This document should be read in conjunction with the current Summary of Product Characteristics (http://www.medicines.org.uk)

1. INDICATIONS

As set out in NICE CG87, MANAGEMENT OF TYPE 2 DIABETES

GLP 1 analogues are licensed to be given in combination with Metformin and/or Sulphonylurea or Glitazone in patients who have not achieved adequate glycaemic control on maximum tolerated doses of oral therapies.

**GLP 1 analogues are not indicated as First Line Therapy**

In combination with Metformin and/or a Sulphonylurea and/or Pioglitazone (only as dual therapy) if blood glucose control remains or becomes inadequate:

- Hba1c more than or equal to 7.5% / 59mmols or other higher level agreed with the individual
  AND
- BMI 35kg/m2 or more in people of European descent (adjust for other ethnic groups) and there are problems associated with high weight
  OR
- BMI less than 35kg/m2 and insulin is unacceptable of occupational implications or if weight loss would benefit other co-morbidities

GLP 1 can be used in combination with some oral antidiabetic medications (see section 8 table)
With the exception of Bydureon GLP 1 can be used as add-on to basal Insulin. Novo Nordisk recommend to use Levemir once daily with Liraglutide, initially at a dose of 10 U or 0.1-0.2 U/kg. The dose of Levemir should be titrated based on individual patients’ needs.
GLP 1 treatment should only be continued if the patient has a beneficial metabolic response at 6 months (Hba1c reduction by at least 1% AND initial bodyweight reduction by at least 3%) 

2. Therapeutic background and use

Naturally:
- GLP-1 is secreted in the intestine mostly in response to food intake. It stimulates the secretion of insulin and reduces hepatic glucose production
- GLP-1 also reduces GI motility and increases the feeling of being full
- GLP-1 agonists lower fasting and post-prandial blood glucose levels and are associated with weight loss
- GLP-1 agonists suppresses glucagon secretions which is inappropriately increased in Type 2 Diabetes

3. Contraindications/Caution
- See formulary for guidance
- Limited therapeutic experience in eGFR<50mls/minute
- Not recommended in Moderate to Severe renal impairment (eGFR < 50 ml/min)
- Hypersensitivity to the active ingredients or any of the excipients
- Type 1 Diabetes
- Not recommended in severe inflammatory bowel disease or gastroparesis
- Previous history of pancreatitis
- Pregnancy and breastfeeding (lack of data)
- Paediatric and adolescents < 18yr (lack of data)
LIRAGLUTIDE only
- Hepatic Impairment: mild, moderate and severe—no adequate data
- Personal or any family history of Medullary Thyroid Cancer (MTC) or Multiple Endocrine Neoplasia Syndrome type 2 (MEN 2).

4. Drug Interactions NB: also refer to the BNF and Summary of Product Characteristics
Below applicable to Exenatide and Bydureon
Drugs with narrow therapeutic index and/or which require clinical monitoring:
- GLP 1 slows gastric emptying (amount of medicine absorbed and rate of absorption may be effected). Take other medicines 1hr before or 4hrs after Exenatide

Gastro-resistant Formulations:
- Take 1hr before or 4hrs after

Sulphonylureas:
- Increased risk of hypoglycaemia therefore consider temporary dose reduction by 50% initially then titrate dose back up
- Initial blood glucose monitoring may be required

Warfarin:
- Not known but INR has increased in some patients. Recommendation is to monitor INR more frequently

Oral Contraceptive Pill:
- Recommendation to be taken at least 1hr before or after Exenatide. No dose adjustment required.
5. Adverse Drug Reactions NB: also refer to BNF and Summary of Product Characteristics

Most serious toxicity is seen with long term use therefore patients may present to the GP first

Common side effects
- Nausea/Vomiting – eases with continued use, try short course of anti emetic, lesser extent with Liraglutide and Bydureon
- Diarrhoea/ Constipation/ Abdominal pain/ Dyspepsia
- Headache
- Nasopharyngitis
- Hypoglycaemia – when used in combination with Sulphonylurea or insulin

Less Common side effects
- Pancreatitis – discontinue immediately
- Altered renal function – if significant change review treatment
- Local reaction

Unknown rare
- Thyroid and Parafollicular cell pathology with Liraglutide

If the patient has symptoms of acute pancreatitis, (persistent, severe abdominal pain) they should stop treatment immediately and seek medical attention urgently.

