IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Lixisenatide – Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment "Lixisenatid – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 13 June 2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Matthias Breidert, Altmühltal Clinics, Kösching Hospital, Teaching Hospital of the *Technische Universität München*, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

IQWiG employees involved in the dossier assessment:[2]

- Susanne Haag
- Thomas Kaiser
- Ulrike Lampert
- Stefan K. Lhachimi
- Regine Potthast
- Christoph Schürmann
- Min Zhou

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[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BMI	body mass index
BOT	basal supported oral therapy
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
ICT	intensified conventional insulin therapy
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
IU	international units
NPH	neutral protamine Hagedorn
RCT	randomized controlled trial
SGB	*Sozialgesetzbuch* (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug lixisenatide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 18 March 2013.

Research question

The benefit assessment of lixisenatide was conducted according to the approval status for the following therapeutic indication: treatment of adults with type 2 diabetes mellitus in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

Within this therapeutic indication, different subindications for the use of lixisenatide and thus different research questions result from the type of prior treatment.

According to the company's consultation request to the G-BA, an appropriate comparator therapy (ACT) was specified for each of the subindications[4]. This benefit assessment concurs with the G-BA's specification.

[4] According to Section 4.2 of the Summary of Product Characteristics (SPC), lixisenatide should not be given in combination with basal insulin and a sulfonylurea due to increased risk of hypoglycaemia. The research question is therefore not relevant for the benefit assessment.

Table 2: Overview of the ACT for lixisenatide

Research question	Subindication	ACT specified by the G-BA
1	Lixisenatide plus metformin	Sulfonylurea (glibenclamide or glimepiride) plus metformin
2	Lixisenatide plus sulfonylurea	
	▪ Subpopulation 2a[a]	Metformin plus sulfonylurea (glibenclamide or glimepiride) (Note: In this case, metformin is the preferred option over human insulin if it is suitable according to the SPC)
	▪ Subpopulation 2b[b]	Human insulin, if applicable plus sulfonylurea (glibenclamide or glimepiride)
3	Lixisenatide plus metformin plus sulfonylurea	Human insulin plus metformin
4[c]	Lixisenatide plus basal insulin, if applicable plus metformin	Human insulin, if applicable in combination with metformin (Note: applicable if metformin is suitable according to the SPC)

a: Patients for whom metformin is suitable as component of the ACT
b: Patients for whom metformin is unsuitable as component of the ACT due to a contraindication or an intolerance
c: Deviating from the company's approach, the subindications 4 and 5 (lixisenatide plus basal insulin [plus metformin]) were considered together in the research question 4 in the benefit assessment.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Deviations by the company

In the subindication **lixisenatide plus metformin** (research question 1), the company defined 2 specific patient groups, namely patients with contraindications or intolerance of sulfonylureas and patients with a body mass index (BMI) of over 30 kg/m^2. For both patient groups, the company specified comparator therapies that deviated from the G-BA's specification. The 2 subpopulations are not considered separately. The patients with contraindications or intolerance of sulfonylureas were not considered to be relevant subpopulations in the therapeutic indication. There was no deviating comparator therapy for patients with a BMI of over 30 kg/m^2.

In the subindication **lixisenatide plus metformin plus sulfonylurea** (research question 3), the company deviated from the ACT specified by the G-BA and cited a basal supported oral therapy (BOT) consisting of human insulin (neutral protamine Hagedorn [NPH]) plus metformin plus sulfonylurea. This triple combination is not considered to be medically advisable. The company's rationale was not accepted.

In the subindications **lixisenatide plus sulfonylurea** (research question 2b) and **lixisenatide plus basal insulin, if applicable plus metformin** (research question 4), the company limited itself to one part of the ACT specified by the G-BA (only human insulin [NPH] or only intensified conventional insulin therapy [ICT], each instead of human insulin). Only conclusions on the added benefit versus this specified comparator therapy could therefore be drawn from the respective studies.

Additional comment

According to the SPC, other combinations with lixisenatide (e.g. with acarbose) are also approved. The company did not provide any data on this, however, hence an added benefit cannot be derived.

Results

The company did not provide a direct comparative study versus the ACT for any of the 4 research questions considered in the benefit assessment.

Combination of lixisenatide plus metformin

The company conducted an adjusted indirect comparison versus the ACT. It identified 2 studies in the subindication (GetGoal-X, EFC10780), which, in principle, allow an indirect comparison using 2 intermediate comparators (intermediate comparator 1: exenatide plus metformin; intermediate comparator 2: sitagliptin plus metformin). In a bibliographical literature search, the company identified 3 studies it assigned to the indirect comparisons (intermediate comparator 1: Derosa 2010 and Derosa 2011; intermediate comparator 2: Arechavaleta 2011). The studies by Derosa were not relevant for the benefit assessment because the sulfonylureas (glibenclamide or glimepiride) used in the studies were not administered with approval-compliant starting dose and titration scheme. The study Arechavaleta 2011 was unsuitable for the indirect comparison because the population differed considerably from the one in the study EFC10780 (particularly with regards to the baseline HbA1c level, but also with regards to age and BMI). Because of this, the treatment effects resulting from the indirect comparison could not be interpreted.

Combination of lixisenatide plus sulfonylurea

The company did not identify any study on the combination of lixisenatide plus sulfonylurea versus the ACT (subpopulation 2a: metformin plus sulfonylurea [glibenclamide or glimepiride]; subpopulation 2b: human insulin, if applicable plus sulfonylurea).

Combination of lixisenatide plus metformin plus sulfonylurea

As the company deviated from the G-BA's ACT it did not present any relevant study.

Combination of lixisenatide plus basal insulin, if applicable plus metformin

The company presented an adjusted indirect comparison of lixisenatide plus basal insulin plus metformin versus an ICT, if applicable in combination with metformin. On the lixisenatide side, the company included a placebo-controlled approval study (GetGoal-L). The 4 studies (Robbins 2007, Ligthelm 2011, Rosenstock 2008, Fritsche 2010) it identified in a bibliographical literature search were unsuitable for an indirect comparison versus the study GetGoal-L for content-related reasons (e.g. different intermediate comparators, different patient populations, deviating treatment goals). Because of this, the treatment effects resulting from the indirect comparison could not be interpreted.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[5]

On the basis of the results presented, the extent and probability of the added benefit of the drug lixisenatide compared with the ACT is assessed as follows:

Table 3: Lixisenatide – extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
1	Lixisenatide plus metformin	Sulfonylurea (glibenclamide or glimepiride) plus metformin	Added benefit not proven
2	Lixisenatide plus sulfonylurea		
	▪ Subpopulation 2a[a]	Metformin plus sulfonylurea (glibenclamide or glimepiride) (Note: In this case, metformin is the preferred option over human insulin if it is suitable according to the SPC.)	Added benefit not proven
	▪ Subpopulation 2b[b]	Human insulin, if applicable plus sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
3	Lixisenatide plus metformin plus sulfonylurea	Human insulin plus metformin	Added benefit not proven
4	Lixisenatide plus basal insulin, if applicable plus metformin	Human insulin, if applicable in combination with metformin (Note: applicable if metformin is suitable according to the SPC)	Added benefit not proven
Other approved therapeutic combinations		None specified	Added benefit not proven

a: Patients for whom metformin is suitable as component of the ACT
b: Patients for whom metformin is unsuitable as component of the ACT due to a contraindication or an intolerance
ACT: appropriate comparator therapy; SPC: Summery of Product Characteristics

As the added benefit is not proven for any subindication, there are also no patient groups for whom a therapeutically important added benefit could be derived.

