Pharmacotherapeutic report liraglutide (Victoza®) for the indication type 2 diabetes mellitus

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1. Summary

The Medicines Evaluation Committee (CFH) has approved a pharmacotherapeutic report for the medicine liraglutide (Victoza®) injection solution. In order to determine its therapeutic value, it was compared with NPH insulin and exenatide. They reached the following conclusions:

Efficacy In a single direct comparative study with liraglutide in combination with metformin and/or a sulphonyllurea (SU)-derivative, a reduction was achieved in the HbA1c and fasting blood sugar levels. Significantly more patients achieved the <7% target value for HbA1c in comparison with exenatide in combination with metformin and/or an SU-derivative. However, the clinical relevance of the difference in the HbA1c reduction is limited, the liraglutide dose in the study is higher than the recommended 1,2 mg daily dose, the doses of metformin and the SU-derivatives are unknown. It was also an open-label study. In a single, direct, open-label study, liraglutide in combination with metformin and glimepiride significantly reduced the HbA1c-value in comparison with insulin glargine. In this study the liraglutide dose was also higher than the recommended dose, which may have a limited but extra effect on the reduction in the HbA1c. Furthermore, there is some doubt as to whether the regulation on insulin was optimal in the comparative study with insulin. Unlike insulin, the use of liraglutide and exenatide induces weight loss.
Efficacy For liraglutide data demonstrating its efficacy with respect to micro- and macrovascular complications and life expectancy are not available. Neither has the efficacy of exenatide on clinically relevant final outcomes been demonstrated.The efficacy of insulin has been demonstrated, particularly on the occurrence of microvascular complications.
Side effects Disorders of the gastrointestinal system (nausea and diarrhoea) are the most frequent side effects of liraglutide. In the comparative study the incidence of gastrointestinal side effects was comparable for liraglutide and exenatide, although the nausea of patients treated with liraglutide did not last as long in the study.
Experience Experience with liraglutide is limited. Sufficient experience has been obtained with exenatide and ample experience with insulin.
Applicability Liraglutide and exenatide are not as broadly applicable as (NPH) insulin.
User-friendliness In comparison with exenatide, liraglutide has the advantage that it can be injected independently of meals and once daily. In comparison with insulin, liraglutide and exenatide have the advantage that self-testing is generally not required for dose adjustment. For the rest, testing is limited when adding an evening dose of the medium-acting NPH insulin and when target values have been reached.

Final conclusion on therapeutic value

Unlike liraglutide, in the treatment of type 2 diabetes mellitus the effectiveness and safety of insulin in the long-term has been demonstrated, particularly its

effect on the occurrence of microvascular complications. Therefore, in the case of the sub-group that is unsuccessful with the combination of metformin and a sulphonylureum derivative at maximum tolerated dose, the therapeutic value of liraglutide is lower than that of insulin Preference still goes out to the addition of NPH insulin overnight. Liraglutide has the same therapeutic value as exenatide. There is insufficient evidence of an increased efficacy of liraglutide in comparison with exenatide.

2. Introduction

Medicine	Liraglutide
Composition	Solution for injection 6 mg/ml in a pre-filled pen: 18 mg in 3 ml.
Marketing authorization	Type 2 diabetes mellitus in combination with: - Metformin or a SU-derivative, for patients who achieve insufficient glycaemic regulation with maximum tolerated doses of monotherapy with metformin or a SU-derivative. - Metformin and a SU-derivative or metformin and a thiazolidinedione for patients who achieved insufficient glycaemic regulation with dual therapy.
Dose	Due to the risk of gastrointestinal side effects, the dose is introduced gradually. Initial dose s.c. 0.6 mg 1 x/day. After at least one week, raise the dose to 1.2 mg 1 x /day. A number of patients may benefit from increasing the dose from 1.2 to 1.8 mg 1 x/day in order to improve glycaemic control. Doses exceeding 1.8 mg are not recommended. When liraglutide is added to a SU-derivative (with or without metformin), a reduction in the dose of the SU-derivative should be considered in order to reduce the risk of hypoglycaemia.
Working mechanism	Liraglutide is a glucagon-like peptide (GLP-1) analogue with 97% sequence homology with human GLP-1. Liraglutide binds to the GLP-1-receptor. Similar to GLP-1, activation leads to an increase in cyclic AMP. At high blood sugar levels, liraglutide increases the secretion of insulin by the β-cells, independently of glucose, and reduces the release of glucagon. Vice versa, liraglutide reduces insulin secretion during hypoglycaemia, whilst leaving the secretion of glucagon unimpeded. The mechanism for reducing the blood sugar concentration ensures a slight delay in stomach emptying and reduces the hunger sensation.

For detailed information about the medicine, see the product text as it will appear in the next edition of the *Farmacotherapeutisch Kompas* (see appendix 1).

3. Points of departure for the assessment

3.a. Field of application

Diabetes mellitus is a chronic disorder that is caused by a relative or absolute shortage of insulin. It goes hand-in-hand with significant changes in the metabolism of carbohydrates, proteins and fats. The most important characteristic is the excessive blood sugar value. This value is determined by an interaction between insulin, produced by the β-cells of the islands of Langerhans in the pancreas, and substances produced in the body with an antagonistic effect on insulin, such as glucagon, catecholamines, growth hormones and glucocorticoids. Under normal circumstances, the blood sugar value remains between 4–8 mmol/l. This balance is disturbed in cases of diabetes mellitus.

