Considerations for Commissioners:

- The NICE clinical guideline on the management of type 2 diabetes in adults (NG 28 - Dec 2015) set out factors to be considered in selecting drug treatments for type 2 diabetes, including: effectiveness (metabolic response), safety and tolerability, the individual’s personal and clinical circumstances and preferences, the licensed indications of the treatments available, and the cost (if two drugs in the same class are appropriate, choose the option with the lower acquisition cost). The HbA1c targets agreed should reflect an individual’s clinical circumstances and preferences, and the balance of likely long-term benefits/ adverse effects.

- In the NICE guideline, in patients who can tolerate metformin, GLP-1 RAs are recommended (after the second intensification step and consideration of insulin treatment) in combination with metformin and a sulfonylurea in patients with type 2 diabetes who:
  - have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or,
  - have a BMI lower than 35 kg/m², and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities.

- People treated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) should be reviewed every six months during therapy to ascertain the continuing effectiveness of therapy (e.g. agreed HbA1c targets, achievement of acceptable weight loss).

- A review of the local prescribing arrangements for GLP-1 RAs in combination with insulin, given the NICE recommendation that patients should receive ongoing support from a consultant-led multidisciplinary team.

Description of the technology

GLP-1 receptor agonists (RAs) mimic the endogenous hormone glucagon-like peptide 1 (GLP-1). GLP-1 is an incretin, a gastrointestinal hormone released in the circulation in response to food and drink. GLP-1 regulates glucose levels by stimulating glucose-dependent insulin secretion, suppressing glucagon secretion and slowing gastric emptying. Five GLP-1 RAs are licensed for use in the UK, licensed indications are summarised in the table below. The box below summarises key points identified from a review of the evidence for the comparative efficacy of GLP-1 RAs.

### Efficacy:

#### Comparative effectiveness of GLP-1 RAs (outcome: change in glycosylated haemoglobin [HbA1c] from baseline to the end of the study [24 to 52 weeks]):

- **As triple therapy added to metformin and pioglitazone or a sulfonylurea (SU):**
  - Weekly dulaglutide was more effective than twice-daily exenatide.
  - Daily liraglutide was more effective than weekly albiglutide, twice-daily exenatide, and weekly exenatide (60 – 64 % of participants in DURATION 6 and LEAD-6 were receiving triple therapy).
- **As dual therapy, in addition to metformin:**
  - Weekly dulaglutide was non-inferior to daily liraglutide 1.8 mg.
  - Daily lixisenatide was non-inferior to twice daily exenatide.

#### Patient factors:

- Frequency of administration (by subcutaneous injection):
  - Albiglutide, dulaglutide and exenatide (Bydureon) are once weekly formulations
  - Liraglutide and lixisenatide are administered once daily
  - Exenatide (Byetta) is administered twice daily
- There may be patient preference as to the ease of use of the different pen delivery devices
- Weight decreases with the use of GLP-1 RAs reported in the head-to-head trials range from -0.64kg with albiglutide to -3.98 kg with exenatide (twice daily).

### Safety:

- **Cardiovascular (CV) outcome data**
  - In the ELIXA trial, lixisenatide was non-inferior to placebo (both in addition to standard therapy) for the primary composite outcome of cardiovascular death, myocardial infarction, stroke or hospitalisation for unstable angina. Superiority was not shown.
  - The ‘time-to-event’ LEADER trial reported that liraglutide was superior to placebo for the composite outcome of first occurrence of death from CV causes, non-fatal MI, or non-fatal stroke.
  - GLP-1 RAs may be associated with gastrointestinal adverse events (nausea, vomiting and diarrhoea).
  - Acute pancreatitis is listed as a potential risk in the Summary of Product Characteristics (SPC). Patients should be alerted to characteristic symptoms: sudden severe pain in centre of abdomen, nausea or vomiting, diarrhoea, fever, jaundice.