The G-BA decides on added benefit.

[5] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research question

The benefit assessment of lixisenatide was conducted according to the approval status [3] for the following therapeutic indication: treatment of adults with type 2 diabetes mellitus in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

Within this therapeutic indication, different subindications for the use of lixisenatide and thus different research questions result from the type of prior treatment.

According to the company's consultation request to the G-BA, an ACT was specified for each of the subindications.[6]

Table 4: Overview of the ACT for lixisenatide

Research question	Subindication	ACT specified by the G-BA
1	Lixisenatide plus metformin	Sulfonylurea (glibenclamide or glimepiride) plus metformin
2	Lixisenatide plus sulfonylurea	
	▪ Subpopulation 2a[a]	Metformin plus sulfonylurea (glibenclamide or glimepiride) (Note: In this case, metformin is the preferred option over human insulin if it is suitable according to the SPC)
	▪ Subpopulation 2b[b]	Human insulin, if applicable plus sulfonylurea (glibenclamide or glimepiride)
3	Lixisenatide plus metformin plus sulfonylurea	Human insulin plus metformin
4	Lixisenatide plus basal insulin, if applicable plus metformin	Human insulin, if applicable in combination with metformin (Note: applicable if metformin is suitable according to the SPC)
a: Patients for whom metformin is suitable as component of the ACT b: Patients for whom metformin is unsuitable as component of the ACT due to a contraindication or an intolerance ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

Research question 1: lixisenatide plus metformin

The benefit assessment of lixisenatide plus metformin was conducted according to the SPC for adult patients with type 2 diabetes mellitus, in whom metformin (together with diet and exercise) does not provide adequate glycaemic control [3]. Within this population, the company defined 2 specific patient groups in this subindication, namely patients with contraindications or intolerance to sulfonylureas (research question 1b in the company's dossier) and patients with a BMI of over 30 kg/m^2 (research question 7 in the company's

[6] According to Section 4.2 of the SPC, lixisenatide should not be given in combination with basal insulin and a sulfonylurea due to increased risk of hypoglycaemia. The research question is therefore not relevant for the benefit assessment.

dossier). For both patient groups, the company specified comparator therapies that deviated from the G-BA's specification. The company's specification was not accepted. The patients with contraindications or intolerance of sulfonylureas were not considered to be relevant subpopulations in the therapeutic indication. There was no deviating comparator therapy for patients with a BMI of over 30 kg/m^2. Hence both subpopulations were not considered separately (see Section 2.8.1.1 of the full dossier assessment).

Therapy with sulfonylureas (glibenclamide or glimepiride) plus metformin specified by the G-BA was used as ACT. This deviated from the company's approach, which cited sulfonylureas without limitation to the drugs specified by the G-BA as ACT and defined the patient groups cited above (see Section 2.8.1.1 of the full dossier assessment).

Research question 2: lixisenatide plus sulfonylurea

The benefit assessment of lixisenatide plus sulfonylurea was conducted according to the SPC for adult patients with type 2 diabetes mellitus, in whom sulfonylurea (together with diet and exercise) does not provide adequate glycaemic control [3]. The patient population for whom metformin is unsuitable as component of the ACT was specifically considered (subpopulation 2b, see Table 4). This was justified by the fact that sulfonylureas in monotherapy are mainly an option as second-choice drugs in case of metformin intolerance or a contraindication to metformin [4,5]. It can therefore be assumed that, if monotherapy with sulfonylureas was used, this was often the case because of metformin intolerance. Metformin cannot be used as combination partner in these patients (see Section 2.8.1.2 of the full dossier assessment).

Therapy with metformin plus sulfonylurea (glibenclamide or glimepiride) specified by the G-BA was used as ACT for the subpopulation 2a. This deviated from the company's approach, which cited metformin plus sulfonylureas without limitation to the drugs specified by the G-BA, as comparator therapy (see Section 2.8.1.1 of the full dossier assessment).

For patients for whom metformin is not an option as component of the ACT (subpopulation 2b, see Table 4), the therapy with human insulin, if applicable in combination with sulfonylurea (glibenclamide or glimepiride), which resulted from the G-BA's consultation documents, was used [6]. The company did not fully concur with the ACT specified by the G-BA: It cited sulfonylurea plus human insulin (NPH) as ACT and thus limited the use of human insulin to one basal insulin (NPH). The exclusive administration of a basal insulin (if applicable in combination with a sulfonylurea) was only one part of the ACT and further therapeutic schemes as ACT are reasonable and possible.

Research question 3: lixisenatide plus metformin plus sulfonylurea

The benefit assessment of lixisenatide plus metformin plus sulfonylurea was conducted according to the SPC for adult patients with type 2 diabetes mellitus, in whom metformin (together with diet and exercise) plus sulfonylurea does not provide adequate glycaemic control [3].

Therapy with human insulin plus metformin specified by the G-BA was used as ACT. This deviated from the company's approach, which cited BOT consisting of human insulin (NPH) plus metformin plus sulfonylurea as ACT. This triple combination is not considered to be medically advisable. The company's rationale was not accepted (see Section 2.8.1.3 of the full dossier assessment).

Research question 4: lixisenatide plus basal insulin, if applicable plus metformin

The benefit assessment of lixisenatide plus basal insulin, if applicable plus metformin, was conducted according to the SPC for adult patients with type 2 diabetes mellitus, in whom basal insulin, if applicable plus metformin (together with diet and exercise) does not provide adequate glycaemic control [3].

The subindications 4 (lixisenatide plus basal insulin) and 5 (lixisenatide plus basal insulin plus metformin) were considered together in the benefit assessment. This deviated from the company’s approach, which considered them separately. The G-BA also specified the same ACT for both subindications (human insulin, if applicable in combination with metformin).

Therapy with human insulin, if applicable in combination with metformin, specified by the G-BA was used as ACT. However, the company did not fully concur with the ACT specified by the G-BA: It cited an ICT consisting of a basal and a bolus insulin, if applicable in combination with metformin, as ACT. It specified the insulin therapy as normal insulin administered 3 to 4 times a day in combination with NPH insulin administered once to twice a day. The ICT only represents a part of the ACT specified by the G-BA. Other strategies may be medically advisable to optimize the treatment for the individual patient (e.g. conventional insulin therapy, BOT). Hence only conclusions on the added benefit versus this specified insulin therapy can therefore be drawn from studies with an ICT. A detailed explanation can be found in Section 2.8.1.4 of the full dossier assessment.

Summary

In summary, the assessment of lixisenatide in the different subindications was conducted versus the ACTs specified by the G-BA. These are shown in Table 4. The subindications 4 and 5 of the company were considered together in the benefit assessment.

The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs). Only studies of a minimal duration of 24 weeks were included.

Additional comment

According to the SPC, other combinations with lixisenatide (e.g. with acarbose) are also approved. The company did not provide any data on this; hence an added benefit cannot be derived.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.8.1 and 2.8.2.1 of the full dossier assessment.

