moderate renal impairment (eGFR 30-50ml/minute/1.73m²) or severe renal impairment (eGFR 30ml/minute/1.73m²)  &lt;br&gt;Caution if eGFR is 30-50ml/minute/1.73m² (moderate impairment)  &lt;br&gt;Avoid if eGFR is less than 30ml/minute/1.73m² (severe impairment)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic impairment</strong></td>
<td>No dosage adjustment is necessary in patients with hepatic impairment</td>
<td>The therapeutic experience in all patients with hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment.</td>
<td>No dosage adjustment is needed in patients with hepatic impairment</td>
</tr>
</tbody>
</table>
Reduced Shared Care Protocol – remains open to review in light of any new evidence

**Amber with guidance (Amber-G)** = To be initiated and titrated to a stable dose by a specialist prescriber with follow up prescribing by primary care. Once medical condition and drug dosage is stable, there is no specific requirement for ongoing monitoring.

<table>
<thead>
<tr>
<th>Precautions and contraindications</th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute pancreatitis</strong> - 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. Caution should be exercised in patients with a history of pancreatitis.</td>
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<tr>
<td><strong>Severe gastrointestinal disease</strong> - Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions.</td>
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<tr>
<td>Delay in gastric emptying - The delay of gastric emptying with exenatide may reduce the rate of absorption of orally administered medicinal products therefore use with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, require careful clinical monitoring or have a narrow therapeutic ratio.</td>
<td></td>
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</tr>
<tr>
<td><strong>Hypoglycaemia</strong> - Patients receiving a GLP-1 agonist with a sulfonylurea and/or with basal insulin may have an increased risk of hypoglycaemia. Reduction of the dose of the sulfonylurea or the basal insulin should be considered to reduce the risk of hypoglycaemia. Lixisenatide should not be given in combination with basal insulin and a sulfonylurea due to increased risk of hypoglycaemia</td>
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</tbody>
</table>

Avoid in pregnancy and breastfeeding and children under 18 years

**Relevant monitoring**

Monitor the patient’s response to the treatment by measuring HbA1c and weight at 3 months, 6 months and then 6 monthly thereafter.

Renal function should also be monitored at regular intervals

**Storage**

| Byetta® - The pen should be stored in a refrigerator before first use. Once opened it should be stored at room temperature (below 25°C) for no longer than its shelf-life of 30 days. | Store in a refrigerator. Do not freeze. | Store in a refrigerator. Do not freeze. |
| Bydureon® - Store in a refrigerator (2°C - 8°C). Do not freeze. The kit may be kept for up to 4 weeks below 30°C prior to use. Store in the original package in order to protect from light. | | |

GLP-1 agonist Shared care Guideline (Amber-G)
Reduced Shared Care Protocol—remains open to review in light of any new evidence

**Amber with guidance (Amber-G)** = To be initiated and titrated to a stable dose by a specialist prescriber with follow up prescribing by primary care. Once medical condition and drug dosage is stable, there is no specific requirement for ongoing monitoring.

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Lixisenatide</th>
</tr>
</thead>
</table>
|                   | Exenatide slows gastric emptying so may reduce the extent and rate of absorption of orally administered drugs.  
• Patients receiving oral medicines that have a narrow therapeutic ratio or require careful clinical monitoring should be followed closely. If such medicines are to be given with food, they should be taken with a meal when exenatide is not administered.  
• Medicines dependent on threshold concentrations for efficacy, (e.g. contraceptives and antibiotics) should be taken at least 1 hour before exenatide injection.  
• Gastroresistant formulations should be taken at least 1 hour before or more than 4 hours after exenatide injection.  
Warfarin. Increased INR has been reported during concomitant use with warfarin. INR should be closely monitored during initiation and dose increase of exenatide therapy in patients on warfarin. | No specific drug interactions listed. Advise to monitor INR more frequently when liraglutide started in patients on warfarin or other coumarin derivatives | Patients receiving medicinal products of a narrow therapeutic ratio or that require careful clinical monitoring should be followed closely, especially at initiation of lixisenatide treatment. If such medicinal products are to be administered with food, patients should be advised to, if possible, take them with a meal when lixisenatide is not administered.  
For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, patients should be advised to take those medicinal products at least 1 hour before or 4 hours after lixisenatide injection.  
Gastro-resistant formulations should be administered 1 hour before or 4 hours after lixisenatide injection.  
No dose adjustment for warfarin is required when co-administered with lixisenatide; however, frequent monitoring of INR in patients on warfarin and/or coumarin derivatives is recommended at the time of initiation or ending of lixisenatide treatment. |
Reduced Shared Care Protocol—remains open to review in light of any new evidence

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**Communication**

**Specialist to GP**
The specialist will inform the GP when they have initiated a GLP-1 agonist. When the patient is near completing the satisfactory initiation period, the specialist will write to the GP to request they take over prescribing and where possible give an indication as to the expected length of treatment. The Specialist will also send a Shared care request form to support the GP in undertaking reduced shared care. (Appendix A)

**GP to specialist**
If the GP has concerns over the prescribing of a GLP-1 agonist, they will contact the specialist as soon as possible.

