Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Ertugliflozin (type 2 diabetes mellitus)

of 19 May 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient ertugliflozin in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 December 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 1 December 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 March 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of ertugliflozin compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements

submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of ertugliflozin.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of ertugliflozin (Steglatro) in accordance with the product information

Steglatro is indicated for the treatment of adults aged 18 and above with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindication.
- in addition to other medicinal products for the treatment of diabetes.

Therapeutic indication of the resolution (resolution of 19 May 2022):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) **Insulin-naïve** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

Appropriate comparator therapy for ertugliflozin:

Patient-individual therapy, taking into account the patient-individual therapeutic goal, depending on comorbidities, diabetes duration, any risks of hypoglycaemia, under selection of:

- metformin + sulphonylureas (glibenclamide or glimepiride),
- metformin + sitagliptin,
- metformin + empagliflozin,
- Metformin + liraglutide

a2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy for ertugliflozin:

- metformin + empagliflozin, or
- metformin + liraglutide, or
- Metformin + dapagliflozin

b1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Appropriate comparator therapy for ertugliflozin:

- metformin + empagliflozin + sitagliptin, or
- Metformin + empagliflozin + liraglutide

b2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Appropriate comparator therapy for ertugliflozin:

- metformin + empagliflozin + liraglutide, or
- metformin + dapagliflozin + liraglutide

c1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

Appropriate comparator therapy for ertugliflozin:

- human insulin + metformin

c2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for an insulin therapy**.

Appropriate comparator therapy for ertugliflozin:

- human insulin + metformin + empagliflozin, or
- human insulin + metformin + dapagliflozin, or
- human insulin + metformin + liraglutide

d1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Appropriate comparator therapy for ertugliflozin:

- Escalation of insulin therapy (conventional therapy (CT) if necessary + metformin or dulaglutide or intensified insulin therapy (ICT))

d2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Appropriate comparator therapy for ertugliflozin:

- Escalation of insulin therapy (conventional therapy (CT) if necessary + metformin or empagliflozin or liraglutide or dapagliflozin or intensified insulin therapy (ICT))

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. Any non-medicinal treatment considered as a comparator therapy must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. The following active ingredients or product classes are approved for the treatment of adults with type 2 diabetes mellitus: Alpha-glucosidase inhibitors, dipeptidyl-peptidase-4 (DPP-4) inhibitors (gliptins), glinides, GLP-1 receptor agonists (glutides/ incretin mimetics), metformin, SGLT-2 inhibitors (gliflozins), sulphonylureas and insulin (human insulin, insulin analogues).

on 2. A non-medicinal treatment cannot be considered as a comparator therapy in this therapeutic indication.

on 3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.

- Linagliptin (resolution of 21 February 2013; resolution of 16 May 2013),
- Lixisenatide (resolution of 5 September 2013),
- Saxagliptin/ metformin (resolution of 1 October 2013; resolution of 15 December 2016; resolution of 1 February 2018),
- Vildagliptin (resolution of 1 October 2013; resolution of 21 May 2015),
- Vildagliptin/ metformin (resolution of 1 October 2013),
- Canagliflozin (resolution of 4 September 2014),
- Insulin degludec (resolution of 16 October 2014; resolution of 20 August 2015; resolution of 16 May 2019),
- Canagliflozin/ metformin (resolution of 5 February 2015),
- Albiglutide (resolution of 19 March 2015),
- Insulin degludec/ liraglutide (resolution of 15 October 2015; resolution of 4 February 2016),
- Empagliflozin (resolution of 1 September 2016),
- Empagliflozin/ metformin (resolution of 1 September 2016),
- Saxagliptin (resolution of 15 December 2016),
- Sitagliptin (resolution of 15 December 2016; resolution of 22 March 2019),
- Sitagliptin/ metformin (resolution of 15 December 2016),
- Insulin glargine/ lixisenatide (resolution of 16 August 2018; resolution of 15 October 2020),
- Ertugliflozin/ sitagliptin (resolution of 1 November 2018),
- Empagliflozin/ linagliptin (resolution of 22 November 2019),
- Dapagliflozin (resolution of 19 December 2019),
- Dapagliflozin/ metformin (resolution of 19 December 2019),
- Dulaglutide (resolution of 16 July 2020),
- Semaglutide (resolution of 15 April 2021).

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

It is assumed that pharmacotherapy is only started after failure of a sole basic therapy (non-medicinal measures such as diet, exercise, etc.) and is always carried out in combination with this.

In all guidelines relevant in the therapeutic indication, medicinal therapy with metformin is named as the standard in the care of patients with type 2 diabetes

mellitus. It is assumed that anti-diabetic therapy is initially started with metformin monotherapy.

According to guideline recommendations, if glycaemic control is inadequate under metformin monotherapy, the administration of metformin is continued in the context of intensifying therapy with another medicine. In this respect, in the case of a possible abandonment of a treatment regimen with metformin, it must be explained in what way a therapy with metformin was not indicated for the patients.

According to the current dosing recommendation of metformin[2], metformin is eligible for a broader patient population, including patients with moderate renal failure (GFR ≥ 30 ml/min). Since only a small percentage of patients with type 2 diabetes mellitus have a metformin contraindication compared to the total population, patients with a metformin contraindication are not mentioned separately.

Based on the results of cardiovascular Outcome studies and the recommendations of the guideline[3], which indicate that the most robust data were shown in diabetics with existing cardiovascular disease, a distinction is made between patients **with and without manifest cardiovascular disease** for the determination of the appropriate comparator therapy. The operationalisation for defining patients with manifest cardiovascular disease should be based on criteria that are generally recognised and established in medical science.

In **patient group a1**, taking into account the patient-individual therapeutic goal, depending on comorbidities, diabetes duration, any risks of hypoglycaemia, a patient-individual therapy is determined by selecting the active ingredients sulphonylureas (glibenclamide or glimepiride), sitagliptin, empagliflozin, liraglutide, in each case as a dual combination with metformin.

In **patient group a1**, the sulphonylureas glibenclamide or glimepiride, which are classified as equivalent by the G-BA for the determination of the appropriate comparator therapy come into question. Glipizide is pharmacologically-therapeutically comparable to glimepiride in the group of sulphonylureas and is therefore accepted as a comparator in studies, according to previous resolutions in the field of type 2 diabetes mellitus.

