Scottish Medicines Consortium

liraglutide 6mg/mL prefilled pen for injection (3mL) (Victoza®)
Novo Nordisk Ltd. No. (585/09)

06 November 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

liraglutide (Victoza®) is accepted for restricted use within NHS Scotland.

Licensed indication under review: Liraglutide for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:
- in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea;
- in combination with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

Five randomised controlled studies have demonstrated efficacy of liraglutide against relevant comparators in terms of the primary endpoint, change from baseline in glycated haemoglobin (HbA_{1c}) after 26 weeks of treatment.

Restriction: Liraglutide is restricted to use as a third-line antidiabetic agent. The economic case for second-line use, added to metformin in place of a sulphonylurea, has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

- In combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea;
- In combination with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

Dosing information

A starting dose of liraglutide 0.6mg daily is recommended to improve gastro-intestinal tolerability. After at least one week, the dose should be increased to 1.2mg daily. Some patients are expected to benefit from an increase in dose from 1.2mg to 1.8mg daily and based on clinical response, after at least one week the dose can be increased to 1.8mg to further improve glycaemic control. Liraglutide is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm.

Liraglutide can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged.

Liraglutide can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy. When liraglutide is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia.

Product availability date

06 July 2009

Summary of evidence on comparative efficacy

Liraglutide, a human glucagon-like peptide-1 (GLP-1) analogue (the same class as exenatide), is produced by recombinant DNA technology in *Saccharomyces cerevisiae.* The evidence to support the efficacy of liraglutide comes from five randomised controlled studies in which liraglutide was added to metformin or glimepiride monotherapy in two studies and to two oral antidiabetic (OAD) drugs in two further studies. It has also been compared with exenatide in an open-label study. In the study programme liraglutide was administered as a once daily subcutaneous injection at doses of 0.6mg to 1.8mg/day.

All studies recruited patients aged 18 to 80 years with type 2 diabetes treated with oral OAD drugs as monotherapy or combination therapy for at least 13 weeks, a glycated haemoglobin (HbA_{1c}) of 7.0 - 10.0%, 7.0 - 11.0% or 7.5 - 10% (inclusive, dependent on study and whether OAD was combination or monotherapy) and a body mass index ≤ 40.0 kg/m^2 or ≤ 45kg/m^2. The primary endpoint was the change from baseline in HbA_{1c} after 26 weeks of treatment. Secondary efficacy endpoints included change from baseline to end of treatment in body weight and systolic blood pressure (SBP) and proportion of patients achieving an HbA_{1c} ≤ 6.5%. Four of the studies included a run-in period prior to randomisation in which the baseline drugs were titrated.

Evidence to support use in combination with metformin or sulphonylurea monotherapy

Two randomised double-blind double-dummy active control studies of similar design have been conducted and included a pre-planned subgroup analysis of patients who had received previous monotherapy. In both studies the intention-to-treat (ITT) analysis set was used and last observation carried forward was applied for missing data.

In the first study patients taking metformin 1.5g to 2g/day were randomised (2:2:2:1:2) to treatment with liraglutide 0.6mg, 1.2mg, 1.8mg, placebo or glimepiride 4mg/day for a 26-week period. Thirty-five percent of patients had received previous monotherapy, while the remaining 65% had received combination therapy. There was a significant reduction in HbA_{1c} for the glimepiride and all liraglutide arms versus placebo (table 1) but no significant difference for the liraglutide arms versus glimepiride. Compared to all patients, the subgroup previously treated with monotherapy had greater reductions in HbA_{1c} across all arms. There was a significant decrease in body weight for all liraglutide arms (1.8kg to 2.8kg) compared to a mean increase of 1.0kg for glimepiride. Also there was a significant reduction in SBP for liraglutide 1.2mg and 1.8mg arms versus glimepiride. The proportion of patients who achieved a target $HbA_{1c} \leq 6.5\%$ was comparable for the liraglutide (1.2mg and 1.8mg) and glimepiride arms (20 - 25%) and higher than the placebo arm (4%).