**Contact names and details**

<table>
<thead>
<tr>
<th>Contact Name</th>
<th>Telephone number</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr K Sands Consultant Endocrinologist</td>
<td>01226 434050</td>
<td><a href="mailto:keith.sands@swyt.co.uk">keith.sands@swyt.co.uk</a></td>
</tr>
<tr>
<td>Dr E Uchegbu Consultant Diabetologist</td>
<td>01226 432598</td>
<td><a href="mailto:elizabeth.uchegbu@nhs.net">elizabeth.uchegbu@nhs.net</a></td>
</tr>
<tr>
<td>Dr Z Merza Consultant Endocrinologist and Diabetologist</td>
<td>01226 435366</td>
<td><a href="mailto:z.merza@nhs.net">z.merza@nhs.net</a></td>
</tr>
<tr>
<td>Prof TH Jones Consultant Endocrinologist and Diabetologist</td>
<td>01226 432147</td>
<td><a href="mailto:Hugh.jones@nhs.net">Hugh.jones@nhs.net</a></td>
</tr>
<tr>
<td>Natasha Kelly Diabetes Specialist Nurse</td>
<td></td>
<td><a href="mailto:natashakelly@nhs.net">natashakelly@nhs.net</a></td>
</tr>
<tr>
<td>Community Diabetes Specialist Nurse Team Apollo Court – Sue Jones</td>
<td>01226 209884</td>
<td><a href="mailto:sue.jones@swyt.nhs.uk">sue.jones@swyt.nhs.uk</a></td>
</tr>
<tr>
<td>Gillian Smith Medicines Information Pharmacist</td>
<td>01226 432857</td>
<td><a href="mailto:gilliansmith2@nhs.net">gilliansmith2@nhs.net</a></td>
</tr>
</tbody>
</table>

**Development Process**

*This guidance has been produced by Caron Applebee, Medicines Management Pharmacist, following an AMBER-G classification status of exenatide, liraglutide and lixisenatide by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the Area Prescribing Committee on July 2014 and the LMC on 9th September 2014.*
**Appendix A – Reduced Shared Care (Amber-G) request form**

- Specialist to complete when requesting GP to enter a shared care arrangement.
- GP to return signed copy of form.
- Both parties should retain a signed copy of the form in the patient’s record.

**From (Specialist):** ____________  **To (GP):** ____________

### Patient details

<table>
<thead>
<tr>
<th>Name: ________________________________</th>
<th>ID Number: ____________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address: ______________________________</td>
<td>DOB: _________________</td>
</tr>
<tr>
<td>Diagnosed condition: __________________</td>
<td></td>
</tr>
</tbody>
</table>

### Amber-G Drug details

<table>
<thead>
<tr>
<th>Drug name: ____________________________</th>
<th>Dose: ________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of initiation: _________________</td>
<td>Length of treatment: ________________</td>
</tr>
<tr>
<td>The patient will be reviewed by the Consultant on:</td>
<td>____________________</td>
</tr>
<tr>
<td>The patient should be reviewed by the GP by:</td>
<td>____________________</td>
</tr>
</tbody>
</table>

### Communication

**Consultant**

- Telephone number: ________________  Fax number: ________________
- Email address: ____________________

**Specialist Nurse**

- Telephone number: ________________  Fax number: ________________
- Email address: ____________________

### Confirmation of acceptance of shared care

<table>
<thead>
<tr>
<th>Specialist name: ____________________</th>
<th>Specialist signature: ________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: ________________________________</td>
<td></td>
</tr>
<tr>
<td>I, Dr __________________________ can confirm I:</td>
<td></td>
</tr>
<tr>
<td>□ accept the request to participate in shared care for the patient named above.</td>
<td></td>
</tr>
<tr>
<td>□ reject the request to participate in shared care for the patient named above. The reason for this being ……………………………………………………………………………………………………</td>
<td></td>
</tr>
</tbody>
</table>

| GP signature: ________________________ | Date: ________________ |