For sitagliptin in the dual combination with metformin, positive study results are available from the P803, HARMONY 3 and P024 studies. For the dual combination sitagliptin with metformin, there was a hint for a minor additional benefit compared to the appropriate comparator therapy - determined in the resolution for sitagliptin - metformin in combination with sulphonylureas (glimepiride or glipizide) for all adults with type 2 diabetes mellitus and is therefore designated as part of the appropriate comparator therapy in the **patient group a1**.

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[2] Federal Institute for Medicinal Products and Medical Devices (2017): Metformin for the treatment of type 2 diabetes: Adoption of the EU implementation resolutions
https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RV_STP/m-r/metformin.html

[3] National Health Care Guideline (NVL): Type 2 diabetes, partial publication of the long version - 2nd edition, version 1 https://www.leitlinien.de/mdb/downloads/nvl/diabetes-mellitus/diabetes-2aufl-vers1.pdf [published on 25.03.2021]

For the dual combination empagliflozin with metformin, the 1245.28 study showed a hint for a minor additional benefit compared to the appropriate comparator therapy metformin in combination with sulphonylureas (glimepiride) for all adults with type 2 diabetes mellitus and was therefore designated as part of the appropriate comparator therapy in the **patient group a1**.

Furthermore, liraglutide is established in the care of insulin naïve patients with type 2 diabetes mellitus in particular; against this background, liraglutide is determined as part of the appropriate comparator therapy in **patient groups a1 and b1**.

In patients with manifest cardiovascular disease, there is, among others, evidence from cardiovascular endpoint studies on empagliflozin, liraglutide and dapagliflozin. This evidence on these active ingredients was taken into account in the early benefit assessment to derive an additional benefit or to determine the appropriate comparator therapy:

Positive study results are available for empagliflozin in the dual combination with metformin from the EMPA-REG Outcome study (exclusively in adults with type 2 diabetes mellitus with manifest cardiovascular disease). Based on the EMPA-REG Outcome study, there was a hint for a considerable additional benefit of empagliflozin in combination with other medication for the treatment of cardiovascular risk factors for the combination with one or more hypoglycaemic agents for adults with type 2 diabetes mellitus and manifest cardiovascular disease. Based on these results, empagliflozin was therefore likewise designated as part of the appropriate comparator therapy in these patient groups for patients with manifest cardiovascular disease **(patient group a2, b2, c2, d2)**.

Furthermore, the IQWiG rapid report on the long-term cardiovascular LEADER study is available for liraglutide, which showed advantages in overall mortality, strokes and the combined endpoint MACE in adults with type 2 diabetes mellitus and manifest cardiovascular disease, as well as in patients with renal failure with an eGFR < 60 ml/min/1.73 m^2. Based on these positive study results on cardiovascular endpoints, the G-BA concluded that liraglutide in addition to at least one other hypoglycaemic agent is to be considered as another therapy option of the appropriate comparator therapy for adults with type 2 diabetes mellitus with established cardiovascular disease and further medication for the treatment of cardiovascular risk factors **(patient group a2, b2, c2, d2)**.

In addition, there are positive study results for dapagliflozin from the DECLARE-TIMI 58 study in adults with inadequately controlled type 2 diabetes mellitus and with increased cardiovascular risk or manifest cardiovascular disease. Based on the DECLARE-TIMI 58 study, a hint for a minor additional benefit of dapagliflozin in combination with other medication for the treatment of cardiovascular risk factors was derived for the combination with one or more hypoglycaemic agents for type 2 diabetics with increased cardiovascular risk. Patients with increased cardiovascular risk as well as patients with manifest cardiovascular disease were enrolled in the DECLARE-TIMI 58 study. In adults with type 2 diabetes mellitus and at high cardiovascular risk, as well as in those with manifest cardiovascular disease, the priority is to prevent a cardiovascular event. Therefore, the G-BA concluded that dapagliflozin is to be

considered appropriate in addition to at least one other hypoglycaemic agent for patients with manifest cardiovascular disease **(patient group a2, b2, c2, d2)**.

For the other active ingredients for which cardiovascular endpoint studies are available and were assessed in the early benefit assessment, it was determined that an additional benefit is not proven.

In insulin-naïve adults with type 2 diabetes mellitus, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of two hypoglycaemic agents, in addition to diet and exercise, and for whom there is no indication for insulin therapy **(patient group b1, b2)**, an insulin-free multiple combination consisting of metformin and two other active ingredients previously named as part of the appropriate comparator therapy is to be used (b1: empagliflozin, liraglutide, sitagliptin; b2: empagliflozin, dapagliflozin, liraglutide). If a third active ingredient is added, it should be checked whether this can achieve sufficient glucose lowering or whether the start of insulin therapy should be considered.

Human insulin has been shown to reduce diabetes-related microvascular complications[4].

The indication for insulin therapy should be carefully considered.

According to the guideline, an insulin therapy is[3] recommended in the following situations: if the individual therapeutic goal is not achieved despite intensification with other anti-diabetics, in the case of metabolic derailments, in the case of administration of diabetogenic medicines (e.g. glucocorticoids) and in the case of severely impaired renal function. The start of insulin therapy includes the administration of human insulin in combination with metformin **(patient group c1)** or human insulin in combination with metformin and another of the active ingredients named as part of the appropriate comparator therapy (empagliflozin, dapagliflozin, liraglutide) **(patient group c2)**, in each case as part of a so-called basal supported oral therapy (BOT).

If insulin-dependent patients receiving BOT do not achieve adequate glycaemic control, the guideline recommends an escalation of insulin therapy, which is recommended in the context of conventional insulin therapy (CT, mixed insulin) or intensified conventional insulin therapy (ICT), taking into account the individual life situation of the patients **(patient group d)** and is determined as the appropriate comparator therapy in this patient group.

In insulin-dependent patients with inadequately controlled type 2 diabetes mellitus, positive results are available for dulaglutide in the AWARD-4 (without renal failure) and AWARD-7 (with moderate or severe renal failure) studies. In the corresponding sub-population of insulin-dependent patients, without or with renal failure, a hint for a minor additional benefit was derived in each case. Therefore, dulaglutide is determined for the patient population of insulin-experienced patients without

[4] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131):837-853

manifest cardiovascular disease in the context of a CT as an additional treatment option of the appropriate comparator therapy, if necessary **(patient group d1)**.

In addition to CT, metformin or dulaglutide **(patient group d1)** or metformin, empagliflozin, liraglutide or dapagliflozin **(patient group d2)** may be administered, if necessary.