### Annual cost:

- Albiglutide 30 mg once weekly: £923
- Dulaglutide 1.5 mg once weekly: £952
- Exenatide 5-10 µg twice daily: £830
- Exenatide 2mg once weekly: £954
- Liraglutide 1.2-1.8 mg once daily: £954-£1432
- Lixisenatide 10-20 µg once daily: £755

*Summary includes the direct head-to-head trial evidence comparing different GLP-1 RAs in dual therapy or triple therapy regimes, available at the time of publication. Not all GLP-1 RAs have been compared in RCTs.*
Clinical evidence for efficacy and safety

Direct head-to-head comparison trials of GLP-1 RAs

Direct comparative evidence is not available for all GLP-1 RAs, but six phase 3 RCTs were identified that compared different GLP-1 RAs for the treatment of type 2 diabetes in adults and evaluated HbA1c change from baseline as a primary outcome.2,7

Four trials evaluated dulaglutide, liiraglutide, albiglutide, and weekly and daily exenatide as triple therapy with metformin plus a sulfonlurea (SU) or pioglitazone.2,6

Reported changes from baseline in HbA1c in these trials were (after 26 or 32 weeks’ treatment):7

- Albiglutide 50 mg weekly vs. liiraglutide 1.8 mg daily: -0.78% (-8.5 mmol/mol) vs. -0.99% (-11 mmol/mol); liiraglutide superior to albiglutide.
- Dulaglutide 0.75 mg or 1.5 mg weekly vs. exenatide 10 mcg twice daily: -1.5% (-16.5 mmol/mol) or -1.3% (-14 mmol/mol) vs. -0.99% (-11 mmol/mol); dulaglutide superior to exenatide daily.
- Exenatide 2 mg weekly vs. liiraglutide 1.8 mg daily: -1.28% (-14 mmol/mol) vs. -1.48% (-16 mmol/mol); criteria for non-inferiority of exenatide weekly to liiraglutide not met.
- Liiraglutide 1.8 mg daily vs. exenatide 10 mcg twice daily: -1.1% (-12 mmol/mol) vs. -0.8% (-9 mmol/mol); p < 0.0001 for superiority; liiraglutide superior to exenatide daily.

Two trials evaluated dual therapy combinations with metformin plus dulaglutide, liixisenatide or exenatide daily.6,7 In these trials, reported changes from baseline in HbA1c were:

- Dulaglutide 1.5 mg weekly vs. liiraglutide 1.8 mg daily: -1.42% (-16 mmol/mol) vs. -1.36% (-15 mmol/mol); dulaglutide non-inferior to liiraglutide.
- Liixisenatide 20 mcg daily vs. exenatide 10 mcg twice daily: -0.79% (-8.6 mmol/mol) vs. -0.96% (-10.5 mmol/mol); liixisenatide non-inferior to exenatide daily.

Cardiovascular outcome trials of GLP-1 RAs

The European Medicines Agency (EMA) specifies that the effect of a diabetes treatment on a patient’s CV risk factors must be neutral or beneficial.6 Two such trials evaluating the effect of GLP-1 RAs on rates of cardiovascular (CV) events (e.g. death due to CV causes, non-fatal myocardial infarction [MI], stroke or hospitalisation for unstable angina) or all-cause mortality as the primary outcome have been published,8,10, and two more are ongoing.11,12 These are described below.

In the published trials, eligible participants were those with a recent acute coronary event (within 180 days of trial entry; ELIXA3), or had at least one CV co-existing condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease ≥ stage 3, or NYHA class 2 or 3 chronic heart failure; LEADER13). The LEADER trial also included participants aged over 60, with at least one CV risk factor.9

In the ELIXA trial (n = 6,068; standard care plus liixisenatide 10-20 µg daily or placebo) the primary outcome was a composite of the first occurrence of: cardiovascular death, MI, stroke or hospitalisation for unstable angina. This outcome occurred in 406 (13.4%) participants taking liixisenatide, and in 399 (13.2%) participants taking placebo; hazard ratio (HR) of 1.02 (95% CI 0.89 to 1.17); this showed non-inferiority of liixisenatide to placebo (p < 0.001) but did not show superiority (p = 0.81). There were no significant between-group differences in the rate of hospitalisation for heart failure (HR in the liixisenatide group 0.96 [95% CI 0.75 to 1.23]), or the rate of death from any cause (HR 0.94 [0.78 to 1.13]).