In the second study patients taking glimepiride 2 to 4mg/day were randomised (2:2:2:1:2) to treatment with liraglutide 0.6mg, 1.2mg, 1.8mg, placebo or rosiglitazone 4mg/day for a 26-week period. Thirty percent of patients had received previous monotherapy, while the remaining 70% had received combination therapy. There was a significant reduction in HbA_{1c} for the rosiglitazone and all liraglutide arms versus placebo (table 1) and also significant differences for liraglutide 0.6mg versus rosiglitazone ($p<0.0429$) and for liraglutide 1.2mg and 1.8mg arms versus rosiglitazone ($p<0.0001$). Compared to all patients, the subgroup previously treated with monotherapy had greater reductions in HbA_{1c} across all arms. There were significant treatment differences in change in body weight for the liraglutide arms versus rosiglitazone; however mean body weight decreased in the liraglutide 1.8mg (0.2kg) and placebo arms (0.1kg) only. Generally, reductions in SBP were seen in all five treatment arms and no significant differences between any of the three liraglutide arms versus the placebo and rosiglitazone arms were observed. The proportions of patients who achieved a target $HbA_{1c} \leq 6.5\%$ were 22% and 21% for the liraglutide 1.2mg and 1.8mg arms respectively, 10% for rosiglitazone and 4% for placebo.

Table 1: Primary endpoint for studies where liraglutide added to metformin or sulphonylurea

Study:	**Metformin in combination with**				
	Liraglutide 0.6mg (n=242)	Liraglutide 1.2mg (n=240)	Liraglutide 1.8mg (n=242)	Placebo (n=121)	Glimepiride 4mg (n=242)
Mean HbA_{1c} at baseline	8.4	8.3	8.4	8.4	8.4
Change from baseline; LS mean	-0.7	-1.0	-1.0	+0.1	-1.0
Change vs. placebo; LS mean (95%CI)	-0.8 (-1.0 to -0.6)	-1.1 (-1.3 to -0.9)	-1.1 (-1.3 to -0.9)	-	-1.1 (-1.3 to -0.9)
Study:	**Glimepiride in combination with**				
	Liraglutide 0.6mg (n=233)	Liraglutide 1.2mg (n=228)	Liraglutide 1.8mg (n=234)	Placebo (n=114)	Rosiglitazone 4mg (n=231)
Mean HbA_{1c} at baseline	8.4	8.5	8.5	8.4	8.4
Change from baseline; LS mean	-0.6	-1.1	-1.1	+0.2	-0.4
Change vs. placebo; LS mean (95%CI)	-0.8 (-1.1 to -0.6)	-1.3 (-1.5 to -1.1)	-1.4 (-1.6 to -1.1)	-	-0.7 (-0.9 to -0.4)

Evidence to support use in combination with metformin and/or a sulphonylurea or metformin and a thiazolidinedione

One study randomised subjects taking metformin (up to 2g/day) plus glimepiride (4mg/day) (2:1:2) to treatment with liraglutide 1.8mg, placebo or open-label insulin-glargine administered once daily. Liraglutide 1.8mg produced significant reductions in HbA_{1c} versus placebo and insulin glargine (table 2). Significantly more patients achieved an $HbA_{1c} \leq 6.5\%$ with liraglutide than with placebo or insulin glargine. There were significant decreases in body weight and SBP in the liraglutide 1.8mg arm (1.8kg and 4mm Hg respectively) versus the insulin glargine arm where body weight and SBP increased (1.6kg and 0.5mm Hg).

Another study randomised subjects taking metformin (up to 2g/day) plus rosiglitazone (8mg/day) to treatment with liraglutide 1.2mg, 1.8mg or placebo. There were significant decreases in HbA_{1c} for both liraglutide arms versus placebo (table 2). $HbA_{1c} \leq 6.5\%$ was achieved in 37%, 36% and 14% of patients respectively. Also, mean reductions in body weight and SBP for the liraglutide arms were significant compared to placebo.

In an open-label study subjects inadequately controlled on metformin, sulphonylurea or a combination of both were randomised equally to receive subcutaneous injections of liraglutide 1.8mg daily or exenatide 10 micrograms twice daily in addition to their OAD treatment regimen. Approximately 63% of patients were on a combination of metformin and sulphonylurea, 10% on a sulphonylurea alone and 27% on metformin alone. Liraglutide 1.8mg was superior to exenatide for change in HbA_{1c} at 26 weeks (table 2). There were no significant differences between the two arms for change in body weight or SBP. More patients had a $HbA_{1c} \leq 6.5\%$ on liraglutide (35%) than on exenatide (21%). Patient reported outcomes were measured in 379 patients using Diabetes Treatment Satisfaction Questionnaire (DTSQ) status and DTSQ change and comprised patients' self-assessments of treatment satisfaction. Overall treatment satisfaction was significantly better in the liraglutide group (n=161) than the exenatide group (n=143). In addition, patients perceived a greater reduction in hypoglycaemia at week 26 with liraglutide.