In the context of ICT, the administration of an additional hypoglycaemic agent is not usually considered indicated.

Patients receiving insulin should be regularly checked to see whether the indication for insulin therapy still exists or whether de-escalation of insulin therapy is possible and indicated.

Sufficiently valid long-term safety data on the other active ingredients or product classes approved in the therapeutic indication are currently lacking, or an additional benefit could not be proven; these are therefore not considered as appropriate comparator therapy in the present assessment procedure.

It is assumed that for the treatment of comorbidities in adults with type 2 diabetes mellitus (such as hypertonia, dyslipoproteinaemia, CHD, etc.) and especially in patients with manifest cardiovascular disease, who are receiving further medication for the treatment of cardiovascular risk factors, a patient-individual treatment of the respective comorbidities, in particular by anti-hypertensive drugs, anticoagulants and/or lipid-lowering agents, is carried out in accordance with the state of medical knowledge, taking into account the special features of the disease of type 2 diabetes mellitus.

According to the current generally recognised state of medical knowledge, there are neither advantages nor disadvantages for insulin analogues compared to human insulin, but there are no long-term data with advantages regarding hard endpoints for insulin analogues. The benefit assessment also considers evidence from studies in which insulin analogues were used, provided that the results from studies with insulin analogues are transferable to human insulin. The authorisation status of the insulin analogues must be taken into account. Study results should be examined for possible effect modification by the type of insulin used if the studies were conducted with both human insulin and insulin analogues.

However, when comparing costs, the treatment costs for human insulin must be taken into account, as this was determined to be the appropriate comparator therapy.

Insulin glargine is an insulin analogue that was not explicitly named as a component of the appropriate comparator therapy, but it is nevertheless accepted as a suitable comparator in view of the current data basis.

The continuation of an inadequate therapy (regimen) for the treatment of type 2 diabetes mellitus does not correspond to the appropriate comparator therapy.

For the implementation of a patient-individual therapy within the scope of the appropriate comparator therapy (patient group a1: see options for selection) and in the escalation of insulin therapy (patient group d: CT or ICT) in a direct comparator study, a single comparator study is usually not sufficient. It is expected that the study doctor will be able to choose from several treatment options (multi-comparator study). The selection and, if necessary, limitation of treatment options must be justified.

The specific options of the appropriate comparator therapy in patient groups a2, b1, b2, c1 and c2 are all equally appropriate therapeutic alternatives (single comparator study).

It is assumed that comparable therapy regimes are used in the intervention and comparator arms (fair comparison of the anti-diabetic agents used, dosages, etc.).

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ertugliflozin is assessed as follows:

a1) **Insulin-naïve** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

An additional benefit is not proven.

a2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

An additional benefit is not proven.

b1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

An additional benefit is not proven.

b2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

An additional benefit is not proven.

c1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal**

therapy consisting of at least two hypoglycaemic agents, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

An additional benefit is not proven.

c2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for an insulin therapy**.

An additional benefit is not proven.

d1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

An additional benefit is not proven.

d2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

An additional benefit is not proven.

Justification:

Patient group a1)

The VERTIS SU study was submitted for the assessment of the additional benefit of ertugliflozin for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current therapy consisting of one hypoglycaemic agent.

VERTIS SU study

The three-arm, double-blind, randomised, parallel-group study investigates the comparison of ertugliflozin *(two arms)* versus glimepiride *(one arm)*, each in combination with metformin. A total of 1,316 adults with type 2 diabetes mellitus were treated *(approximately 430 per arm)*, who had an HbA1c value in the range ≥ 7.0% and ≤ 9.0% on stable prior therapy with at least 1,500 mg metformin per day. During the 104-week treatment phase, with either 5 mg or 15 mg ertugliflozin or glimepiride, study participants continued their stable metformin therapy.

Comparator therapy and suitability for the early benefit assessment

The patients enrolled in the VERTIS SU study did not achieve adequate glucose lowering with their previous metformin therapy and did not have any manifest cardiovascular disease. As comparator therapy in this patient group, the G-BA determined a patient-individual therapy, taking into account the patient-individual therapeutic goal, depending on comorbidities, diabetes duration, any risks of hypoglycaemia, under selection of:

- metformin + sulphonylureas (glibenclamide or glimepiride),
- metformin + sitagliptin,
- metformin + empagliflozin,
- metformin + liraglutide.

Depending on which of the above-mentioned criteria are present in the study participants examined, for example in the case of a higher risk of hypoglycaemia, taking into account the patient-individual therapeutic goal, the most suitable patient-individual therapy is to be selected from the given therapeutic alternatives. This requires the implementation of a multi-comparator study. In contrast, the VERTIS SU study is a single comparator study in which all participants without exception and without consideration of the above criteria were treated with glimepiride. The pharmaceutical company did not demonstrate that the single comparator design with the choice of glimepiride and metformin is the most appropriate therapeutic option of the appropriate comparator therapy for all enrolled patients.

Instead of titration according to individual blood glucose target values, depending on age, comorbidities, diabetes duration, risk of adverse effects, etc., as recommended in the guideline, glimepiride was administered in the study according to a predefined, fixed titration scheme. Thus, in patients who initially received 1 mg glimepiride per day, the glimepiride dose should be increased up to a maximum dose of 6 mg or 8 mg (depending on the marketing authorisation) for blood glucose values ≥ 110 mg/dl (6.1 mmol/l). However, the titration scheme does not correspond to the marketing authorisation of glimepiride in Germany. This is because, according to the product information of glimepiride, gradual titration is only recommended up to a dose of 4 mg per day, and the maximum recommended dosage of 6 mg improves the effect only in specific cases. Therefore, the approach chosen in the study is not considered appropriate.

Conclusion of the VERTIS SU study

In summary, the VERTIS SU study is unsuitable for the early benefit assessment. On the one hand, the study design with the choice of a single comparator for all study participants does not correspond to the appropriate comparator therapy's specification of a patient-individual therapy by selecting the most suitable treatment option named by the appropriate comparator therapy, taking into account the patient-individual therapeutic goal, depending on comorbidities, diabetes duration, any risks of hypoglycaemia. On the other, the selected fixed titration scheme of glimepiride neither corresponds to the recommendations of the product information of glimepiride nor to the recommendations of the guideline for an individualised therapeutic goal.

An additional benefit is not proven.

Patient group a2)

The VERTIS CV study was submitted for the assessment of the additional benefit of ertugliflozin for the treatment of adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current therapy consisting of one hypoglycaemic agent.