Both genetic and environmental factors, such as overweight and physical inactivity, play a role in the development of *type 2 diabetes mellitus*. Two phenomena are central to its pathogenesis: increased insulin resistance in tissues of the liver, muscles and fat, and a degree of dysfunction of the β-cells of the islands of Langerhans, which leads to insufficient insulin secretion. Body weight plays an important role in the development of insulin resistance. The disturbed glucose tolerance of adipose patients can often be repaired by weight loss, particularly in the early stages of the disease. Insulin resistance is often accompanied by hypertension, excess weight, hypertriglyceridemia and a reduced HDL-cholesterol level. This cluster of metabolic disorders is also referred to as syndrome X or the insulin-resistance syndrome. The frequent existence of a multitude of risk factors for heart and vascular diseases in patients with type 2 diabetes mellitus helps explain why the incidence of cardiovascular disorders and mortality is higher than in the average population (2–4x higher among men and 4–6x higher among women with type 2 diabetes mellitus).

In the Netherlands more than 600,000 persons were identified as having type 1 or type 2 diabetes mellitus in 2003. About 85 to 90% of all diabetes patients have type 2 diabetes mellitus, 510,000 to 540,000 persons. The incidence and prevalence of type 2 diabetes in the Netherlands have increased rapidly, particularly during the past few years. Underlying reasons are the improved diagnosis, demographic developments and an increase in the number of people who are overweight.[1]

When treating diabetes mellitus, optimal blood sugar regulation can prevent complications in the short term. The following target values apply: fasting glucose 4-7 mmol/l, glucose 2 hours postprandial <9 mmol/l, HbA1c <7%.[2]
Glycaemic regulation is mainly assessed according to the fasting blood sugar value and the HbA1c value (particularly informative about the metabolic system during the previous 5-8 weeks). At the moment there is still no evidence for focussing in general on the postprandial blood sugar values when assessing blood sugar regulation.[3]

There is a relationship between the severity of the hyperglycaemia and the development of long-term complications such as microvascular (retinopathy, nephropathy) and macrovascular (coronary heart disease, CVA) complications. Optimal blood sugar regulation with oral blood sugar lowering medicines (metformin and SU-derivatives) and/or insulin leads mainly to a drop in the number of microvascular complications. In order to reduce macrovascular complications, it is much more important to treat other risk factors for heart and vascular diseases, such as hypertension and hypercholesterolemia, as well as ceasing to smoke.[4]

3.b. Choice of comparative treatment

In principle, when treating type 2 diabetes mellitus, oral medicines for lowering the blood sugar are initiated only in the case that target values for blood sugar levels are not reached with dietary advice during three months, particularly aimed at weight loss and stimulating physical activity. The following oral (groups of) medicines are available: SU-derivatives, metformin, repaglinide, thiazolidinediones and dipeptidylpeptidase IV (DPP-4)-inhibitors (sitagliptin and vildagliptin). The use of acarbose is not recommended due to poor efficacy and side effects. A reduction in long-term complications has only been demonstrated for SU-derivatives and metformin. The following step-by-step plan is advised where lifestyle advice is insufficiently effective.

Step 1: start with metformin. *Step 2*: add a SU-derivative. *Step 3*: add a once daily evening dose of a medium-long acting NPH insulin to the oral medicines for lowering blood sugar. *Step 4*: twice daily NPH insulin or mix-insulin (mixture of short-acting and medium-acting insulin) or, possibly, insulin four times daily (basal bolus regimen).

If glycaemic regulation is still insufficient, whilst increasing the dose is no longer possible due to side effects or having reached the maximum daily dose, switch to the next step in the treatment schedule. Change to a different medicine in the event of contraindications or side effects.

Re step 1 The long-term safety (heart infarction) of thiazolidinediones, particularly rosiglitazone, is still open to discussion and their efficacy on clinically relevant final outcomes has not been proven. Thiazolidinediones only have a place as monotherapy if metformin or a SU-derivative cannot be used as monotherapy. Data on long-term effectiveness and safety are not available.

Re step 2 Thiazolidinediones can be considered for dual combination therapy in combination with a SU-derivative or metformin as long as treatment with a combination of SU-derivatives and metformin is not possible. In combination with metformin: particularly for cases of obesity, in combination with SU-derivatives: only in the event of intolerance or contraindications to metformin. Sitagliptin and vildagliptin can also form an alternative in combination with a SU-derivative or metformin, as long as treatment with a combination of SU-derivatives and metformin is not possible.

Re step 3 Insulin is preferred for patients who do not benefit from the combination metformin/SU-derivative at the maximum tolerated dose. Due to the advantage of weight loss (5 kg maximum), the addition of exenatide can be

considered, but only for patients with a BMI ≥35 kg/m^2 who find it difficult to lose weight even with guidance. It is important to realise that, for exenatide, unlike insulin, there is a lack of effectiveness (eg. reduced complications) and safety data. If there are objections to the addition of insulin, such as persistent injection-site problems (due to skin disorders/too little subcutaneous fatty tissue/local reactions such as infections, contact allergy), physical limitations (hand function, eyesight), mental limitations or a phobia for injections, then the addition of a thiazolidinedione (triple oral combination therapy) can be considered. It is important to realise that the long-term safety of thiazolidinediones (heart infarction) is open to debate, and that, unlike insulin, their efficacy on clinically relevant final outcomes has not been demonstrated. Preference does not go out to combining pioglitazone with insulin because this combination goes hand-in-hand with increased fluid retention and heart failure.