*Report any adverse reaction to a black triangle drug to the CHM - MHRA via the yellow card scheme or online:*

[www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)
6. Baseline Investigations

Prior to commencing GLP-1 the following should be undertaken:

- LFTs / Renal / Glycated Haemoglobin
- Weight / BMI
- Advised to inform DVLA if appropriate - only if taken in combination with other diabetes medications that may cause hypoglycaemia
- TFT for Liraglutide

7. Monitoring

Self Monitoring - If used in combination with Sulphonylurea/Basal insulin as there is a small risk of hypoglycaemia

GLP 1 treatment should only be continued if the patient has a beneficial metabolic response at 6months (Hba1c reduction by at least 1% AND initial bodyweight reduction by at least 3%)

<table>
<thead>
<tr>
<th>MONITORING</th>
<th>FREQUENCY</th>
<th>RESULTS</th>
<th>ACTION</th>
<th>BY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hba1c</td>
<td>6 monthly</td>
<td>At 6 months at least 1% reduction</td>
<td>Review treatment</td>
<td>Consultant/GP</td>
</tr>
<tr>
<td>Bodyweight</td>
<td>6 monthly</td>
<td>At 6 months at least 3% reduction</td>
<td>Review treatment</td>
<td>Consultant/GP</td>
</tr>
<tr>
<td>U&amp;E, eGFR</td>
<td>1 monthly then 6 monthly</td>
<td>Significant change</td>
<td>Review treatment</td>
<td>Consultant/GP</td>
</tr>
</tbody>
</table>
### Comparative Table

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Prolonged release exenatide (Bydureon)</th>
<th>*Lixisenatide (LYXUMIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>5mcg to 10mcg sc BD ½ to 1 hour before meal</td>
<td>0.6mg to 1.2 mg sc OD, independent of meals</td>
<td>2mg SC once weekly, requires reconstitution</td>
<td>10mcg to 20mcg SC, once daily, 1 hour before the first meal or evening meal of the day</td>
</tr>
<tr>
<td></td>
<td>Start at 5mcg BD increasing to 10mcg after 1 month</td>
<td>Start at 0.6 mg and increase to 1.2mg after at least 1 week</td>
<td>(NICE has not approved use of 1.8mg)</td>
<td>Start at 10mcg SC OD increasing to 20mcg SC OD after 14 days</td>
</tr>
<tr>
<td></td>
<td>They may need to stay on 5mg for a further month if nausea persists</td>
<td>(NICE has not approved use of 1.8mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant Anti hyperglycaemic drug</strong></td>
<td>Metformin +/- Sulphonylurea</td>
<td>Metformin +/- Sulphonylurea</td>
<td>Metformin +/- Sulphonylurea</td>
<td>Metformin +/- Sulphonylurea</td>
</tr>
<tr>
<td></td>
<td>Metformin +/- glitazone</td>
<td>Metformin +/- glitazone</td>
<td>Metformin + glitazone</td>
<td>Basal Insulin +/- Metformin +/- pioglitazone</td>
</tr>
<tr>
<td></td>
<td>Basal insulin +/- Metformin +/- pioglitazone</td>
<td>Basal Insulin +/- Metformin +/- pioglitazone</td>
<td>Basal Insulin +/- Metformin +/- pioglitazone</td>
<td>Basal Insulin +/- Metformin</td>
</tr>
<tr>
<td><strong>Specific Counselling</strong></td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Pregnancy/lactation</td>
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<td>Pregnancy/lactation</td>
<td>Pregnancy/Lactation</td>
</tr>
<tr>
<td></td>
<td>Thyroid Tumour</td>
<td></td>
<td></td>
<td>If a dose is missed, inject within 1 hour before the next meal—do not administer after a meal. Some oral</td>
</tr>
</tbody>
</table>


medications should be taken at least 1 hour before or 4 hours after l injection—consult product literature for details

NOTE: *Lixisenatide has been added to the MK Formulary Dec 2013 with the following restrictions:
- Recommended locally to be used in the same way as Exenatide / Liraglutide whilst we wait for it to be assessed by NICE
- In line with NICE guideline 87 for use in patients for whom a GLP-1 agonist is appropriate, as an alternative to existing GLP-1 agonists
- It should only be prescribed by primary care following hospital recommendation. Contact Dr Chandran / Dr Ali by phone or email to discuss individual cases

References:
NICE (2009) CG87 Type 2 diabetes - newer agents (a partial update of CG66): quick reference guide
NHS Milton Keynes CCG Prescribing News Jan 2014

Dr Shanthi Chandran – MK Diabetes Care Oct 2012
Updated Feb 2014