See the following explanations on the cross-patient aspects of populations a2), b2), c2) and d2) on page 15 et seq.

An additional benefit is not proven.

Patient group b1)

No data were submitted for the assessment of the additional benefit of ertugliflozin for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current therapy consisting of two hypoglycaemic agents - without insulin.

An additional benefit is not proven.

Patient group b2)

The VERTIS CV study was submitted for the assessment of the additional benefit of ertugliflozin for the treatment of adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous therapy consisting of two hypoglycaemic agents - without insulin.

See the following explanations on the cross-patient aspects of populations a2), b2), c2) and d2) on page 15 et seq.

An additional benefit is not proven.

Patient group c1)

No data were provided for the assessment of the additional benefit of ertugliflozin for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current therapy consisting of at least two hypoglycaemic agents and for whom insulin therapy is indicated for the first time.

An additional benefit is not proven.

Patient group c2)

The VERTIS CV study was submitted for the assessment of the additional benefit of ertugliflozin for the treatment of adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous therapy consisting of at least two hypoglycaemic agents and for whom insulin therapy is indicated for the first time.

See the following explanations on the cross-patient aspects of populations a2), b2), c2) and d2) on page 15 et seq.

An additional benefit is not proven.

Patient group d1)

No data were provided to assess the additional benefit of ertugliflozin for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current insulin regimen.

An additional benefit is not proven.

Patient group d2)

The VERTIS CV study was submitted to assess the additional benefit of ertugliflozin for the treatment of adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current insulin regimen.

See the following explanations on the cross-patient aspects of populations a2), b2), c2) and d2) on page 15 et seq.

An additional benefit is not proven.

Cross-patient aspects relating to patient groups a2), b2), c2) and d2)

The pharmaceutical company submits the VERTIS CV study for the early benefit assessment of ertugliflozin for the treatment of adults with type 2 diabetes mellitus and a cardiovascular disease. The patients studied had inadequately controlled type 2 diabetes mellitus and were assigned to different therapy levels; consequently, they received different anti-diabetic treatments as prior therapy. The study medication in the intervention and comparator arm was given in addition to a so-called standard therapy of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities. Due to the design of the VERTIS CV study, the total population includes patients with different comparator therapies. These cannot be divided into the different patient populations according to the specifications of the G-BA for the corresponding patient groups as well as the comparator treatment options defined in each case. Therefore, an assessment of the VERTIS CV study can only be made across the patient groups a2), b2), c2) and d2) together.

VERTIS CV study

The VERTIS CV study is a three-arm, placebo-controlled, double-blind, randomised, parallel-group study. VERTIS CV was a multicentre study conducted multinationally from the end of 2013 to the end of 2019. Adults ≥ 40 years with type 2 diabetes mellitus and an HbA1c value of 7.0 to 10.5% and atherosclerosis of the coronary, cerebral or peripheral vascular system were enrolled in the study. Both therapy-naïve and pretreated patients could be enrolled in the study.

A total of 8,246 patients were randomised in a 1:1:1 ratio to the treatment arms of 5 mg ertugliflozin (N = 2,752), 15 mg ertugliflozin (N = 2,747) or placebo (N = 2,747), each administered in addition to existing concomitant therapy for the treatment of type 2 diabetes mellitus, cardiovascular risk factors and comorbidities. In the two ertugliflozin intervention arms, no patient-individual dose adjustments were planned.

Comparator therapy and suitability for the early benefit assessment

The pharmaceutical company submits the VERTIS CV study for its question of treatment with ertugliflozin in addition to a standard therapy compared to a standard therapy, in each case in adults with type 2 diabetes mellitus and at high cardiovascular risk. In the VERTIS CV study, almost all patients in the comparator arm received anti-diabetic therapy right from the start, consisting of treatment with one, two or three or more anti-diabetic agents. Just under half of the study participants were treated with insulin or insulin analogues. Due to the different prior antidiabetic therapies or therapy levels in the study population, the patients studied cannot be assigned to the corresponding patient groups and options of the appropriate comparator therapy.

According to the G-BA's stipulation, the additional benefit must be demonstrated for all patient groups with manifest cardiovascular disease compared to the appropriate comparator therapy determined. However, the pharmaceutical company does not separately present the results for all of the questions of the G-BA presented under point *"2.1.2 Appropriate comparator therapy"* for patients with manifest cardiovascular disease (populations a2, b2, c2 and d2).

Irrespective of this, the VERTIS CV study is also unsuitable for the pharmaceutical company's intended comparison of ertugliflozin versus standard therapy in type 2 diabetics with high cardiovascular risk.

According to the study protocol, treatment with SGLT-2 inhibitors was not allowed. Accordingly, only one subject in the comparator arm received an SGLT-2 inhibitor at the start of the study, while three subjects were given SGLT-2 inhibitors at the final visit. The percentage of patients receiving GLP-1 receptor agonists (GLP-1-RA) in the comparator arm was only 3.1% at the start of the study and 5.6% at the final visit. In contrast to the standard anti-diabetic therapy carried out in the study, the German Health Care Guideline[3] and the European Guidelines[5] explicitly recommend treatment with SGLT-2 inhibitors or with GLP-1-RA in this patient population. The SGLT-2 inhibitors empagliflozin or dapagliflozin and the GLP-1 RA liraglutide are also named as therapeutic options of the appropriate comparator therapy in the respective sub-populations with manifest cardiovascular disease. For a correct implementation of the appropriate comparator therapy, it would have been expected that the patients in the comparator arm would have been treated with the active ingredients mentioned above. The treatment of the patients in the control arm of the VERTIS CV study is not considered adequate, also against the background that the current guideline recommendations were disregarded in the anti-diabetic therapy in the comparator arm. For this reason, the study is not used for the early benefit assessment.

Conclusion of the VERTIS CV study

Overall, the submitted VERTIS CV study is unsuitable for assessing the additional benefit of ertugliflozin for the treatment of inadequately controlled type 2 diabetes mellitus in adult patients with manifest cardiovascular disease. The reason for this is that the appropriate comparator therapy was not implemented in the study. The guidelines specifically recommend therapy with an SGLT-2 inhibitor or a GLP-1 RA for this patient population. This was not done in the study. An additional benefit is not proven.

2.1.4 Summary of the assessment

This is the early benefit assessment of the new active ingredient ertugliflozin (Steglatro) approved for the treatment of adults with inadequately controlled type 2 diabetes mellitus.

