Novo Nordisk response to 2nd Appraisal Consultation Document (ACD2) for liraglutide for the treatment of type 2 diabetes mellitus

Background

Novo Nordisk appreciates the opportunity to comment on the 2nd ACD for liraglutide for the treatment of type 2 diabetes. We are encouraged that NICE have accepted the clinical and cost effectiveness of liraglutide 1.2 mg and recognised its benefits for the treatment of people with type 2 diabetes. In particular we are pleased that NICE have recognised the value in an important group of patients for use in dual therapy.

Novo Nordisk believes that both doses of liraglutide (1.2mg and 1.8mg) are clinically and cost effective and will be working to demonstrate this in the future. A number of clinical trials are underway that will further demonstrate the effectiveness of liraglutide in the future; including the company’s long-term cardiovascular outcome study LEADER™ (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) announced on 6th May 2010.

It is currently estimated that 10% of the NHS budget is spent on diabetes. Much of this spending is attributed to the complications of diabetes that occur as a result of poor glycaemic control. In England and Wales 33.4% of people with type 2 diabetes fail to reach the NICE target HbA1c level of ≤ 7.5% and the proportion of people failing to reach this target increases with increasing duration of diabetes.

Our specific comments on the ACD2 are presented below.

- Has all of the relevant evidence been taken into account?

We welcome the recommendation to allow use of liraglutide 1.2mg in patients with intolerance/contraindications to DPP-4 inhibitors and TZDs; and intolerance/contraindications to metformin or SU. As this is likely to be a small group of patients with limited choice of treatments we agree that a BMI restriction is not appropriate for this group of patients.

We would like to remind NICE of our initial response to the 1st ACD where we presented ICERs below £20,000 for dual and triple therapy comparisons (Tables 2 & 3 of Novo Nordisk response to ACD) of liraglutide 1.2mg versus sitagliptin 100mg and rosiglitazone 4mg. Furthermore in our response to the 1st ACD we included an explanation of the differences in modelling results between the SMC and NICE submissions. The Evidence Review Group considered this response and commented our explanation was ‘reasonable’ and did not feel that further comparison of the submissions was a high priority.

We are pleased that NICE recognise the importance of allowing selected people with a BMI < 35 kg/m² to benefit from liraglutide 1.2 mg as a treatment option. We believe these groups of selected people (people for whom therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities) should also include patients with a high reluctance to commence insulin therapy; There are many reasons why a patient may be reluctant to commence insulin therapy and whilst it is apparent that liraglutide will not be overcome all of these issues the characteristics of treatment with liraglutide differ from insulin and this may be of importance to patients.
As submitted in our response to the 1st ACD the variability in the ICERs for liraglutide 1.8mg versus liraglutide 1.2mg narrows greatly when only patients with a BMI >35 kg/m² are considered. The 2nd ACD accurately points out that there is limited clinical evidence of dose escalation for patients receiving liraglutide. Two studies (Pratley et al 2010 and Garber et al 2008) have shown a statistically significant difference in glycaemic response between the two maintenance doses (1.2mg and 1.8mg) of liraglutide. Therefore we believe in the following circumstances use of liraglutide 1.8 mg would be appropriate for people not reaching glycaemic control with liraglutide 1.2 mg where treatment with insulin as an alternative would:

- have significant occupational implications, or
- be expected to result in weight gain to a BMI >35.

This is in line with the liraglutide SmPC which states that "the dose can be increased to 1.8 mg to further improve glycaemic control".

Weight gain is a well documented side effect of insulin therapy. For example in the INITIATE study patients commencing insulin therapy with insulin glargine gained a mean 5.6 kg in weight whilst patients commencing biphasic insulin aspart 30 gained 3.0 kg. vii

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

In our original submission we gave details of Patient Reported Outcomes (PRO) from the clinical study 1860 in confidence. This data has now been published (Pratley et al 2010) and a specific publication on the PROs has also been accepted for publication in Diabetic Medicine. Both this study and the results from treatment satisfaction questionnaires in Nauck et al 2009 (LEAD-2) suggest that injection with liraglutide affects neither patient acceptance nor satisfaction versus oral treatments.

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

We agree with NICE's Clinical Experts ix that the general stopping rule for liraglutide 1.2mg in triple therapy use should change from "....a reduction of at least 1 percentage point in HbA1c AND a weight loss of at least 3% of initial body weight at 6 months” to "....a reduction of at least 1 percentage point in HbA1c OR a weight loss of at least 3% of initial body weight at 6 months”. Clinically, improvements in glycaemic control and weight loss are both as isolated outcomes beneficial for patients. Moreover, not allowing patients who do not achieve both 1 percent reduction in HbA1c AND a weight loss of 3% with liraglutide 1.2mg in triple therapy to try the use of liraglutide 1.8mg would mean that these patients would initiate insulin treatment. Insulin treatment is associated with weight gain, significant risk of hypoglycaemia and no improvement in systolic blood pressure unlike with liraglutide. Our recommended and more clinically relevant stopping rule would also be significantly easier to manage in practice for health care professionals.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**

Novo Nordisk welcomes the appropriate adjustment of BMI in ethnic groups. We would also like to clarify that the recommendations regarding BMI are for commencing therapy. Patients with a beneficial metabolic response to treatment should be allowed to continue treatment even if their BMI falls below the threshold of < 35 kg/m², as it would be inappropriate to penalise patients for successful diabetes management.
References


iv Larkin AE, Capasso VA, Chen CL, Mahoney EK, Hazard B, Cagliero E and Nathan DM. Measuring Psychological Insulin Resistance: Barriers to Insulin Use. The Diabetes Educator, Volume 34, No.3 May/June 2008; 511-517

v Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Søndergaard RE and Davies M. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. The Lancet; Vol 375; April 2010 p1447-1456


ix Comments made from clinic experts at the NICE 2nd Appraisal committee meeting (20th April 2010) for liraglutide in the treatment of type 2 diabetes.