2.3 Research question 1: combination of lixisenatide plus metformin

2.3.1 Information retrieval and study pool (research question 1)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study list on lixisenatide (studies completed up to 13 March 2013)
- Bibliographical literature search on lixisenatide (last search 7 March 2013)
- Search in trial registries for studies on lixisenatide (last search 11 March 2013)
- Bibliographical literature search on the ACT "sulfonylureas plus metformin" (last search 20 December 2012)
- Search in trial registries for studies on the ACT "sulfonylureas plus metformin" (last search 28 January 2013)

The data presented by the company were unsuitable to draw conclusions on the added benefit of the combination of lixisenatide plus metformin. The reasons for this are given below.

Direct comparisons

In the subindication "lixisenatide plus metformin", there was no study on the direct comparison with the ACT.

Indirect comparisons

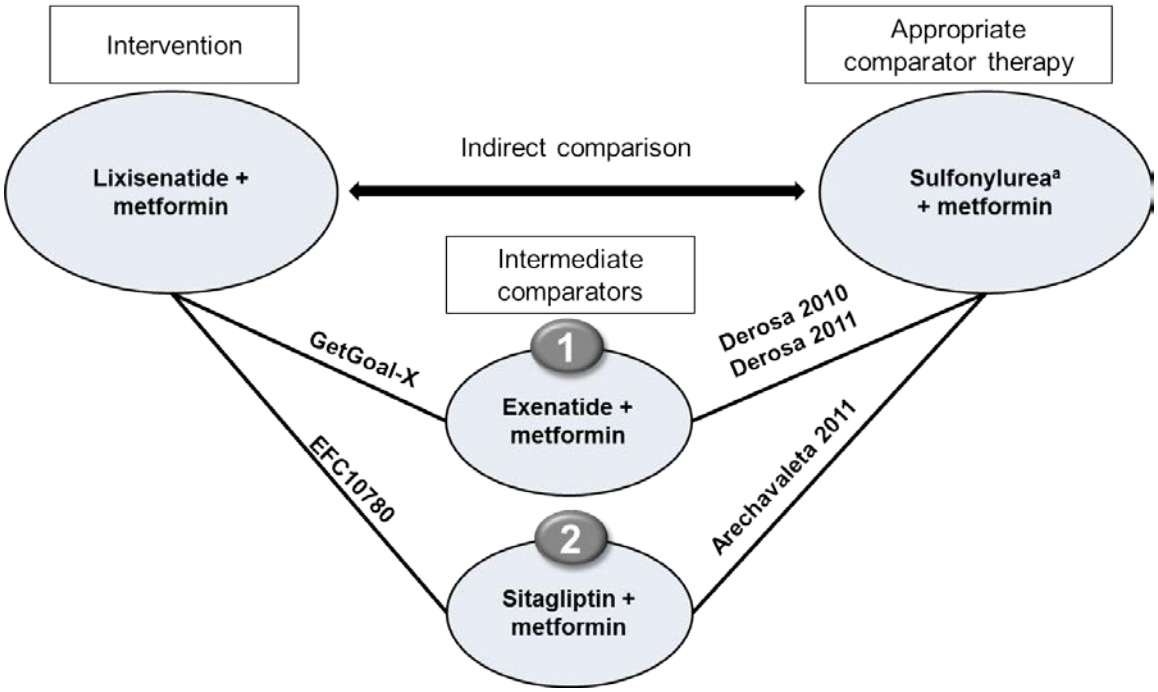
The company used 2 studies with the drug to be assessed in combination with metformin (GetGoal-X and EFC10780) to conduct an indirect comparison versus the ACT (sulfonylurea [glibenclamide or glimepiride] plus metformin). In principle, both studies were suitable for an indirect comparison versus the ACT. 2 different intermediate comparators result from the 2 studies:

- Indirect comparison 1 (study GetGoal-X): intermediate comparator "exenatide plus metformin"
- Indirect comparison 2 (study EFC10780): intermediate comparator "sitagliptin plus metformin"

In a bibliographical literature search, the company identified 3 studies it assigned to the indirect comparisons:

- Indirect comparison 1: Derosa 2010 [7], Derosa 2011 [8]
- Indirect comparison 2: Arechavaleta 2011 [9]

So the company presented the following data for its indirect comparison (see Figure 1).



a: According to the G-BA's specification limited to the 2 sulfonylureas glibenclamide and glimepiride. However, the company did not concur with this limitation in its dossier.

Figure 1: Data of the company for the indirect comparisons in the subindication "lixisenatide plus metformin" (research question 1)

Indirect comparison 1: intermediate comparator "exenatide plus metformin"

- Lixisenatide side: GetGoal-X
- Comparator side: Derosa 2010, Derosa 2011

Table 5 shows the key aspects of the study design of the 3 studies included by the company. Table 6 shows the characteristics of the interventions used in the studies and Table 7 shows the corresponding key characteristics of the patients included.

Table 5: Characteristics of the studies included by the company – RCT, indirect comparison 1: lixisenatide + metformin vs. sulfonylureas (glibenclamide or glimepiride) + metformin

Study	Study design	Population	Prior treatment	Study duration
GetGoal-X	RCT, open-label, parallel, active-controlled, multicentre	Patients with type 2 diabetes mellitus, diagnosed at least 1 year before screening, HbA1c ≥ 7.0% and ≤ 10% at time of screening	Metformin at a stable dose of at least 1500 mg/day for at least 3 months before screening	Primary study duration of 24 weeks[a], follow-up of 3 days
Derosa 2010	RCT, single-blind, parallel, active-controlled, multicentre	Patients with type 2 diabetes mellitus, 18 years or older of both sexes with inadequate glycaemic control (HbA1c > 8%) and overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2)	Metformin 1500 ± 500 mg (mean dose) and intolerant at maximum metformin dosage (3000 mg/day)	12 months
Derosa 2011	RCT, single-blind, parallel, active-controlled, multicentre	Patients with type 2 diabetes mellitus, 18 years or older of both sexes with inadequate glycaemic control (HbA1c > 8%) and overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2)	Prior treatment with metformin 1000 – 2000 mg/day and intolerant at maximum metformin dosage (2500 – 3000 mg/day)	12 months

a: A variable open-label prolongation was possible (up to 52 weeks).
BMI: body mass index; RCT: randomized controlled trial; vs.: versus

Table 6: Characteristics of the interventions – RCT, indirect comparison 1: lixisenatide + metformin vs. sulfonylureas (glibenclamide or glimepiride) + metformin