In the therapeutic indication under consideration, 4 patient populations are included, each with two sub-populations.

Patient group a1)

For insulin-naïve adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of one hypoglycaemic agent, in addition to diet and exercise, the following was determined by the G-BA as an appropriate comparator therapy:
Patient-individual therapy, taking into account the patient-individual therapeutic goal, depending on comorbidities, diabetes duration, any risks of hypoglycaemia, under selection of:

- metformin + sulphonylureas (glibenclamide or glimepiride),
- metformin + sitagliptin,
- metformin + empagliflozin,
- metformin + liraglutide.

[5] Cosentino et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal Volume 41, Issue 2, 7 January 2020, Pages 255–323, https://doi.org/10.1093/eurheartj/ehz486

The VERTIS SU study was presented for the direct comparison of ertugliflozin with glimepiride, both in combination with metformin, in type 2 diabetics who had not achieved adequate glycaemic control with metformin monotherapy. Glimepiride was administered according to a fixed titration schedule in which glimepiride was to be increased up to a maximum dose of 6 mg or 8 mg for blood glucose levels ≥ 110 mg/dl. This approach is neither in line with the marketing authorisation of glimepiride nor with the guideline recommendations for an individualised therapeutic goal. In addition, it was not demonstrated that the single comparator design with the choice of glimepiride and metformin is the most appropriate treatment option of the appropriate comparator therapy for all enrolled patients. The study is therefore unsuitable and an additional benefit is not proven.

Patient group a2)

For insulin-naïve adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of one hypoglycaemic agent, in addition to diet and exercise, the following was determined by the G-BA as an appropriate comparator therapy:

- metformin + empagliflozin, or
- metformin + liraglutide, or
- metformin + dapagliflozin.

The cardiovascular endpoint VERTIS CV study was presented, in which ertugliflozin was investigated in addition to a standard therapy compared to a standard therapy, both in adults with type 2 diabetes mellitus and at high cardiovascular risk. Due to the different prior antidiabetic therapies or therapy levels in the study population, the patients studied cannot be assigned to the corresponding patient groups and options of the appropriate comparator therapy. It is noted that almost no SGLT-2 inhibitors were used in the comparator arm and GLP-1 RA was administered in only about 5%. This means that the active ingredients of the sub-populations with manifest cardiovascular disease named in the appropriate comparator therapy were not taken into account. The guideline recommendations for the treatment of this patient population were disregarded. The study is therefore unsuitable and an additional benefit is not proven.

Patient group b1)

For insulin-naïve adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of two hypoglycaemic agents, in addition to diet and exercise, and for whom there is no indication for insulin therapy, the following was determined by the G-BA as the appropriate comparator therapy:

- metformin + empagliflozin + sitagliptin, or
- metformin + empagliflozin + liraglutide.

No data were presented versus the appropriate comparator therapy. An additional benefit is not proven.

Patient group b2)

For insulin-naïve adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of two hypoglycaemic agents, in addition to diet and exercise, and for whom there is no indication for insulin therapy, the following was determined by the G-BA as an appropriate comparator therapy:

- metformin + empagliflozin + liraglutide, or
- metformin + dapagliflozin + liraglutide.

The cardiovascular endpoint VERTIS CV study was presented, in which ertugliflozin was investigated in addition to a standard therapy compared to a standard therapy, both in adults with type 2 diabetes mellitus and at high cardiovascular risk. Due to the different prior antidiabetic therapies or therapy levels in the study population, the patients studied cannot be assigned to the corresponding patient groups and options of the appropriate comparator therapy. It is noted that almost no SGLT-2 inhibitors were used in the comparator arm and GLP-1 RA was administered in only about 5%. This means that the active ingredients of the sub-populations with manifest cardiovascular disease named in the appropriate comparator therapy were not taken into account. The guideline recommendations for the treatment of this patient population were disregarded. The study is therefore unsuitable and an additional benefit is not proven.

Patient group c1)

For insulin-naïve adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least two blood glucose-lowering drugs in addition to diet and exercise, and for whom there is an indication for insulin therapy, the following was determined by the G-BA as the appropriate comparator therapy:

- human insulin + metformin.

No data were presented versus the appropriate comparator therapy. An additional benefit is not proven.

Patient group c2)

For insulin-naïve adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of at least two hypoglycaemic agents, in addition to diet and exercise, and for whom there is an indication for insulin therapy, the following was determined by the G-BA as the appropriate comparator therapy:

- human insulin + metformin+ empagliflozin, or
- human insulin + metformin + dapagliflozin, or
- human insulin + metformin + liraglutide.

The cardiovascular endpoint VERTIS CV study was presented, in which ertugliflozin was investigated in addition to a standard therapy compared to a standard therapy, both in adults with type 2 diabetes mellitus and at high cardiovascular risk. Due to the different prior antidiabetic therapies or therapy levels in the study population, the patients studied cannot be assigned to the corresponding patient groups and options of the appropriate comparator therapy. It is noted that almost no SGLT-2 inhibitors were used in the comparator arm and GLP-1 RA was administered in only about 5%. This means that the active ingredients of the sub-populations with manifest cardiovascular disease named in the appropriate comparator therapy were not taken into account. The guideline recommendations for the treatment of this patient population were disregarded. The study is therefore unsuitable and an additional benefit is not proven.

Patient group d1)

For insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous insulin regimen, in addition to diet and exercise, the following was determined by the G-BA to be an appropriate comparator therapy:

- escalation of insulin therapy (conventional therapy (CT) if necessary + metformin or dulaglutide or intensified insulin therapy (ICT)).

No data were presented versus the appropriate comparator therapy. An additional benefit is not proven.

Patient group d2)

For insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous insulin regimen, in addition to diet and exercise, was determined by the G-BA to be an appropriate comparator therapy:

- escalation of insulin therapy (conventional therapy (CT) if necessary + metformin or empagliflozin or liraglutide or dapagliflozin or intensified insulin therapy (ICT)).

The cardiovascular endpoint VERTIS CV study was presented, in which ertugliflozin was investigated in addition to a standard therapy compared to a standard therapy, both in adults with type 2 diabetes mellitus and at high cardiovascular risk. Due to the different prior antidiabetic therapies or therapy levels in the study population, the patients studied cannot be assigned to the corresponding patient groups and options of the appropriate comparator therapy. It is noted that almost no SGLT-2 inhibitors were used in the comparator arm and GLP-1 RA was administered in only about 5%. This means that the active ingredients of the sub-populations with manifest cardiovascular disease named in the appropriate comparator therapy were not taken into account. The guideline recommendations for the treatment of this patient population were disregarded. The study is therefore unsuitable and an additional benefit is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information from the statement of the pharmaceutical company and the IQWiG addendum.