NPH insulin is preferred above the use of insulin glargine or insulin detemir. Using these long-acting insulin analogues should be limited to patients who encounter problems with night-time hypoglycaemias in spite of adequate regulation on NPH insulin [*Farmacotherapeutisch Kompas*, 2009].

Comparative treatment

Dual therapy

According to the step-by-step plan, the dual oral therapy for the treatment of type 2 diabetes mellitus is to combine metformin and a SU-derivative.[2] At the moment, if a patient cannot be treated with metformin or a SU-derivative due to intolerance or contraindications, a thiazolidinedione (pioglitazone or rosiglitazone) or a DPP-4-inhibitor (sitagliptin or vildagliptin) should be considered. Liraglutide is registered as dual therapy for patients who achieve insufficient glycaemic regulation with metformin or a SU-derivative in monotherapy. Comparison with an SU-derivative (plus metformin) is eligible for assessing the therapeutic value of liraglutide as dual therapy in combination with metformin. Comparison with metformin (plus a SU-derivative) is eligible for the combination with a SU-derivative. In the case that metformin or a SU-derivative cannot be administered due to contraindications or side effects, then comparison with the oral therapies thiazolidinediones and DPP-4-inhibitors can be considered.

Liraglutide is administered subcutaneously. Previously, the CFH considered it likely that exenatide, also registered for dual therapy in combination with metformin or a SU-derivative, would probably not be used in dual therapy due to its subcutaneous administration route. The NHG (GP) standard protocols state that ‘treatment with insulin is indicated if target values are not achieved via education and the maximum dose of two different oral medicines for reducing blood sugar.’ The use of subcutaneously-administered liraglutide can be considered, similarly to insulin and exenatide, treatment with a combination of metformin and a SU-derivative is insufficiently effective.

Triple therapy

In the case that treatment with the combination of metformin/SU-derivative is not successful, the step-for-step plan suggests the addition of insulin. The addition of exenatide can be considered for patients with a BMI ≥35 kg/m^2 if weight loss is a problem even with guidance. Comparison with medium-acting NPH insulin and exenatide is eligible for assessing the therapeutic value of liraglutide in

combination with metformin and a SU-derivative. Liraglutide is also registered in combination with metformin and a thiazolidinedione. Thiazolidinediones in combination with metformin are only reimbursed if the patient cannot use a SU-derivative due to contraindications, side effects or insufficient effect. If treatment with metformin and a thiazolidinedione to regulate the blood sugar level fails, liraglutide might be added. In the step-for-step plan, insulin can be considered if the blood sugar level is insufficiently regulated with this dual therapy. Comparison with insulin is also eligible for this combination.

3.c. Method of assessment

For the assessment, preference goes out to the IB text from the registration file, the EPAR/NPAR and direct comparative studies that have been published in peer-reviewed journals. A literature study was carried out with the most recent files of Med-line, Embase and Cochrane on 14th September 2009. The following search terms were used: liraglutide, exenatide, GLP-1 analogue, incretin mimetics, GLP-1 receptor agonist. This did not result in any additional literature references.

4. Therapeutic value

The therapeutic value of liraglutide was assessed according to the criteria: efficacy, effectiveness, side effects, experience, applicability and user-friendliness.

Table 1. Phase III studies with liraglutide, the LEAD studies (table taken from Neumiller et al.[5]).

Study	N	co-medication	intervention	Duration (week)	Δ HbA1c (%)	Δweight (kg)
monotherapy						
LEAD-3 (Garber et al.)[6]	746	Diet/phys. activity, 50% max. dose or OAD monotherapy	liraglutide 1.2 mg liraglutide 1.8 mg glimepiride 8 mg	52	-0.84[a] -1.14[b] -0.51	-2.1[b] -2.5[b] +1.1
Dual therapy						
LEAD-1 (Marre et al.)[7]	1041	glimepiride 2-4 mg	liraglutide 1.2 mg liraglutide 1.8 mg rosiglitazone 4 mg placebo	26	-1.08[b,c] -1.13[b,c] -0.44[c] +0.23	+0.3[b] -0.2[b] +2.1 -0.1
LEAD-2 (Nauck et al.)[8]	1091	Metformin 1gr 2x/dag	liraglutide 1.2 mg liraglutide 1.8 mg glimepiride 4 mg placebo	26	-1.0[b,c] -1.0[c,d] -1.0[c] +0.1	-2.6[b,d] -2.8[b,e] +1.0 -1.5

Triple therapy						
LEAD-4 (Zinman et al)[9]	533	Metformin 1gr 2x/dag plus rosiglitazone 8 mg	liraglutide 1.2 mg liraglutide 1.8 mg placebo	26	-1.48[c] -1.48[c] -0.54	-1.0[f] -2.0[f] +0.6
LEAD-5 (Russell-Jones et al.)[10]	581	Metformin 1gr 2x/day plus glimepiride 2-4 mg	liraglutide 1.8 mg insulin glargine placebo	26	-1.33[a,c] -1.09 -0.24	-1.8[b,c] +1.6 -0.4
LEAD-6 (Buse et al)[11]	464	Metformin, SU-derivative or both	liraglutide 1,8 mg exenatide 10 µg 2x/day	26	-1.12[b] -0.79	-3.2 -2.9
LEAD=Liraglutide Effects and Action in Diabetes; OAD = oral antidiabetic drug [a]p=0.0015 versus comparator [b]p<0.0001 versus comparator [c]p≤0.0001 versus placebo [d]not inferior in comparison with active comparator [e]p≤0.01 versus placebo [f]p<0.05 versus placebo						

4.a. Efficacy

Efficacy is assessed according to the degree of blood sugar regulation.