Table 2: Primary endpoint for studies where liraglutide was added to metformin and/or a sulphonylurea or metformin and a thiazolidinedione

Study:	**Metformin and glimepiride in combination with**		
	Liraglutide 1.8mg (n=230)	Placebo (n=114)	Insulin glargine (n=232)
Mean HbA_{1c} at baseline	8.3	8.3	8.2
Change from baseline; LS mean	-1.3	-0.2	-1.1
Change vs. placebo; LS mean (95%CI)	-1.1 (-1.3 to -0.9)	-	-0.9 (-1.0 to -0.7)
Change vs. insulin glargine; LS mean (95%CI)	-0.2 (-0.4 to -0.1)	-	-
Study:	**Metformin and rosiglitazone in combination with**		
	Liraglutide 1.2mg (n=177)	Liraglutide 1.8mg (n=178)	Placebo (n=175)
Mean HbA_{1c} at baseline	8.5	8.6	8.4
Change from baseline; LS mean	-1.5	-1.5	-0.5
Change vs. placebo; LS mean (95%CI)	-0.9 (-1.1 to -0.8)	-0.9 (-1.1 to -0.8)	-
Study:	**Metformin and/or sulphonylurea in combination with**		
	Liraglutide 1.8mg (n=233)	Exenatide (n=231)	
Mean HbA_{1c} at baseline	8.2	8.1	
Change from baseline LS mean	-1.1	-0.8	
Change vs. exenatide superiority LS mean (95%CI)	-0.3 (-0.5 to -0.2)	-	

Summary of evidence on comparative safety

Overall in the clinical study programme (individual studies of 26 weeks or longer) withdrawal rates due to adverse events were 7.8% for liraglutide-treated patients and 3.4% for comparator-treated patients. The most common adverse events leading to withdrawal in liraglutide-treated patients were nausea (2.8%) and vomiting (1.5%). Gastrointestinal (GI) adverse events (AEs) were the most frequently reported AEs with liraglutide treatment and appeared to be dose related. In the combined liraglutide groups the AEs reported by most subjects were nausea (20% in the 1.2mg and 1.8mg dose groups), diarrhoea (11 to 14%) and vomiting (8%) and for the combined active comparator groups were 4.1%, 4.6% and 1.3%, respectively. These events were in general transient, and more GI AEs were seen when liraglutide was given in combination with metformin.

The total rates of serious AEs appeared lower in the liraglutide groups than in the comparator groups (86.6 versus 97.5 events per 1000 subject years of exposure, respectively). The rates of serious and non-serious AEs, and the total AEs for thyroid, pancreatitis and immunogenicity were, however, higher in the liraglutide groups than the comparator groups. The European Medicines Agency (EMEA) commented that, due to the high degree of homology between liraglutide and native GLP-1, a low risk of antibody formation would be expected. Across studies this does appear to be low, reported on average in 8.6% of patients, and antibodies did not appear to have any effect on the glycaemic response (HbA_{1c}) or the AE profile.

In the study where metformin was combined with liraglutide, placebo or glimepiride the proportion of patients with treatment emergent serious AE were comparable.

The rate of minor hypoglycaemia in the liraglutide arms was similar to the placebo arm and lower than in glimepiride-treated patients. In the study where glimepiride was combined with liraglutide, placebo or rosiglitazone more patients reported serious AEs for all three liraglutide doses (3.0 to 4.7%) compared with the placebo and rosiglitazone arms (2.6% each), although most were evaluated as unlikely to be related to study medication by the investigator. Minor hypoglycaemia occurred at a significantly higher rate in liraglutide arms than in the placebo and rosiglitazone arms. Major hypoglycaemia occurred at a rate of 0.009 events per subject year for the liraglutide 1.8mg arm compared with none for the other arms. The summary of product characteristics for liraglutide notes that when liraglutide is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia.

In the open-label exenatide comparator study, treatment emergent serious AEs were slightly higher in the liraglutide arm (5.1%) compared to the exenatide arm (2.6%). However the incidence of minor hypoglycaemia was 26% versus 34% for the liraglutide and exenatide arms. There were no major hypoglycaemic events in the liraglutide group but two cases were reported in the exenatide group.

Summary of clinical effectiveness issues

A number of randomised controlled studies have demonstrated the efficacy of liraglutide in terms of reduction in HbA_{1c} at 26 weeks as dual and triple therapy in the treatment of type 2 diabetes. Furthermore, an open-label study has reported superiority of liraglutide over exenatide, the only other GLP-1 receptor agonist available. The National Institute for Health and Clinical Excellence (NICE) recommends a target of $HbA_{1c} \leq 6.5\%$ in patients on one glucose-lowering drug and $\leq 7.5\%$ for people on two or more oral glucose-lowering drugs or people needing insulin. Across the clinical studies presented between 20% and 37% of patients on liraglutide 1.2 or 1.8mg daily achieved $HbA_{1c} \leq 6.5\%$ and 35% to 57% achieved $HbA_{1c} \leq 7.0\%$. The EMEA noted that in dual and combination treatment, only limited effect could be expected from an increase in dose to 1.8 mg, while GI adverse events might increase. Long-term studies are needed to determine the effects of liraglutide on disease-related morbidity and mortality.