Overall, the estimated number of patients in the SHI target population is subject to uncertainty.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Steglatro (active ingredient: ertugliflozin) at the following publicly accessible link (last access: 10 March 2022):

https://www.ema.europa.eu/en/documents/product-information/steglatro-epar-product-information_en.pdf

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2022).

Treatment duration and consumption

With regard to consumption, the average annual consumption was determined by indicating the number of tablets or individual doses. The daily dosages recommended in the product information were used as a basis for calculation and, if necessary, appropriate ranges were formed. The costs of a possibly necessary titration phase have not been shown, since the anti-diabetic therapy is a continuous long-term therapy and the titration is patient-individual.

The information on treatment duration and dosage was taken from the corresponding product information.

For ertugliflozin, the starting dose is 5 mg once daily. If additional lowering of glucose lowering is necessary, the dose can be increased to 15 mg once daily.

For metformin, starting doses of 500 mg or 850 mg two to three times daily are recommended, but dose increases up to 3,000 mg metformin daily are possible; the total daily dose is usually divided into 2 - 3 doses. Therefore, a potency of 1,000 mg metformin/tablet is used as the basis for the cost representation.

Glibenclamide therapy should be started at 1.75 - 3.5 mg and increased to up to 10.5 mg glibenclamide per day if metabolic control is inadequate. The calculation is based on an potency of 3.5 mg, as this dosage covers all the dosages recommended in the product information.

Therapy with glimepiride in combination with other oral anti-diabetic agents should be started with a low initial dose and gradually increased to the maximum tolerated daily dose depending on the desired metabolic state. The recommended maximum dose is 6 mg, but according to

the product information, glimepiride doses of more than 4 mg per day only improve the effect in isolated cases.

The recommended dose of sitagliptin is 100 mg once daily.

The starting dose of liraglutide is 0.6 mg; after one week, this is increased to 1.2 mg. According to the product information, patients may benefit from a further increase in the dose from 1.2 mg to 1.8 mg. The appropriate dose of liraglutide is injected subcutaneously daily (pre-filled pen).

For empagliflozin, a starting dose of 10 mg once daily is recommended as combination therapy with other hypoglycaemic agents, including insulin. If metabolic control is inadequate, the dose may be increased to 25 mg once daily. Therefore, both strength sizes are taken into account for the cost representation.

The recommended dose of dapagliflozin is 10 mg once daily.

For dulaglutide, as part of combination therapy with other medicines, a starting dose of 0.75 mg once weekly is recommended, which can be increased to a maximum dose of 4.5 mg once weekly.

A variety of different insulin dosing schemes are available for insulin therapy. In addition, according to the insulin dosing scheme used, the amount of insulin and the frequency of application must be individually adjusted according to the patient's physical activity and lifestyle. To ensure comparability of costs, simplified assumptions have been made for the presentation of treatment duration and dosage. In the "Treatment duration" table, the treatment mode for human insulin (NPH insulin or mixed insulin) is shown as "1 - 2 x daily", although the frequency of application may differ for individual patients. According to the product information[6], the average insulin requirement is often 0.5 - 1.0 I.U. per kg body weight per day. The basal insulin daily requirement is usually 40 - 60 % of the insulin daily requirement, the remaining requirement is covered accordingly by meal-dependent bolus insulin. Three main meals are assumed when calculating bolus insulin consumption. This information was used to calculate the dose of insulin per patient.

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. Therefore, an average bodyweight of 77.0 kg is assumed for the bodyweight according to the official representative statistics "Microcensus 2017"[7].

Consequently, weight differences between women and men as well as the fact that the bodyweight of patients with type 2 diabetes mellitus may be higher than the average value of 77.0 kg are not taken into account for the cost calculation.

Treatment period:

a1) **Insulin-naïve** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current**

[6] Product information for Insuman® Basal, last revised: April 2018.

[7] Statistisches Bundesamt (Federal Statistical Office), Wiesbaden 02.08.2018. Microcensus 2017: questions on health - body measurements of the population 2017 [online]. [Accessed: 13.09.2018]. https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

medicinal therapy consisting of one hypoglycaemic agent, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ertugliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[8]:				
Metformin	continuously, 2-3 x daily	365	1	365
Glibenclamide	continuously, 1-1-2 x daily	365	1	365
Glimepiride	continuously, 1 x daily	365	1	365
Sitagliptin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	continuously, 2-3 x daily	365	1	365
Glibenclamide or	continuously, 1-2 x daily	365	1	365
Glimepiride	continuously, 1 x daily	365	1	365
Sitagliptin	continuously, 1 x daily	365	1	365
Empagliflozin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365

a2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

[8] As an example of the combination of ertugliflozin with a hypoglycaemic agent, metformin, glibenclamide, glimepiride, sitagliptin and liraglutide are presented as possible concomitant active ingredients

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ertugliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[9]:				
Metformin	continuously, 2-3 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	continuously, 2-3 x daily	365	1	365
Empagliflozin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Dapagliflozin	continuously, 1 x daily	365	1	365

b1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ertugliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[10]:				
Metformin	continuously, 2-3 x daily	365	1	365

[9] As an example of the combination of ertugliflozin with a hypoglycaemic agent, metformin and liraglutide are presented as possible concomitant active ingredients.

[10] As an example of the combination of ertugliflozin with two hypoglycaemic agents, metformin, sitagliptin and liraglutide are presented as possible concomitant active ingredients.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Sitagliptin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	continuously, 2-3 x daily	365	1	365
Sitagliptin	continuously, 1 x daily	365	1	365
Empagliflozin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365

b2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ertugliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[11]:				
Metformin	continuously, 2-3 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	continuously, 2-3 x daily	365	1	365
Empagliflozin	continuously, 1 x daily	365	1	365

[11] As an example of the combination of ertugliflozin with two hypoglycaemic agents, metformin and liraglutide are presented as possible concomitant active ingredients.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Liraglutide	continuously, 1 x daily	365	1	365
Dapagliflozin	continuously, 1 x daily	365	1	365

c1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ertugliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[12]:				
Metformin	continuously, 2-3 x daily	365	1	365
Human insulin (NPH-insulin)	continuously, 1-2 x daily	365	1	365
Appropriate comparator therapy				
Metformin	continuously, 2-3 x daily	365	1	365
Human insulin (NPH-insulin)	continuously, 1-2 x daily	365	1	365

c2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for insulin therapy**.