DUAL THERAPY WITH LIRAGLUTIDE

As liraglutide is indicated in combination with metformin or an SU-derivative when insufficient glycaemic control is achieved with a monotherapy using metformin or an SU-derivative, the studies with dual therapy are discussed briefly and reproduced in table 1: the LEAD 2 study (Nauck et al.) compared liraglutide (plus metformin) with a SU-derivative (plus metformin) and both products achieved a similar, 1.0% drop in HbA1c. If insufficient glycaemic control is achieved with metformin in monotherapy, then preference is given to the addition of an SU-derivative because for this treatment long-term safety data are available and because of the demonstrated effectiveness in relation to the occurrence of microvascular complications. As the manufacturer is claiming that in dual therapy liraglutide has an added value with respect to the drop in HbA1c in comparison with treatment with a thiazolidinedione or a DPP-4-inhibitor, the study in which liraglutide was compared with rosiglitazone (a thiazolidinedione) in dual therapy is discussed briefly and reproduced in table 1:

The LEAD 1 study (Marre et al.) shows a significant difference in the drop in HbA1c with liraglutide (plus glimepiride) that compares favourably with rosiglitazone (plus glimepiride). However, the 4 mg/day dose of rosiglitazone is fairly low in comparison with the standard treatment of 8 mg/day (EPAR liraglutide)[12]. Furthermore, the assessment report also states that preference goes out to an add-on study and that this study made use of the switch-over principle to a standard dose of metformin. For these reasons, no clear conclusions can be drawn regarding a possible added value of the drop in the HbA1c.

On the grounds of the studies with dual therapy, no added value can be demonstrated for liraglutide in dual therapy. For this reason, and due to its subcutaneous administration, liraglutide is not the preferred choice in dual therapy.

TRIPLE THERAPY WITH LIRAGLUTIDE

Comparison with insulin

Comparisons involving NPH insulin and exenatide are eligible for triple therapy. In the study by Russell-Jones et al.[10], liraglutide was compared with insulin glargine as a triple therapy. The earlier conclusion (CFH-report 03/13 insulin glargine[13]) was that insulin glargine's efficacy is globally comparable with that of NPH insulin with respect to reducing the fasting blood sugar level and reducing the HbA1c-value. Based on this, the comparative study with insulin glargine (LEAD 5) can be used to form an opinion on the effect of liraglutide on glycaemic regulation.
Russell-Jones et al.[10]: In the open, direct, 26-week comparison between liraglutide and insulin glargine, patients with type 2 diabetes mellitus, who had been treated with monotherapy or a combination therapy during a run-in period, were titrated to a standard combination of metformin (2 gram/day) and glimepiride (4 mg/day). Patients were randomised for 1.8 mg liraglutide, placebo or insulin glargine (2:1:2). The average insulin dose after 26 weeks was 24 IU/day.
Study characteristics: 581 patients with type 2 diabetes mellitus (aged 18-80 years), with an HbA1c value between 7.5-10% (monotherapy) and 7-10% (combination therapy). The starting value of the HbA1c level was 8.3% in the liraglutide group and 8.2% in the insulin group, the starting values for BMI were 30.4 kg/m^2 (liraglutide) and 30.3 kg/m^2 (insulin group) and the fasting blood sugar value was 9.1 mmol/l for both groups. The average weight upon initiation was 85.3 kg.

Primary endpoint: Alteration in the HbA1c value after 26 weeks of treatment.
Secondary efficacy endpoints: Among others, alterations in the fasting blood sugar value and an alteration in body weight.
Results (table 1):
After 26 weeks of treatment the HbA1c value in the liraglutide group dropped by 1.33% in comparison with 1.09% in the insulin group (p=0.0015). Blood sugar values dropped by 1.55 mmol/l in the patients treated with liraglutide and by 1.79 mmol/l (not significant) in the patients treated with insulin glargine.

Comparison with exenatide

Buse et al. (LEAD 6)[11]: Liraglutide was compared with exenatide directly in a randomised, open study that lasted 26 weeks, whereby 1.8 mg subcutaneous liraglutide once daily was compared with 10 µg subcutaneous exenatide twice daily, and added to the existing medication: maximum dose of metformin and/or a sulphonylureum derivative (doses unknown).
Study characteristics: This study included 464 patients with type 2 diabetes mellitus (age: 18-80 years), a HbA1c-value between 7-11% and an average BMI of 32.9 kg/m^2. The patients who were included were insufficiently regulated with maximum doses of metformin and a sulphonylureum derivative, metformin alone or a SU-derivative alone. The starting value for the HbA1c level was 8.2% for liraglutide and 8.1% for the exenatide group. The average weight upon initiation was 93.1 kg.