Study	Intervention	Comparator
GetGoal-X	▪ Lixisenatide titration (once a day): 10 µg for 1 week and 15 µg for 1 week, maintenance dose of 20 µg until the end of the treatment duration ▪ Metformin stable dose of 1500 – 3000 mg/day	▪ Exenatide titration (twice a day): 5 µg for 4 weeks, maintenance dose of 10 µg until the end of the treatment duration ▪ Metformin stable dose of 1500 – 3000 mg/day
Derosa 2010	▪ Glibenclamide initial dose: 2.5 mg 3 times a day for 4 weeks, maintenance dose of 5 mg 3 times a day until the end of the treatment duration[a] ▪ Metformin 1500 ± 500 mg/day	▪ Exenatide titration (twice a day): 5 µg for 4 weeks, maintenance dose of 10 µg until the end of the treatment duration ▪ Metformin 1500 ± 500 mg/day
Derosa 2011	▪ Glimepiride initial dose: 1 mg 3 times a day for 4 weeks, maintenance dose of 2 mg 3 times a day until the end of the treatment duration ▪ Metformin 1000 – 2000 mg/day	▪ Exenatide titration (twice a day): 5 µg for 4 weeks, maintenance dose of 10 µg until the end of the treatment duration ▪ Metformin 1000 – 2000 mg/day

a: The nonmicronized form of glibenclamide was used in the study. 15 mg are equivalent to 10.5 mg of the micronized form commonly used in Germany.
RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the study populations – RCT, indirect comparison 1: lixisenatide + metformin vs. sulfonylureas (glibenclamide or glimepiride) + metformin

Study Group	**N**	**HbA1c [%] mean (SD)**	**Age [years] mean (SD)**	**Sex [f/m] %**	**BMI [kg/m²] mean (SD)**
GetGoal-X					
Lixisenatide + M	318	8.0 (0.8)	57.3 (9.2)	52.5 / 47.5	33.7 (6.3)
Exenatide + M	316	8.0 (0.8)	57.6 (10.7)	40.8 / 59.2	33.5 (6.5)
Derosa 2010					
Exenatide + M	63	8.8 (0.7)	57 (8)	52.4 / 47.6	28.7 (1.5)
Glibenclamide + M	65	8.9 (0.8)	56 (7)	49.2 / 50.8	28.5 (1.4)
Derosa 2011					
Exenatide + M	57	8.7 (0.7)	56 (7)	50.9 / 49.1	28.4 (1.3)
Glimepiride + M	54	8.8 (0.8)	55 (6)	51.9 / 48.1	28.5 (1.4)

BMI: body mass index; f: female; M: metformin; m: male; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The study GetGoal-X was a randomized, active-controlled, open-label approval study sponsored by the company with a primary study duration of 24 weeks. It was conducted with patients with type 2 diabetes mellitus in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dose of at least 1500 mg/day (HbA1c $\geq$ 7.0% and $\leq$ 10% at the time of screening). Treatment with lixisenatide plus metformin was compared with a treatment with exenatide plus metformin in the study. All agents used were administered in compliance with their approval.

The 2 studies by Derosa (2010 and 2011) were very similar to each other in design. They were randomized, active-controlled, single-blind studies with a study duration of 12 months. They were conducted with patients with type 2 diabetes mellitus in whom no sufficient glycaemic control was achieved despite treatment with metformin at a medium dose of 1000 to 2000 mg/day (HbA1c $\geq$ 8 %). Overweight patients with a BMI of $\geq$ 25 kg/m^2 and < 30 kg/m^2 were enrolled. The study Derosa 2010 compared treatment with exenatide plus metformin with glibenclamide plus metformin [7]. The study Derosa 2011 compared treatment with exenatide plus metformin with glimepiride plus metformin [8]. The dosages of the sulfonylureas used and their titration schemes were problematic in both studies.

In the study Derosa 2010, all patients in the glibenclamide group received an initial dose of 2.5 mg 3 times a day. After 1 month, the patients changed to a maintenance dose of 5 mg 3 times a day. Thus all patients were treated with the maximum dose approved of 15 mg glibenclamide per day. This titration was conducted independent from the blood glucose level and without considering the individual risk of hypoglycaemia. According to the SPC on glibenclamide, treatment is to be started gradually, starting with a low dose of 2.5 to 5 mg of glibenclamide once a day. Depending on the metabolic situation, the dosage is to be increased

gradually to the daily dose that is therapeutically required. The maximum dose is 3 tablets of 5 mg a day [10][7].

The same approach was used in the study Derosa 2011, where another sulfonylurea was used (glimepiride: starting dose of 3 mg and maintenance dose of 6 mg, which is the maximum daily dose approved).

Hence in both studies, neither the starting dose nor the titration scheme used in the study complied with the approval requirements of the sulfonylureas administered. These studies did not allow to draw conclusions in comparison with the approval-compliant ACT. Accordingly, these studies could not be used for drawing conclusions on the added benefit of the combination of lixisenatide plus metformin in comparison with the ACT (sulfonylureas [glibenclamide or glimepiride] plus metformin).

Additionally, it should be pointed out that the patient populations in both Derosa studies differed considerably from the one in the GetGoal-X study (particularly considerably higher HbA1c level, considerably lower BMI, different metformin dosage).

In summary, the indirect comparison with the intermediate comparator "exenatide plus metformin" presented by the company was unsuitable to draw conclusions on the added benefit of the combination of lixisenatide plus metformin.

Indirect comparison 2: intermediate comparator "sitagliptin plus metformin"

- Lixisenatide side: EFC10780
- Comparator side: Arechavaleta 2011

Table 8 shows the key aspects of the study design of the 2 studies included by the company. Table 9 shows the characteristics of the interventions used in the studies and Table 10 shows the corresponding key characteristics of the patients.

[7] The nonmicronized form was used in the study. 15 mg are equivalent to 10.5 mg of the micronized form commonly used in Germany.

Table 8: Characteristics of the studies included by the company – RCT, indirect comparison 2: lixisenatide + metformin vs. sulfonylureas (glibenclamide or glimepiride) + metformin

Study	Study design	Population	Prior treatment	Study duration
EFC10780	RCT, double-dummy, double-blind, parallel, active-controlled, multicentre	Adult patients (18–< 50 years) with type 2 diabetes mellitus, diagnosed at least 1 year before screening, HbA1c ≥ 7.0% and ≤ 10%, BMI ≥ 30 kg/m^2	Metformin at a stable dose of at least 1500 mg/day for at least 3 months before screening	24 weeks, 3 days of follow-up
Arechavaleta 2011	RCT, double-blind, parallel, active-controlled, multi-national, multicentre	Patients with type 2 diabetes mellitus aged ≥ 18 years and with inadequate glycaemic control (HbA1c ≥ 6.5 and ≤ 9.0%)	Metformin at a stable dose of at least 1500 mg/day	30 weeks
BMI: body mass index; RCT: randomized controlled trial; vs.: versus				

Table 9: Characteristics of the interventions – RCT, indirect comparison 2: lixisenatide + metformin vs. sulfonylureas (glibenclamide or glimepiride) + metformin

Study	Intervention	Intermediate comparator
EFC10780	▪ Lixisenatide titration (once a day): 10 µg for 1 week and 15 µg for 1 week, maintenance dose of 20 µg until the end of the treatment duration	▪ Sitagliptin 100 mg/day (fixed dosage)
	▪ Metformin stable dose of ≥ 1500 mg/day	▪ Metformin stable dose of ≥ 1500 mg/day
Arechavaleta 2011	▪ Glimepiride initial dose: 1 mg/day Depending on the blood glucose levels measured by the patient, this dose could be increased during the first 18 weeks (according to the doctor's assessment in 1 to 2 mg steps; maximum dose: 6 mg/day)	▪ Sitagliptin 100 mg/day (fixed dosage)
	▪ Metformin ≥ 1500 mg/day	▪ Metformin ≥ 1500 mg/day
RCT: randomized controlled trial; vs.: versus		