[12] As an example for the use in diabetics with a first-time indication for insulin therapy, the combination of ertugliflozin with human insulin (NPH insulin) with and without metformin in the context of basal supported oral therapy (BOT) is shown.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ertugliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[13]:				
Metformin	continuously, 2-3 x daily	365	1	365
Human insulin (NPH-insulin)	continuously, 1-2 x daily	365	1	365
Appropriate comparator therapy				
Metformin	continuously, 2-3 x daily	365	1	365
Empagliflozin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Dapagliflozin	continuously, 1 x daily	365	1	365
Human insulin (NPH-insulin)	continuously, 1-2 x daily	365	1	365

d1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ertugliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[14]:				

[13] As an example for the use in type 2 diabetics with a first-time indication for insulin therapy, the combination of ertugliflozin with human insulin (NPH insulin) with and without metformin in the context of a basal supported oral therapy (BOT) is shown

[14] The combination with mixed insulin is shown as an example of the combination of ertugliflozin with insulin in the context of escalation of insulin therapy, in this case with conventional insulin therapy.]

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Conventional insulin therapy (CT) mixed insulin	continuously, 1-2 x daily	365	1	365
Appropriate comparator therapy				
Metformin	continuously, 2-3 x daily	365	1	365
Dulaglutide	continuously, 1 x every 7 days	52.1	1	52.1
Conventional insulin therapy (CT) mixed insulin	continuously, 1-2 x daily	365	1	365
Intensified insulin therapy (ICT) Human insulin (NPH-insulin) Human insulin (bolus insulin)	continuously, 1-2 x daily continuously, 3 x daily	365 365	1 1	365 365

d2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ertugliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[15]:				
Metformin	continuously, 2-3 x daily	365	1	365
Conventional insulin therapy (CT) mixed insulin	continuously, 1-2 x daily	365	1	365

[15] The combination with mixed insulin is shown as an example of the combination of ertugliflozin with insulin in the context of escalation of insulin therapy, in this case with conventional insulin therapy.]

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Metformin	continuously, 2-3 x daily	365	1	365
Empagliflozin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Dapagliflozin	continuously, 1 x daily	365	1	365
Conventional insulin therapy (CT) mixed insulin	continuously, 1-2 x daily	365	1	365
Intensified insulin therapy (ICT) Human insulin (NPH-insulin) Human insulin (bolus insulin)	 continuously, 1-2 x daily continuously, 3 x daily	 365 365	 1 1	 365 365

Consumption:

a1) **Insulin-naïve** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have been treated **with their previous medicinal therapy consisting of one**

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ertugliflozin	5 mg - 15 mg	5 mg - 15 mg	1 x 5 mg 1 x 15 mg	365 365	365 x 5 mg - 365 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed[8]:					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Glibenclamide	1.75 mg - 7 mg /3.5 mg	1.75 mg - 10.5 mg	0.5 x 3.5 mg - 3 x 3.5 mg	365 365	182.5 x 3.5 mg - 1095 x 3.5 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Glimepiride	1 mg - 6 mg	1 mg - 6 mg	1 x 1 mg - 1 x 6 mg	365 365	365 x 1 mg - 365 x 6 mg
Sitagliptin	100 mg	100 mg	1 x 100 mg	365	365 x 100 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Glibenclamide	1.75 mg - 7 mg /3.5 mg	1.75 mg - 10.5 mg	0.5 x 3.5 mg - 3 x 3.5 mg	365 365	182.5 x 3.5 mg - 1095 x 3.5 mg
Glimepiride	1 mg - 6 mg	1 mg - 6 mg	1 x 1 mg - 1 x 6 mg	365 365	365 x 1 mg - 365 x 6 mg
Sitagliptin	100 mg	100 mg	1 x 100 mg	365	365 x 100 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365 365	365 x 10 mg - 365 x 25 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg

a2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease,** who have been treated **with their previous medicinal therapy consisting of one**

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ertugliflozin	5 mg - 15 mg	5 mg - 15 mg	1 x 5 mg 1 x 15 mg	365 365	365 x 5 mg - 365 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed[9]:					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg

[16] According to the product information, each pre-filled pen contains 18 mg liraglutide in 3 ml solution, corresponding to 10 - 15 single doses. Packs of 2, 5 and 10 pre-filled pens are available.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365 365	365 x 10 mg - 365 x 25 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg

b1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ertugliflozin	5 mg - 15 mg	5 mg - 15 mg	1 x 5 mg 1 x 15 mg	365 365	365 x 5 mg - 365 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed[10]:					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Sitagliptin	100 mg	100 mg	1 x 100 mg	365	365 x 100 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Sitagliptin	100 mg	100 mg	1 x 100 mg	365	365 x 100 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365 365	365 x 10 mg - 365 x 25 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg

b2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ertugliflozin	5 mg - 15 mg	5 mg - 15 mg	1 x 5 mg 1 x 15 mg	365 365	365 x 5 mg - 365 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed[11]:					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365 365	365 x 10 mg - 365 x 25 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg

c1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ertugliflozin	5 mg - 15 mg	5 mg - 15 mg	1 x 5 mg 1 x 15 mg	365 365	365 x 5 mg - 365 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed[12]:					
Metformin	500 mg -	1000 mg -	1 x 1000 mg -	365	365 x 1000 mg -

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	1000 mg	3000 mg	3 x 1000 mg	365	1095 x 1000 mg
Human insulin (NPH-insulin)	0.5 - 1 I.U. / kg BW	38.5 - 77 I.U.	1 x 38.5 I.U. - 1 x 77 I.U.	365 365	14,052.5 I.U. - 28105 I.U.
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Human insulin (NPH-insulin)	0.5 - 1 I.U. / kg BW	38.5 - 77 I.U.	1 x 38.5 I.U. - 1 x 77 I.U.	365 365	14,052.5 I.U. - 28105 I.U.