Primary endpoint: Alteration in the HbA1c-value after 26 weeks treatment in comparison with the starting value.
Secondary efficacy endpoints:
Among other things, the percentage of patients who achieve the target value of HbA1c <7%, alterations in fasting blood sugar value and an altered body weight.
Results (table 1)
The results do not differentiate between dual and triple therapy, the reductions in HbA1c of the entire group were compared. 62% of the patients in the liraglutide group and 64% of the exenatide group received tripe therapy. After 26 weeks the HbA1c-value of the entire liraglutide group dropped by 1.12%, compared with 0.79% in the exenatide group (p< 0.0001; table 1). 54% of the 1.8 mg liraglutide group achieved a >7% HbA1c-value, versus 43% of the patients treated with exenatide 2x/day 10 µg (p=0.0015). The fasting blood sugar value dropped significantly in patients treated with 1.8 mg liraglutide (-1.61 mmol/l), compared with the exenatide group (-0.60 mmol/l; p<0.0001).

Discussion:
Based on phase II monotherapy study results, the liraglutide dose used in the comparative studies with insulin and with exenatide is 1.8 mg.[10] The SmPC for liraglutide only states that a number of patients benefit from an increase from 1.2 mg to 1.8 mg in order to improve glycaemic control even more. In practice, the majority of the patients will be treated with the standard 1.2 mg per day dose. The 1.8 mg used in the studies is fairly high. The monotherapy studies with liraglutide showed a clear difference in the HbA1c decrease between the 1.2 and 1.8 mg doses (LEAD-3, see table 1). In the studies with dual and triple treatments, only a limited effect was seen when the dose was increased to 1.8 mg.[7,8,9]

Titration of the insulin dose in the direct comparative study with liraglutide was carried out by the patients (average final dose 24 IU/day).[10] In studies in which titration of the insulin doses was subject to closer guidance, higher doses of insulin were reached, together with an improved drop in the HbA1c.[15-17] In the Heine et al.[14] study, in which exenatide was compared with insulin glargine, the dose was titrated by the patient up to an average of 25 IU/day and a comparable drop in the HbA1c was achieved with insulin glargine. Both this study and the CFH report on exenatide 07/31 discussed the possibility that the patients may not have been treated with the maximum insulin dose. Therefore, there is doubt as to whether regulation with insulin was optimal in the direct comparative study of liraglutide and insulin glargine.[10]

There is no mention of the doses of metformin and SU-derivatives in the study that compared liraglutide with exenatide, which means the division of the doses over the two arms is unknown. There is a statement saying that the doses used were those maximally tolerated by the patient. Nor is there any statement about which SU-derivatives were used. The division of the three combination treatments (Met and/or SU) are described and divided fairly evenly. The direct studies comparing liraglutide with exenatide and with insulin glargine are open-label studies, which may have an effect on the results.

HbA1c regulation: in the study comparing liraglutide and exenatide, the decrease in the HbA1c of the ITT population is comparable with that of the per-protocol analysis: -1.16% (liraglutide) and -0.89% (exenatide). The -0.89% decrease with

exenatide is similar to the -0.89% decrease achieved with exanatide in the combined results of the placebo-controlled studies of DeFronzo et al.[18], Buse et al. 2004[19] and Kendall et al.[20]. However, in the studies in which exenatide was compared with insulin glargine and biphasic insulin, there are -1.11% and -1.04% decreases for exanatide, which are comparable with the 1.16% value for liraglutide in the direct comparison with exenatide (ITT populations).[14,21] In the Russell-Jones et al. study, there were HcA1c decreases of -1.33% (liraglutide) and -1.09% (insulin glargine), whereby the difference is significant (p=0.0015). However, the investigators indicated that the clinical relevance of this effect was dubious.

Weight
See table 1. for the weight changes in the various studies. In the comparative study with insulin glargine the average weight loss in the liraglutide group was 1.8 kg after 26 weeks. The weight of patients treated with insulin glargine increased on average by 1.6 kg. The -3.43 kg difference was statistically significant (p<0.0001). The weight loss in the exenatide and liraglutide groups was comparable.

Conclusion:
One direct comparative study with liraglutide in combination with metformin and/or a SU-derivative achieved a significant decrease in the HbA1c-level and the fasting blood sugar levels and significantly more patients reached the <7% target value for the HbA1c <7% in comparison with exenatide in combination with metformin and/or a SU-derivative. However, the clinical relevance of the difference in the drop in the HbA1c is limited, the liraglutide dose in the study is higher than the usual dose, the doses of metformin and the SU-derivatives are unknown. It was also an open-label study. In one direct open-label study, liraglutide in combination with metformin and glimepiride significantly reduced the HbA1c-level in comparison with insulin glargine. In this study too, the 1.8 mg dose of liraglutide used is higher than the recommended 1.2 mg dose, which may have an extra effect on the drop in the HbA1c. Furthermore, there is doubt as to whether regulation with insulin was optimal in the comparative study with insulin. Weight loss occurs with liraglutide and exenatide, unlike when insulin is used.

4.b. Effectiveness
Effectiveness is assessed according to the delay in microvascular and macrovascular complications and the increased life expectancy.