Table 10: Characteristics of the study populations – RCT, indirect comparison 2: lixisenatide + metformin vs. sulfonylureas (glibenclamide or glimepiride) + metformin

Study Group	N	HbA1c [%] mean (SD)	Age [years] mean (SD)	Sex [f/m] %	BMI [kg/m^2] mean (SD)
EFC10780					
Lixisenatide + M	158	8.3 (0.9)	42.7 (5.2)	65.2 / 34.8	36.8 (7.3)
Sitagliptin + M	161	8.3 (0.8)	43.4 (4.7)	54.7 / 45.3	36.8 (6.3)
Arechavaleta 2011					
Sitagliptin + M	516	7.5 (0.7)	56.3 (9.7)	45 / 55	29.7 (4.5)
Glimepiride + M	519	7.5 (0.8)	56.2 (10.1)	46.2 / 53.8	30.2 (4.4)
BMI: body mass index; f: female; M: metformin; m: male; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus					

The study EFC10780 was a randomized, active-controlled, double-blind approval study sponsored by the company with a study duration of 24 weeks. Patients with type 2 diabetes mellitus aged between 18 and < 50 years and ongoing stable metformin treatment (at least 1500 mg/day) were recruited for the study. Overweight patients with a BMI of over 30 kg/m^2 and HbA1c levels of ≥ 7% and ≤ 10% at the time of screening (the mean level at the start of the study was 8.3% in both treatment arms) were enrolled. The study EFC10780 therefore explicitly included young overweight patients. Treatment with lixisenatide plus metformin was compared with a treatment with sitagliptin plus metformin in the study. All agents used were administered in compliance with their approval.

The study by Arechavaleta 2011 was a randomized, active-controlled, double-blind study with a study duration of 30 weeks. Patients with type 2 diabetes mellitus aged ≥ 18 years who had to have inadequate glycaemic control (HbA1c ≥ 6.5% and ≤ 9.0%) under stable metformin treatment (at least 1500 mg/day) were enrolled in the study. The mean age of the patients enrolled in the study was 56 years at the start of the study. Treatment with sitagliptin plus metformin was compared with a treatment with glimepiride plus metformin in the study.

The patient populations in the 2 studies EFC10780 and Arechavaleta 2011 differed considerably from each other (see Table 10). The treatment effects resulting from the indirect comparison could not be interpreted, particularly because of the differences in mean HbA1c levels at the time of screening (8.3% in EFC10780 versus 7.5 % in Arechavaleta 2011, in both treatment arms). A higher baseline HbA1c level can be reduced more, in absolute terms, than a lower baseline HbA1c level. This can also be seen in the comparison of the average HbA1c reduction by the intermediate comparator "sitagliptin plus metformin" used in both studies: In the study EFC10780, treatment with sitagliptin (100 mg/day) plus metformin (stable dose of ≥ 1500 mg/day) resulted in an average reduction of HbA1c of 0.7% after 24 weeks (HbA1c at the start of the study: 8.1%, HbA1c after 24 weeks: 7.4%). In Arechavaleta 2011, on the other hand, a reduction of only 0.4% was achieved in a similar amount of time (30 weeks) (HbA1c at the start of the study: 7.5%, HbA1c after 30 weeks: 7.1%). This shows that the blood-glucose lowering potency of lixisenatide (study EFC10780) and glimepiride (Arechavaleta 2011) cannot be compared in these 2 studies. It remains unclear whether the average HbA1c reduction would have been similar under lixisenatide and glimepiride if the patients in the 2 studies would have started from the same HbA1c level.

Moreover, the different rates of hypoglycaemia in the 2 studies are an indicator of the differing patient populations: Whereas in the study Arechavaleta 2011, 7% of the patients treated with sitagliptin plus metformin had symptomatic hypoglycaemia, in the study EFC10780, this was only the case for 2% in the corresponding treatment arm.

In addition, approximately 23% of the patients in the study Arechavaleta 2011 had an HbA1c level of below 7.0% [9]. Based on current findings, it cannot be assumed for a relevant part of the patients that they had inadequate glycaemic control that would have needed intensified treatment. Particularly in these patients – who were explicitly not included in the study

EFC10780 – intensifying blood-glucose lowering treatment is associated with an increased risk of hypoglycaemia. Yet it is precisely with regards to the outcome "symptomatic hypoglycaemia" that the company considered there to be an advantage of the treatment with lixisenatide plus metformin versus the treatment with sulfonylureas plus metformin, and it derived an added benefit for this indication on the basis of these results. However, differences cannot be interpreted in a meaningful way because of the differences in baseline HbA1c described.

Moreover, the populations of the 2 studies differed considerably regarding mean age and BMI. The study EFC10780 explicitly included young overweight patients (mean age: approximately 43 years; mean BMI: approximately 37 kg/m^2). The patients in the study by Arechavaleta 2011, on the other hand, were considerably older (mean age: approximately 56 years) and weighed less (mean BMI: approximately 30 kg/m^2).

In summary, the indirect comparison with the intermediate comparator "sitagliptin plus metformin" presented by the company was unsuitable to draw conclusions on the added benefit of the combination of lixisenatide plus metformin.

Further information about the result of information retrieval and the resulting study pool can be found in Module 4, Sections 4.3.1.1 and 4.3.2.2.1 of the dossier and in Section 2.8.2.3 of the full dossier assessment.

2.3.2 Results on added benefit (research question 1)

No relevant studies were available for the research question "lixisenatide plus metformin", neither for a direct comparison, nor for an indirect comparison. Hence the added benefit versus the ACT is not proven.

2.3.3 Extent and probability of added benefit (research question 1)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of lixisenatide plus metformin in comparison with the ACT specified by the G-BA (sulfonylureas [glibenclamide or glimepiride] plus metformin). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company, which derived a hint of a minor added benefit versus the ACT on the basis of the indirect comparison. Furthermore, the company claimed an indication of a minor added benefit for patients with a BMI of over 30 kg/m^2 versus the alternative comparator therapy "exenatide plus metformin" defined by the company.

2.4 Research question 2: combination of lixisenatide plus sulfonylurea

2.4.1 Information retrieval and study pool (research question 2)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study list on lixisenatide (studies completed up to 13 March 2013)
- Bibliographical literature search on lixisenatide (last search 7 March 2013)
- Search in trial registries for studies on lixisenatide (last search 11 March 2013)

The company did not identify any relevant study from the steps of information retrieval mentioned.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.8.2.1 and 2.8.2.3.1.2 of the full dossier assessment.

2.4.2 Results on added benefit (research question 2)

No relevant data were available for the 2 research questions 2a and 2b. Hence the added benefit versus the ACTs (subpopulation 2a: metformin plus sulfonylurea [glibenclamide or glimepiride]; subpopulation 2b: human insulin, if applicable plus sulfonylurea) is not proven.

2.4.3 Extent and probability of added benefit (research question 2)

Since no relevant study was presented for the 2 research questions 2a and 2b, there is no proof of an added benefit of lixisenatide plus sulfonylurea in comparison with the ACTs (subpopulation 2a: sulfonylurea [glibenclamide or glimepiride]; subpopulation 2b: human insulin, if applicable plus sulfonylurea). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result concurred with that of the company.