Liraglutide is administered as a once daily subcutaneous injection at around the same time each day and independent of meals. This may offer advantages over exenatide, which is administered twice daily and within a 60-minute period before the morning and evening meals. In the study comparing liraglutide and exenatide the overall treatment satisfaction was higher with liraglutide. However this study was limited by its open-label design. The marketing authorisation for liraglutide covers a wider indication than exenatide, which may only be used with metformin and/or sulphonylurea.

In the two studies in which there was pre-planned subgroup analysis of patients on previous monotherapy, the studies were not sufficiently powered to detect a difference for this subgroup analysis. In addition the EMEA noted that, in the study comparing glimepiride in combination with liraglutide, rosiglitazone or placebo, the dose of rosiglitazone was low; the safety of the rosiglitazone arm may have been enhanced but the efficacy may have been decreased. The duration of the trial was only 26 weeks, while the efficacy of rosiglitazone is expected to be more pronounced after one year, therefore limiting meaningful conclusions.

Self-monitoring of blood glucose is not needed in order to adjust the dose of liraglutide. However, when used in combination with a sulphonylurea, blood glucose monitoring may still be necessary to adjust the dose of the sulphonylurea.

Summary of comparative health economic evidence

The manufacturer presented five related economic evaluations of liraglutide at various places in the type 2 diabetes treatment pathway as follows:

a) – add-on therapy to a sulphonylurea versus a thiazolidinedione
b) – add-on therapy to metformin versus a sulphonylurea
c) – add-on therapy to metformin and/or a sulphonylurea versus exenatide
d) – add-on therapy to metformin and a thiazolidinedione versus insulin glargine
e) – add-on therapy to metformin and a sulphonylurea versus insulin glargine

Comments from clinical experts suggested the comparison with exenatide (c) would be of most interest.

Clinical data were taken from the appropriate clinical efficacy studies and used in the CORE diabetes economic model. For some comparisons, including the one with exenatide (c) and one of the insulin comparisons (e), the direct comparison in the trial involved a dose of 1.8mg of liraglutide. The manufacturer estimated the relationship between the efficacy of the 1.2mg and 1.8mg doses in the studies where both were used, and then applied this to the clinical study of liraglutide 1.8mg versus exenatide to produce an estimate of the results 1.2mg of liraglutide would have had in the same trial. For comparisons (a) and (b) pre-planned subgroup analyses were used and for comparison (d) with insulin glargine, an indirect comparison was used

It was assumed that treatment with each of the medicines lasted for three years and then all patients were switched to basal insulin. Results were extrapolated to the lifetime of the patient assuming a gradual upward trend in variables such as HbA_{1c}. Utilities were taken from a variety of sources, but were mainly from a UK setting. Costs were also from UK sources.

At a dose of 1.2mg, the manufacturer estimated that liraglutide was cost-effective in all the five positions reporting the following results:

a) – versus a thiazolidinedione (in addition to sulphonylurea), £10,751/QALY (incremental costs of £2,188 and incremental QALYs of 0.204)
b) – versus a sulphonylurea (in addition to metformin), £23,598/QALY (incremental costs of £3,639 and incremental QALYs of 0.154)
c) – versus exenatide (in addition to metformin and/or a sulphonylurea), dominant (cost savings of £80 and incremental QALYs of 0.071)
d) – versus insulin glargine (in addition to metformin and a thiazolidinedione), £7,801/QALY (incremental costs of £1,933 and incremental QALYs of 0.248)
e) – versus insulin glargine (in addition to metformin and a sulphonylurea), £8,847/QALY (incremental costs of £1,652 and incremental QALYs of 0.187)

The corresponding figures for the 1.8mg dose were £17,394, £43,369, £15,581, £14,923, and £17,777.

One criticism of the approach used was that differences in clinical variables that were not statistically significant in the clinical studies were used in the economic model. When these were excluded, the cost per QALY for the comparison with exenatide (c) was £253 (1.2mg dose) and £21,580 (1.8mg dose). The impact on the figures for the thiazolidinedione comparison (a) was much smaller. For the comparison with a sulphonylurea (b), the ICERS were £28, 120 for the 1.2mg dose and £54,908 for the 1.8mg dose.