Data demonstrating a beneficial effect of liraglutide with respect to microvascular and macrovascular complications and life expectancy are not available. The effect of exenatide on clinically relevant final outcomes has not been demonstrated either. The efficacy of insulin has been demonstrated, particularly on the occurrence of microvascular complications.

4.c. Side effects
The most frequent side effects of liraglutide are disorders of the gastrointestinal system: nausea and diarrhoea. These side effects occurred extremely often in clinical studies, whilst vomiting, constipation, abdominal pain and dyspepsia occurred frequently. These gastrointestinal side effects occur more frequently at the start of treatment with liraglutide. If treatment is continued these side effects are usually reduced within a number of days or weeks. Headache and

rhinopharyngitis also occurred often, and extremely often when liraglutide was used in combination with a SU-derivative. Severe hypoglycaemia was mainly seen in combination with a SU-derivative. On average 8.6% of the patients treated with liraglutide developed antibodies. See table 3 for a comparison of the side effects with exenatide and insulin glargine.

Table 3. Side effects mentioned in the 1B text for triple therapy

Treatment	Extremely frequent (≥ 1/10)	frequent (≥1/100, < 1/10)
Liraglutide*	hypoglycaemia, nausea, diarrhoea, vomiting	rhinopharyngitis, bronchitis, anorexia, reduced appetite, headache, dyspepsia, stomach-ache, constipation, flatulence, abdominal bloating, gastro-oesophageal reflux, viral gastroenteritis, tiredness, pyrexia
Exenatide**	hypoglycaemia, nausea, vomiting, diarrhoea	Reduced appetite, headache, dizziness, dyspepsia, stomach-ache, gastro-oesophageal reflux, abdominal bloating, hyperhidrosis, nerviness, asthenia
Insulin glargine***	hypoglycaemia	Lipohypertrophy, reactions at the injection site

* side effects reported in phase 3 studies with liraglutide + metformin + glimepiride or with liraglutide + metformin + rosiglitazone
** side effects reported in phase 3 studies versus placebo, insulin glargine, biphasic insulin aspart and added to metformin, SU-derivative or thiazolidones.
*** reported during clinical research.

Gastrointestinal side effects

In the Russel-Jones et al. study, nausea (13.9%) and diarrhoea (10.0%) occurred significantly more often in the liraglutide group than in the insulin glargine group (1.3% for both, p<0.0001). Dyspepsia (6.5%) and vomiting (6.5%) also occurred significantly more often in patients with liraglutide than during treatment with insulin glargine (resp. 1.7%, p=0.0042 and 0.4% p=0.0005).[10]
In the comparative study with exenatide the number of patients that reported gastrointestinal side effects in the liraglutide group (45.5%, n=107) was comparable with the exenatide group (42.7%, n=99). The incidence of nausea was the same in both groups (liraglutide: 25.5% (n=60); exenatide: 28.0% (n=65), although the nausea did not last as long in the liraglutide group: in week 26, 5 of the 202 patients in the liraglutide group reported nausea (3%) in comparison with 16 of the 186 (9%) in the exenatide group (p<0.0001).[11]

Hypoglycaemia

In the Russel-Jones et al. study, five patients (2.2%) reported a severe hypoglycaemia, five in the liraglutide group and none in the insulin group. In the comparative study with exenatide, two patients developed a severe hypoglycaemia, only in the exenatide group. All these patients were also taking an SU-derivative. The percentage of patients who developed mild hypoglycaemia

(blood sugar value <3.1 mmol/l) in the group treated with liraglutide was comparable with the percentage in the insulin glargine group (27.4% and 28.9%). In the comparison with exenatide, the frequency of mild hypoglycaemias was lower in patients treated with liraglutide (1.9 per patient per year) than in the exenatide group (2.6 hypoglycaemias per patient per year; p=0.0131).

Termination of treatment
In the Russel-Jones et al. study, in the liraglutide group 4.7% of the patients terminated treatment due to side effects and 2.1% in the insulin group. In the Buse et al. study, 33 of the 235 patients (14%) in the liraglutide group stopped with the study in comparison with 45 of the 232 patients (19%) in the exenatide group (not significant). The main reason for terminating treatment was side effects.

Discussion: As discussed in point 4a., the 1.8 mg dose of liraglutide is fairly high, whilst the incidence of side effects is comparable with patients treated with exenatide. There were few severe hypoglycaemias and these were mostly in combination with an SU-derivative. Patients generally were able to treat the mild hypoglycaemias themselves so these are less important for the comparison between treatments than the severe hypoglycaemias.

Conclusion:
The most frequent side effects with liraglutide are disorders of the gastrointestinal system: nausea and diarrhoea. In the comparative study the incidence of the gastrointestinal side effects is comparable for liraglutide and exenatide, although in the study the nausea of patients treated with liraglutide did not last as long.

4.d. Experience

More than 4,600 patients have been treated with liraglutide in clinical research. Liraglutide is not yet available throughout the world. Experience with liraglutide is limited. Exenatide has been available in the United States since June 2005. Sufficient experience with exenatide has been obtained in the meantime. Ample experience has been obtained with insulin.

Conclusion:
Experience with liraglutide is limited. Sufficient experience has been obtained with exenatide and ample experience with insulin.