2.5 Research question 3: combination of lixisenatide plus metformin plus sulfonylurea

2.5.1 Information retrieval and study pool (research question 3)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study list on lixisenatide (studies completed up to 13 March 2013)
- Bibliographical literature search on lixisenatide (last search 7 March 2013)
- Search in trial registries for studies on lixisenatide (last search 11 March 2013)

The company targeted its information retrieval towards a different ACT (see Section 2.2). No relevant study for the comparison with the ACT specified by the G-BA was identified from the steps of information retrieval mentioned.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.8.2.1 and 2.8.2.3.1 of the full dossier assessment.

2.5.2 Results on added benefit (research question 3)

No relevant data were available for the research question "lixisenatide plus metformin plus sulfonylurea" versus the ACT (human insulin plus metformin). Hence the added benefit is not proven.

2.5.3 Extent and probability of added benefit (research question 3)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of lixisenatide plus metformin plus sulfonylurea in comparison with the ACT specified by the G-BA (human insulin plus metformin). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company. The company derived a hint of a minor added benefit versus the comparator therapy defined by the company on the basis of an indirect comparison.

2.6 Research question 4: combination of lixisenatide plus basal insulin, if applicable plus metformin

2.6.1 Information retrieval and study pool (research question 4)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier (for subindications 4 and 5):

- Study list on lixisenatide (studies completed up to 13 March 2013)
- Bibliographical literature search on lixisenatide (last search 7 March 2013)
- Search in trial registries for studies on lixisenatide (last search in trial registries on 11 March 2013)

Sources of the company in the dossier (for subindication 5):

- Bibliographical literature search on the ACT ICT (human insulin): 3 – 4 times normal insulin plus 1 – 2 times NPH insulin (if applicable in combination with metformin) (last search on 4 February 2013)
- Search in trial registries for studies on the ACT ICT (human insulin): 3 – 4 times normal insulin plus 1 – 2 times NPH insulin (if applicable in combination with metformin) (last search on 4 February 2013)

For the subindication 4 (lixisenatide plus basal insulin), the company itself did not identify any studies. For the subindication 5 (lixisenatide plus basal insulin plus metformin), it presented an adjusted indirect comparison. The subindications 4 and 5 are considered together in the benefit assessment.

The data presented by the company were unsuitable for assessing the added benefit of lixisenatide plus basal insulin, if applicable plus metformin, in comparison with the ACT. The reasons for this are given below.

Direct comparisons

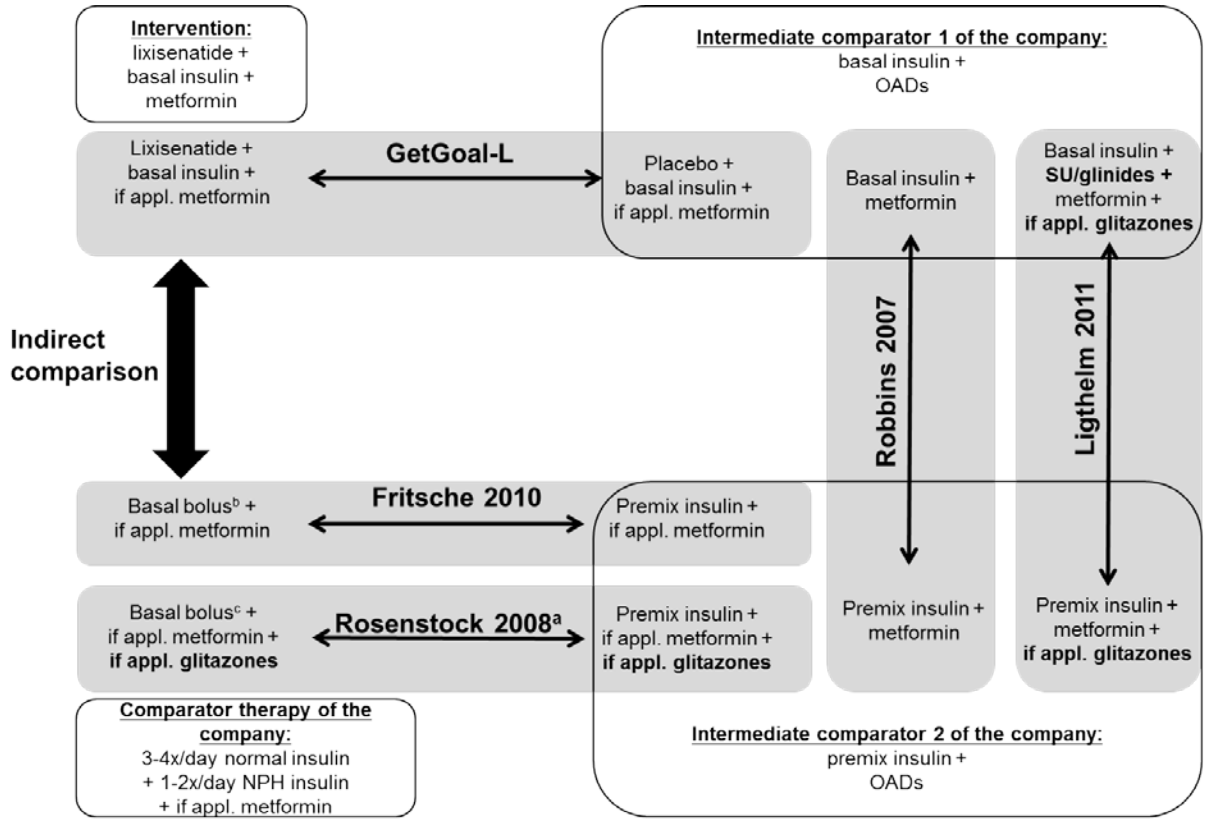
The company did not present any studies on the direct comparison versus the ACT in the subindication "lixisenatide plus basal insulin, if applicable plus metformin".

Indirect comparisons

The company used 1 study with the drug to be assessed in combination with basal insulin plus metformin (GetGoal-L) to conduct an indirect comparison versus the ACT (human insulin, if applicable in combination with metformin). In principle, the study met the inclusion criteria for the assessment.

In a bibliographical literature search for studies with the comparator therapy, the company identified 4 studies (Robbins 2007 [11], Ligthelm 2011 [12], Rosenstock 2008 [13], Fritsche 2010 [14]). These studies allow to conduct an indirect comparison versus the comparator therapy specified by the company (ICT, if applicable plus metformin) by chaining 2 intermediate comparators (1: basal insulin plus oral antidiabetics, 2: premix insulin plus oral antidiabetics).

The company presented the following data for its indirect comparison (see Figure 2).



a: In this study, 28.4% and 25.1% respectively of the patients received glitazones (with or without metformin).
b: Insulin glargine (once a day) plus insulin lispro (3 times a day)
c: Insulin glargine (once a day) plus insulin glulisine (3 times a day)
if appl.: if applicable; NPH: neutral protamine Hagedorn; OAD: oral antidiabetic; SU: sulfonylurea

Figure 2: Data of the company for the indirect comparison in the subindication "lixisenatide plus basal insulin, if applicable plus metformin" (research question 5)

Table 11 shows the key aspects of the study design of the studies included by the company. Table 12 shows the characteristics of the interventions used in the studies.