In the LEADER trial (n = 9,340; standard care plus liiraglutide 1.8 mg daily [or the maximum tolerated dose] or placebo) the primary composite outcome was the first occurrence of death from CV causes, non-fatal MI, or non-fatal stroke. This outcome occurred in 608 (13%) liiraglutide-treated participants and 694 (14.9%) placebo-treated participants, HR 0.87 (95% CI 0.78 to 0.97; p = 0.01 for superiority). There were fewer deaths from CV causes with liiraglutide vs. placebo treatment (HR 0.78 [95% CI 0.66 to 0.93]; p = 0.007) and fewer deaths with any cause (381 [8.2%] vs. 447 [9.6%]; HR, 0.85,95% CI, 0.74 to 0.97; p = 0.02).

Adverse events leading to discontinuation from ELIXA and LEADER were most commonly gastrointestinal in nature; nausea and vomiting were significantly more frequent with liixisenatide treatment than placebo (p < 0.001).8,10 The LEADER trial also reported significantly more acute gallstone disease with liiraglutide than in the placebo treatment group (3.1% vs. 1.9%; p < 0.001).

Future developments: Two further trials are ongoing in participants treated with dulaglutide (REWIND11) and exenatide (EXSCEL12). These are as yet no meta-analyses of GLP-1 RA trials with these major CV adverse event outcomes. Two published meta-analyses of prospectively defined CV event data from the clinical trial development programmes for dulaglutide13 and albiglutide14 reported that the risks of a cardiovascular event were not increased vs. comparators. None of the trials included in the analyses were powered to detect a difference in cardiovascular event rates between treatment groups.

References

Table: Summary of the licensed indications for GLP-1 RAs and some suggested dose adjustments (see SPCs for details)

<table>
<thead>
<tr>
<th>Product (Trade name, manufacturer)</th>
<th>Formulation and dosing</th>
<th>Licensed indications</th>
<th>Need for dose adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered appropriate due to contraindications or intolerance</td>
<td>Renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Add-on combination therapy&lt;sup&gt;a&lt;/sup&gt; in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.</td>
<td>Mild&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Abbiglutide (Eperzan®, GSK); SC injection, 30mg or 50mg weekly</td>
<td>✓</td>
<td>✓</td>
<td>NDA</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity®, Eli Lilly)</td>
<td>Monotherapy: SC injection, 0.75 mg weekly</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Add-on therapy: 1.5 mg weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide daily (Byetta®, AstraZeneca) SC injection, 5-10 µg twice daily</td>
<td>✓</td>
<td>✓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NDA</td>
</tr>
<tr>
<td>Exenatide weekly (Bydureon®, AstraZeneca) SC injection, 2 mg weekly</td>
<td></td>
<td></td>
<td>NDA</td>
</tr>
<tr>
<td>Liraglutide (Victoza®, Novo Nordisk) SC injection, 1.2 or 1.8 mg once daily</td>
<td>✓</td>
<td>✓</td>
<td>NDA</td>
</tr>
<tr>
<td>Lixisenatide (Lyxumia®, Sanofi) SC injection, 10 to 20 µg once daily</td>
<td>✓</td>
<td>✓</td>
<td>NDA</td>
</tr>
</tbody>
</table>

<sup>a</sup> Combinations specified for this product only: with metformin, SU, thiazolidinediones; or in addition to metformin + SU or metformin + thiazolidinediones; or Byetta only: adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.

<sup>b</sup> Definitions of creatinine clearance or eGFR ranges differ, see individual SPCs for details;

NDA – no dose adjustment, NR – not recommended, LCE – limited clinical experience in this patient group.

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics. This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.