4.e. Applicability

Table 4. Applicability of liraglutide, exenatide and insulin NPH

	liraglutide	**exenatide**	**Insulin NPH**
Warnings and precautions	*Elderly/children* - Lack of experience with children <18 years - Use on the elderly >75 years discouraged, due to limited experience	*Elderly/children* - Limited experience with a BMI ≤25 and with the elderly >75 years - Safety and efficacy have not been established among	*Elderly/children* No limitations *Liver/renal function disorder* -No limitations *Other*

	Liver/renal function disorder - Use in cases of liver function disorder and moderate renal insufficiency is discouraged due to limited experience. - Lack of experience in cases of severe renal insufficiency. *Other* - Use of GLP-1-analogues is associated with the risk of pancreatitis - Due to limited experience, use in cases of gastrointestinal disease is not recommended and caution is necessary in cases of heart failure -Intravenous or intramuscular injection is not recommended - Patient may need to check his/her own blood sugar in order to adjust the dose of the sulphonylureum derivative	children and adolescents <18 years *Liver/renal function disorder* - Extremely limited clinical experience with moderate renal insufficiency - Use in cases of terminal renal disease or severe renal insufficiency is not recommended - Treatment should be terminated in the event of a renal function disorder, vomiting, diarrhoea, etc. - The risk of hypoglycaemia increases in cases of mild renal insufficiency in combination with a sulphonylureum derivative *Other* - The use of GLP-1-analogues is associated with the risk of pancreatitis - Use is not recommended in cases of severe gastrointestinal disease - The frequency and severity of undesired gastrointestinal effects increased in cases of terminal renal diseases - Intravenous or intramuscular injection is not recommended - Patient may need to check their own blood	- long-acting insulin increases the risk of undetected night-time hypoglycaemias - When the blood sugar level drops rapidly, an alteration in the osmotic balance between the lens and the ocular fluid can lead to alterations in refraction and accommodation capacity - The correct injection technique must be used in order to avoid lipodystrophy at the injection site - insulin requirement may be reduced in cases of diseased adrenals, hypothysis or thyroid - hyperglycaemia can occur (especially in cases of type 1 DM) when the dose is inadequate - dose adjustment may be necessary during increased physical activity or an alteration in the diet or when switching to a different insulin - may never be administered i.v.

		sugar in order to adjust the dose of the sulphonylureum derivative.	
Pregnancy and lactation	Pregnancy: used discouraged Lactation: use discouraged	Pregnancy: use discouraged Lactation: use discouraged	Can be used with no risk to the unborn foetus
Contraindications	- diabetes mellitus type 1 - diabetic ketoacidosis	- diabetes mellitus type 1 - diabetic ketoacidosis	none
Interactions	- During simultaneous use with coumarin derivatives, more frequent INR checks are recommended, especially during initiation of therapy with liraglutide and during dose adjustments. - the combination with insulin is not recommended due to the lack of study data.	- Caution is required during simultaneous use of medicines with a narrow therapeutic application or with medicines that require careful clinical monitoring (antibiotics, contraceptives, proton pump inhibitors, statins, coumarin derivatives), because exenatide can reduce the degree and rapidity with which the orally administered medicines are absorbed - simultaneous use with insulin has not been studied - limited experience has been gained in combination with TZDs	The insulin requirement can be altered by other medicines: - *Reduction in the insulin requirement by:* androgenous and anabolic steroids, ACE-inhibitors, alcohol, MAO-inhibitors, octreotide and high doses (> 2 g) of salicylates. - *Increased insulin requirement by:* oral contraceptives, corticosteroids, thiazide diuretics, sympathicomimetics, thyroid hormones, danazol, protease inhibitors and atypical antipsychotics - β-Blockers can mask the adrenergic symptoms of hypoglycaemia

The use of insulin NPH is discussed in the table. The use of insulin glargine is not recommended in cases of diabetic ketoacidosis. Furthermore, there is a lack of data on safe use during pregnancy and lactation. Efficacy and safety have not been established for insulin glargine in cases of a liver function disorder and moderate to severe renal insufficiency.

Conclusion: Liraglutide and exenatide cannot be used as broadly as (NPH) insulin.

4.f. User-friendliness

Subcutaneously-administered liraglutide is used once daily at an arbitrary time of day, independently of mealtimes. Liraglutide should preferably be injected each day at about the same time. Similarly to exenatide, the dose of liraglutide does not need daily adjustment according to self-checked blood sugar levels. For the rest, self-checking blood sugar values may be necessary for adjustments in the dose of the sulphonylureum derivative, in order to reduce the risk of hypoglycaemia. In order to increase tolerance, treatment is initiated with 0.6 mg liraglutide; after at least 1 week the dose should be increased to 1.2 mg. The dose can be increased to 1.8 mg after at least 1 week for the minority of patients who benefit from taking 1.8 mg. Exenatide is administered subcutaneously, within 60 minutes of a prior meal either in the morning or evening. Treatment should be initiated with 5 µg twice daily for at least one month. Subsequently, it can be raised to the normal dose of 10 µg twice daily .