Table 11: Characteristics of the studies included by the company – RCT, indirect comparison: lixisenatide + basal insulin + if appl. metformin vs. human insulin + if appl. metformin

Study	Study design; study duration	Population	Prior treatment	Interventions (N)
GetGoal-L	RCT, double-blind, parallel, placebo-controlled, multicentre; 24 weeks	Patients with type 2 diabetes mellitus diagnosed at least 1 year before screening with inadequate glycaemic control (HbA1c ≥ 7.0% and ≤ 10% at the time of screening)	Stable dose of basal insulin[a] of at least 30 IU/day for at least 2 months before screening, if applicable metformin	▪ Lixisenatide + basal insulin + if appl. metformin (N = 329) ▪ Placebo + basal insulin + if appl. metformin (N = 167)
Robbins 2007	RCT, open-label, parallel, active-controlled, multicentre; 24 weeks	Patients with type 2 diabetes mellitus (35 – 75 years old) with an HbA1c between 6.5% and 11%	Metformin and/or sulfonylureas together with a stable dose of 0 - 2 insulin injections within the last 3 months	▪ Insulin glargine + metformin (N = 159) ▪ Premix insulin (insulin lispro mix 50) + metformin (N = 158)
Ligthelm 2011	RCT, open-label, parallel, active-controlled, multicentre; 24 weeks	Patients with type 2 diabetes mellitus with inadequate glycaemic control, HbA1c ≥ 8%, BMI ≤ 45 kg/m^2	Insulin glargine or NPH insulin (once to twice a day) in addition to metformin (≥ 1000 mg/day) ± additional oral antidiabetics	▪ Insulin glargine + metformin + sulfonylurea/glinides + if appl. glitazones (N = 143) ▪ Premix insulin (biphasic insulin aspart) + metformin + if appl. glitazone (N = 137)
Rosenstock 2008	RCT, open-label, parallel, active-controlled, multicentre; 24 weeks	Patients with type 2 diabetes mellitus aged 30 – 75 years and with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 12.0%)	Insulin glargine for at least 90 days (≥ 30 IU/day) in combination with oral antidiabetics as monotherapy, dual or triple combination (sulfonylureas or glinides, metformin and glitazones)	▪ Premix insulin (insulin lispro mix 50) + if appl. metformin + if appl. glitazones (N = 187) ▪ Basal-bolus therapy (insulin glargine + insulin lispro) + if appl. metformin + if appl. glitazones (N = 187)
Fritsche 2010	RCT, open-label, parallel, active-controlled, multicentre; 52 weeks	Patients with type 2 diabetes mellitus for ≥ 5 years aged 18 – 75 years; HbA1c 7.5% – 11.0%; BMI < 38 kg/m^2	Stable dose of a premix insulin (twice a day) ± metformin for ≥ 3 months before screening	▪ Premix insulin + if appl. metformin (N = 157) ▪ Basal-bolus therapy (insulin glargine and insulin glulisine) + if appl. metformin (N = 153)

a: The dose was only allowed to deviate by a maximum of ± 20% from the daily dose.

BMI: body mass index; if appl.: if applicable; IU: international units; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 12: Characteristics of the interventions: RCT, indirect comparison: lixisenatide + basal insulin + if applicable metformin vs. human insulin + if applicable metformin

Study	Group 1	Group 2
GetGoal-L	▪ Lixisenatide titration (once a day): 10 µg for 1 week and 15 µg for 1 week, maintenance dose of 20 µg until the end of the treatment duration	▪ Placebo
	▪ Basal insulin dose was to be maintained unchanged (± 20%) ▪ If applicable metformin stable dose of ≥ 1500 mg/day; applicable to approximately 79% of the patients in both treatment arms **Target value:** not explicitly formulated for both treatment arms	
Robbins 2007	▪ Basal insulin (insulin glargine) once a day	▪ Premix insulin twice a day (50% insulin lispro protamine suspension and 50% insulin lispro)[b]
	▪ Metformin stable maximum tolerated dose of 1000 to 2000 mg/day	
	Target value[a]: fasting blood glucose < 6.7 mmol/l (< 120 mg/dl)	**Target value[a]:** fasting blood glucose < 6.7 mmol/l (< 120 mg/dl) and postprandial blood glucose < 8.0 mmol/l (< 144 mg/dl)
Ligthelm 2011	▪ Basal insulin (insulin glargine) once a day ▪ Sulfonylurea/glinides	▪ Premix insulin twice a day (70% soluble insulin aspart and 30% protamine-bound insulin aspart)
	▪ Metformin 2000 – 2500 mg/day ▪ If applicable glitazones **Target value[a]:** fasting blood glucose < 110 mg/dl	
Rosenstock 2008	▪ Premix insulin 3 times a day (50% insulin lispro protamine suspension and 50% insulin lispro)[b]	▪ Basal-bolus therapy (insulin glargine [once a day] and insulin lispro [3 times a day])
	▪ If applicable metformin (dosage unclear) ▪ If applicable glitazones **Target value[a]:** preprandial blood glucose < 110 mg/dl[c]	
Fritsche 2010	▪ Premix insulin twice a day (NPH insulin + normal/fast-acting insulin in a ratio of 70/30 or 75/25)	▪ Basal-bolus therapy (insulin glargine [once a day] and insulin glulisine [3 times a day])
	▪ If applicable metformin, stable dose (approximately 58%)[d]	
	Target value[a]: preprandial blood glucose ≤ 100 mg/dl (5.6 mmol/l) and postprandial blood glucose ≤ 135 mg/dl (≤ 7.5 mmol/l)	**Target value[a]:** insulin glargine: preprandial blood glucose ≤ 100 mg/dl (≤ 5.6 mmol/l) insulin glulisine: postprandial blood glucose ≤ 135 mg/dl (≤ 7.5 mmol/l)

(continued on next page)

Table 12: Characteristics of the interventions: RCT, indirect comparison: lixisenatide + basal insulin + if applicable metformin vs. human insulin + if applicable metformin (continued)

a: The insulin dosage was to be adjusted to the blood glucose level according to the insulin titration scheme specified (until meeting the target values specified).
b: If the target value of the fasting blood glucose could not be met during the study, it was allowed to change from insulin lispro mix 50/50 to insulin lispro mix 75/25.
c: 2 different dose adjustment algorithms were used in the study: a more aggressive adjustment scheme based on the plasma glucose levels and the total daily insulin dose, and a more conservative adjustment scheme based exclusively on the plasma glucose levels.
d: Proportion of patients with metformin treatment at the start of the study; the metformin dosage at enrolment was to be maintained unchanged.
NPH: neutral protamine Hagedorn; RCT: randomized controlled trial; vs.: versus

The studies presented by the company were not relevant for the following reasons.

In the study by **Ligthelm 2011**, the intervention with the additional use of insulin secretagogues (sulfonylureas or glinides) and glitazones did not concur with the comparator therapy in the GetGoal-L study. It was therefore unsuitable as intermediate comparator [15].