Results were based on an adjustment to the clinical efficacy data to adapt the 1.8mg dose of liraglutide to 1.2mg and some of the predicted differences may not have been statistically significant. However, sensitivity analysis was provided to show that, with the exception of the comparison with a sulphonylurea, excluding non-significant differences did not have a major impact on the results.

The main concern therefore related to the comparison with sulphonylurea The cost per QALY submitted by the manufacturer was particularly high for the 1.8mg dose. The cost per QALY for the 1.2mg dose was also over £20k and uncertainty in the evaluation (e.g. concern that non-significant differences in key clinical variables had been used in the cost-effectiveness calculation) means that the economic case for use in this setting has not been made. The economic case for third-line use has been made.

Summary of patient and public involvement

A Patient Interest Group submission was received from Diabetes UK Scotland.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published *clinical guideline 66; Type 2 Diabetes* in May 2008 and the NICE *short clinical guideline 87; type 2 diabetes: newer agents* in May 2009. A care pathway includes the use of metformin, sulphonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, insulin, and exenatide. The guideline predates the availability of liraglutide.

The Scottish Intercollegiate Guidelines Network published *national clinical guideline; management of diabetes (number 55)* in November 2001. A selective update is expected in spring 2010.

Additional information: comparators

NICE recommend metformin, sulphonylureas, DPP-4 inhibitors, thiazolidinediones, insulin, and exenatide in their care treatment pathway.

Cost of relevant comparators

Costs for addition of liraglutide to existing therapy in patients inadequately controlled by metformin and/or a sulphonylurea or metformin and a thiazolidinedione are compared below to costs for selected oral antidiabetic agents licensed as add-on therapy. Add-on costs are also given for some insulin preparations. Costs per drug are included only, not cost per treatment regimen.

Drug	Dose regimen	Cost / year (£)
GLP-1 receptor agonists		
Liraglutide	**1.2 to 1.8mg sc daily**	**952 to 1,428**
Exenatide	5 to 10 micrograms sc twice daily	828
Thiazolidinediones		
Pioglitazone	15 to 45mg po once daily	185 to 480
Rosiglitazone	4 to 8mg po once daily	260 to 390
Sulphonylureas		
Glipizide	2.5mg po once daily to 10mg po twice daily	19 to 66
Glimepiride	1 to 4mg po once daily	24 to 62
Gliclazide	40mg po once daily to 160mg po twice daily	6.89 to 55
DPP-4 inhibitors		
Sitagliptin	100mg po once daily	432
Vildagliptin	50mg po once or twice daily depending on concurrent OADs	206 to 413
Insulin		
Insulin glargine	25 to 40 units sc daily	237 to 379
Insulin detemir	25 to 40 units sc daily	237 to 379
Isophane insulin (Humulin I)	25 to 40 units sc daily	143 to 228
Isophane insulin (Insulatard)	25 to 40 units sc daily	116 to 185

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2 September 2009. sc=subcutaneous, po= oral.

Additional information: budget impact

The manufacturer estimated that the net impact of liraglutide would be £425k in year 1 rising to £1.6m in year 5. This estimate included medicines, needles and self-monitoring of blood glucose but excluded hospital costs for complications such as an MI or stroke. 812 patients were estimated to receive liraglutide 1.2mg in year 1, increasing to 3,067 in year 5. These estimates are based on liraglutide being used as a 3rd line treatment option.

There are some issues with the budget impact, particularly what agent would otherwise have been prescribed. Only 10% of patients were assumed to have otherwise received exenatide (the main comparator in the comments from clinical experts). As exenatide is the most expensive comparator the budget impact may be overestimated. Of note, the comparators described include gliptins that were not included in the economic evaluation.

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 16 October 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

First part of indication:
Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009;32:84-90.

Marre M, Shaw J, Brandle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med 2009;26:268-278.

Second part of indication:
Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide versus insulin glargine and placebo in combination with metformin and sulphonylurea therapy in type 2 diabetes mellitus. LEAD+5 met + SU: a randomized controlled trial. Diabetologia, in press 2009.

Zinman B, Gerich J, Buse JB, et al. Efficacy and Safety of the Human Glucagon-Like Peptide-1 Analog Liraglutide in Combination wtih Metformin and Thiazolidinedione in Patients with Type 2 Diabetes (LEAD-4 Met+TZD). Diabetes Care 2009;32:1224-1230.

Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39-47.

The European Medicines Agency (EMEA) European Public Assessment Report. liraglutide (Victoza®). EMEA/379172/2009. www.emea.europa.eu