When insulin is used, where necessary patients may adjust the insulin dose by carrying out self-checks. To this end patients are instructed on the use of a blood sugar indicator, strips, target values and a diabetes diary. Depending on motivation and capacities, patients adjust their own dose according to a schedule or after consultation with a nurse or GP. In principle, under the present treatment schedule, in the event that the maximum possible or allowable dose of two different types of oral blood sugar reducing medicines is unsuccessful, then the addition of an evening dose of medium long-term acting NPH insulin is initiated. Regulation is based on the fasting glucose concentration; this does not require daily graphs. This schedule leads to a slight weight gain and few hypoglycaemias. Once target values have been reached, it is possible to suffice with less frequent (self-) checks.[2]

Conclusion:
In comparison with exenatide, liraglutide has the advantage that it can be injected independently of mealtimes and once per day. In comparison with insulin, liraglutide and exenatide have the advantage that self-checks are not necessary for dose adjustment. For the rest, only limited checks are required upon adding an evening dose of medium long-term acting NPH insulin and once target values have been reached.

5. Other considerations

5.a. Costs

Table 4. Pharmacy purchase price (excl. VAT)

Medicine		Dose	Costs (€) per month
liraglutide	2 pre-filled pens, each with 15 doses á 1.2 mg	1.2 mg/dag	95.71 euro
exenatide	1 pre-filled pen (60 doses á 10 µg)	10 µg twice daily (=standard dose)	96.20 euro
Insulin glargine	Vial 300 IE = 3 ml	40 IE (=DDD)	44.32 euro (vial)

(Lantus)	Disposable syringe 300 IE = 3 ml		45.46 euro (disposable syringe)
Insulin, isophane (Humulin NPH)	Vial 300 IE = 3 ml Disposable syringe 300 IE = 3 ml	40 IE (=DDD)	24.06 euro (vial) 27.56 euro (disposable syringe)

6. Value of liraglutide as indicated by the manufacturer

6.a. Manufacturer's claim

"Liraglutide has a therapeutic added value for patients with type 2 diabetes mellitus who are unsuccessful on the combination of metformin and an SU-derivative:
- In dual therapy: as combination therapy with metformin or an SU-derivative for patients in whom adequate glycaemic regulation cannot be achieved with the combination of metformin and an SU-derivative or who cannot use an SU-derivative or metformin due to a contraindication or a clinically relevant side effect.
- In triple therapy: as adjuvant to a combination therapy with 2 oral medicines for a sub-group of patients who cannot achieve adequate glycaemic regulation with the combination of 2 oral medicines."

6.b. CFH opinion

Dual therapy: On the basis of dual therapy study data, no added value could be demonstrated for liraglutide in dual therapy. If insufficient glycaemic regulation is achieved with metformin in monotherapy, then preference goes out to the addition of a SU-derivative because for this treatment long-term safety data are available as well as data on demonstrating effectiveness with respect to microvascular complications. Furthermore, preference will go out to oral therapy above a subcutaneous injection. Partly because of the low dose of rosiglitazone, no clear conclusions could be drawn from the Marre et al. study regarding a possible added value in the drop in HbA1c with liraglutide. The subcutaneous administration of liraglutide, along with insulin and exenatide, will be considered in the case that treatment metformin *and* a SU-derivative is ineffective.

Triple therapy comparison with insulin: The possible advantage of weight loss that occurs when liraglutide is used, and the fact that self-checks are generally not necessary, do not weigh up against the disadvantage of the lack of long-term data on the effectiveness and safety of liraglutide. This is a limitation in view of the chronic nature of the disorder. For patients who do not benefit from the combination of metformin and a SU-derivative at the maximum tolerated doses, preference goes out to the addition of insulin.

Triple therapy comparison with exenatide: The clinical relevance of the difference in the decrease of the HbA1c level in the study in which liraglutide was directly compared with exenatide is limited. The liraglutide dose is higher than the recommended dose, which may have a limited effect on the reduction in the

HbA1c. It was alo an open-label study. The greater effectiveness of liraglutide in comparison with exenatide has been insufficiently demonstrated.
The conclusion of the article by Neumiller et al., which discussed the LEAD studies with liraglutide, is that liraglutide has an advantage in comparison with exenatide due to the once daily dose, but that the effect on the HbA1c and body weight is the same.[5] Doggrell concluded that liraglutide was more effective than exenatide in the LEAD-6 study, but that this only applies for the formulas and doses used in the study.[22] The conclusion in the review article of Hansen et al., which discusses the GLP-1 receptor agonists, is that the only direct comparison between liraglutide and exenatide is an open-label study, and that more direct comparisons are required to be able to draw conclusions.[23] This supports the idea that there is insufficient evidence for determining an added value. The value of liraglutide is the same as that of exenatide.

7. CFH-advice

For patients who do not benefit from the combination treatment with metformin and a sulphonylureum derivative at the maximum tolerated dose, preference goes out to the addition of insulin. Due to the advantage of weight loss, the addition of exenatide or liraglutide may be considered, but only for patients with a BMI ≥35 kg/m², for whom weight loss remains problematic in spite of guidance. One should bear in mind that for liraglutide and exenatide, unlike insulin, there are no data on effectiveness (reduction of complications) and safety in the long term. Liraglutide can be administered once daily, independently of mealtimes.

8. Literature

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This text was approved by the Medicinal Products Reimbursement Committee during their meeting on 9th November 2009.

The data in this pharmacotherapeutic report will be incorporated into section 14/D/12 *of the Farmacotherapeutisch Kompas.*