In the study **Rosenstock 2008**, the intervention with the use of glitazones, which was additionally allowed, did not concur with the ACT, and the comparator therapy did not concur with the intermediate comparator 2 of the study Robbins 2007. It was unclear whether an interaction and which interaction the additional administration of glitazones caused with the ACT specified, and how big the impact of this interaction was on the treatment effects. Moreover, the glitazones are excluded from prescription because of a balancing of the relation of benefit and harm by the G-BA [16]. The study was therefore unsuitable for an indirect comparison versus the ACT (human insulin, if applicable plus metformin).

Hence the studies **GetGoal-L**, **Robbins 2007** and **Fritsche 2010** remain for a possible indirect comparison. Due to the content-related reasons explained below, these studies could not be compared with one another in an indirect comparison.

Patients with considerably different baseline HbA1c levels were enrolled in the 3 studies. The baseline HbA1c level in the study by Robbins 2007 (mean HbA1c 7.8%) was considerably lower than the baseline HbA1c levels in the studies GetGoal-L (mean HbA1c 8.4%) and Fritsche 2010 (mean HbA1c 8.5% [see Module 4, Section 4.3.2.8.1.4, page 406 ff.]). Because of these differences, the treatment effects resulting from the indirect comparison could not be interpreted. In addition, because of the different baseline HbA1c levels, the patients enrolled in the studies differed with regards to the risk of hypoglycaemia. This can also be seen when considering the results on the outcome "(any) hypoglycaemia" presented in the company's dossier (Module 4, Section 4.3.2.8.3.1, page 414 ff.). Whereas in the study GetGoal-L, approximately 22% of the patients under treatment with basal insulin, if applicable plus metformin, had hypoglycaemia, in the study by Robbins 2007, this was the case in approximately 48% in the corresponding treatment arm. An additional difficulty was that, in

the indirect comparison presented, the operationalization of individual outcomes differed in the different studies (e.g. hypoglycaemia). The definition of hypoglycaemic events had a big influence on the reliability of the results to reduce subjective and unwanted influencing, and has to be considered when interpreting the results.

Similarly to the risk of hypoglycaemia, the mean change of HbA1c levels can also not be interpreted in the indirect comparison because there was a different potential of reducing the HbA1c level depending on how high the baseline HbA1c was. The comparison of the treatment with premix insulin, if applicable plus metformin, in the studies Robbins 2007 and Fritsche 2007 shows the different potential to reduce the HbA1c level depending on the baseline HbA1c level (see Module 4, Section 4.3.2.8.3.3, page 428 ff.): In the study Robbins 2007 (baseline HbA1c level: 7.8%), the treatment with premix insulin and metformin resulted in a mean reduction of the HbA1c level by 0.7 percentage points after 24 weeks, whereas in the study by Fritsche 2010 (baseline HbA1c level: 8.5%) the HbA1c level was reduced by 1 percentage point after 24 weeks.

In addition, the treatment goals differed in the studies for the indirect comparison (see Table 12). In the GetGoal-L study, no treatment goals were given in the 2 treatment arms, i.e. the optimization of the treatment regimen used was not aimed at achieving a specified target blood glucose level. In contrast, treatment goals of near-normal blood glucose levels were specified in the studies by Robbins 2007 and Fritsche 2010. Due to the different baseline HbA1c levels, no concrete conclusion can be drawn on the influence of the treatment aimed at target levels on the changes of HbA1c levels. It is not certain however that the effects observed in the studies can be attributed to the drug combinations used. They may also have been caused solely by the different therapeutic strategies. No target blood glucose level was defined for the intervention (lixisenatide plus basal insulin) in the study GetGoal-L, but one was defined for the ACT (ICT, if applicable plus metformin) in the study by Fritsche 2010. The indirect comparison therefore did not constitute a comparison of the 2 drug combinations alone, but a comparison of 2 combined interventions (therapeutic strategy plus drug combination).

In addition, the patients enrolled in the studies GetGoal-L, Robbins 2007, and Fritsche 2010 also differed with regards to their prior treatment (see Table 11). Patients were enrolled in the studies GetGoal-L and Fritsche 2010 who had not achieved sufficient glycaemic control with a stable dose of a basal insulin (with or without metformin; GetGoal-L) or with an insulin therapy specified as premix insulin (with or without metformin; Fritsche 2010). In the study by Robbins 2007, in contrast, insufficient treatment with an insulin was not stipulated for all patients enrolled. The publication also showed that a relevant proportion of patients (approximately 21%) had not received prior insulin therapy, and therefore did not correspond to the target population [11]. Metformin and/or other sulfonylureas were allowed as oral antidiabetics in the prior therapy. Hence because of the differing prior treatments it could not be excluded that the patients enrolled in the studies were at different stages of disease, which may have resulted in different treatment effects in the studies.

Overall, the indirect comparison presented by the company could not be interpreted.

Further investigations

The non-adjusted comparison cited in the chapter "Further investigations" was not presented completely by the company, and was therefore not considered in the benefit assessment.

Further information about the result of information retrieval and the resulting study pool can be found in Module 4, Sections 4.3.1.1 and 4.3.2.8.1 of the dossier and in Section 2.8.2.3 of the full dossier assessment.

2.6.2 Results on added benefit (research question 4)

No relevant data were available for the research question "lixisenatide plus basal insulin, if applicable plus metformin", neither for a direct comparison, nor for an indirect comparison. Hence the added benefit versus the ACT is not proven.

2.6.3 Extent and probability of added benefit (research question 4)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of lixisenatide plus basal insulin, if applicable plus metformin, in comparison with the ACT specified by the G-BA (human insulin, if applicable in combination with metformin). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company. The company itself did not present any data for the combination of lixisenatide plus basal insulin (research question 4 of the company), and did not derive an added benefit. However, the company derived a hint of a minor added benefit versus the ACT on the basis of an indirect comparison for the combination of lixisenatide plus basal insulin plus metformin (research question 5 of the company).

2.7 Extent and probability of added benefit - summary

An overview of the extent and probability of added benefit for the various subindications of lixisenatide in comparison with the relevant ACTs is given below.

Table 13: Lixisenatide – extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
1	Lixisenatide plus metformin	Sulfonylurea (glibenclamide or glimepiride) plus metformin	Added benefit not proven
2	Lixisenatide plus sulfonylurea		
	▪ Subpopulation 2a[a]	Metformin plus sulfonylurea (glibenclamide or glimepiride) (Note: In this case, metformin is the preferred option over human insulin if it is suitable according to the SPC.)	Added benefit not proven
	▪ Subpopulation 2b[b]	Human insulin, if applicable plus sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
3	Lixisenatide plus metformin plus sulfonylurea	Human insulin plus metformin	Added benefit not proven
4	Lixisenatide plus basal insulin, if applicable plus metformin	Human insulin, if applicable in combination with metformin (Note: applicable if metformin is suitable according to the SPC)	Added benefit not proven
Other approved therapeutic combinations		None specified	Added benefit not proven

a: Patients for whom metformin is suitable as component of the ACT
b: Patients for whom metformin is unsuitable as component of the ACT due to a contraindication or an intolerance
ACT: appropriate comparator therapy; SPC: Summary of Product Characteristics

The G-BA decides on added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.8.2.8 of the full dossier assessment.

References for English extract

Please see full dossier assessment for full reference list.

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