c2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for insulin therapy**.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ertugliflozin	5 mg - 15 mg	5 mg - 15 mg	1 x 5 mg 1 x 15 mg	365 365	365 x 5 mg - 365 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed[13]:					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Human insulin (NPH-insulin)	0.5 - 1 I.U. / kg BW	38.5 - 77 I.U.	1 x 38.5 I.U. - 1 x 77 I.U.	365 365	14,052.5 I.U. - 28105 I.U.
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365 365	365 x 10 mg - 365 x 25 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Human insulin (NPH-insulin)	0.5 - 1 I.U. / kg BW	38.5 - 77 I.U.	1 x 38.5 I.U. - 1 x 77 I.U.	365 365	14,052.5 I.U. - 28105 I.U.

d1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ertugliflozin	5 mg - 15 mg	5 mg - 15 mg	1 x 5 mg 1 x 15 mg	365 365	365 x 5 mg - 365 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed[14]:					
Conventional insulin therapy (CT) Mixed insulin	0.5 - 1 I.U. / kg BW	38.5 I.U. - 77 I.U.	1 x 38.5 I.U. - 1 x 77 I.U.	365 365	14,052.5 I.U. - 28105 I.U.
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Dulaglutide	0.75 mg - 4.5 mg	0.75 mg - 4.5 mg	1 x 0.75 mg - 1 x 4.5 mg	52.1 52.1	52.1 x 0.75 mg - 52.1 x 4.5 mg
Conventional insulin therapy (CT) Mixed insulin	0.5 - 1 I.U. / kg BW	38.5 I.U. - 77 I.U.	1 x 38.5 I.U. - 1 x 77 I.U.	365 365	14,052.5 I.U. - 28105 I.U.
Intensified insulin therapy (ICT) Human insulin (NPH-insulin) Human insulin (Bolus insulin)	 0.2 - 0.6 I.U./kg BW 0.2 - 0.6 I.U./kg BW	 15.4 - 46.2 I.U. 15.4 - 46.2 I.U.	 1 x 15.4 I.U. - 1 x 46.2 I.U. 1 x 15.4 I.U. - 1 x 46.2 I.U.	 365 365 365 365	 5,621 I.U. - 16863 I.U. 5621 I.U. - 16,863 I.U.

d2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ertugliflozin	5 mg - 15 mg	5 mg - 15 mg	1 x 5 mg 1 x 15 mg	365 365	365 x 5 mg - 365 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed[15]:					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Conventional insulin therapy (CT) Mixed insulin	0.5 - 1 I.U. / kg BW	38.5 I.U. - 77 I.U.	1 x 38.5 I.U. - 1 x 77 I.U.	365 365	14,052.5 I.U. - 28105 I.U.
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	1000 mg - 3000 mg	1 x 1000 mg - 3 x 1000 mg	365 365	365 x 1000 mg - 1095 x 1000 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365 365	365 x 10 mg - 365 x 25 mg
Liraglutide[16]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365 365	365 x 1.2 mg - 365 x 1.8 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Conventional insulin therapy (CT) Mixed insulin	0.5 - 1 I.U. / kg BW	38.5 I.U. - 77 I.U.	1 x 38.5 I.U. - 1 x 77 I.U.	365 365	14,052.5 I.U. - 28105 I.U.
Intensified insulin therapy (ICT) Human insulin (NPH-insulin)	0.2 - 0.6 I.U./kg BW	15.4 - 46.2 I.U.	1 x 15.4 I.U. - 1 x 46.2 I.U.	365 365	5,621 I.U. - 16863 I.U.
Human insulin (Bolus insulin)	0.2 - 0.6 I.U./kg BW	15.4 - 46.2 I.U.	1 x 15.4 I.U. - 1 x 46.2 I.U.	365 365	5621 I.U. - 16,863 I.U.

Costs:

Costs of the medicinal products:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

The fixed reimbursement rate was used as the basis for calculating the treatment costs for the active ingredients metformin, glibenclamide and glimepiride, human insulin and mixed insulin.

In the case of conventional insulin therapy, the costs for mixed insulin (i.e. a human insulin preparation in a specific mixing ratio of 30% normal insulin to 70% basal insulin) were used as a basis.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Ertugliflozin 5 mg	98 FCT	€ 127.84	€ 1.77	€ 6.45	€ 119.62
Ertugliflozin 15 mg	98 FCT	€ 127.84	€ 1.77	€ 6.45	€ 119.62
If necessary + metformin[17] 1,000 mg	180 FCT	€ 19.08	€ 1.77	€ 0.62	€ 16.69
If necessary + glibenclamide[17] 3.5 mg	180 TAB	€ 15.23	€ 1.77	€ 0.31	€ 13.15
If necessary + glimepiride 1 mg[17]	180 TAB	€ 17.17	€ 1.77	€ 0.47	€ 14.93
If necessary + glimepiride 6 mg[17]	180 TAB	€ 82.82	€ 1.77	€ 5.67	€ 75.38
If necessary + sitagliptin 100 mg	98 FCT	€ 137.66	€ 1.77	€ 0.00	€ 135.89
If necessary + liraglutide 18 mg	100 - 150 SD	€ 570.94	€ 1.77	€ 30.99	€ 538.18
If necessary + human insulin (NPH insulin)[17]	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95
If necessary + conventional insulin therapy (CT) Mixed insulin[17]	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95
Appropriate comparator therapy					
Metformin[17] 1,000 mg	180 FCT	€ 19.08	€ 1.77	€ 0.62	€ 16.69

[17] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Glibenclamide[17] 3.5 mg	180 TAB	€ 15.23	€ 1.77	€ 0.31	€ 13.15
Glimepiride 1 mg[17]	180 TAB	€ 17.17	€ 1.77	€ 0.47	€ 14.93
Glimepiride 6 mg[17]	180 TAB	€ 82.82	€ 1.77	€ 5.67	€ 75.38
Sitagliptin 100 mg	98 FCT	€ 137.66	€ 1.77	€ 0.00	€ 135.89
Empagliflozin 10 mg	100 FCT	€ 192.64	€ 1.77	€ 10.04	€ 180.83
Empagliflozin 25 mg	100 FCT	€ 192.64	€ 1.77	€ 10.04	€ 180.83
Liraglutide 18 mg	100 - 150 SD	€ 570.94	€ 1.77	€ 30.99	€ 538.18
Dapagliflozin 10 mg	98 FCT	€ 269.73	€ 1.77	€ 14.31	€ 253.65
Dulaglutide 0.75 mg	12 SFI	€ 287.72	€ 1.77	€ 15.30	€ 270.65
Dulaglutide 4.5 mg	12 SFI	€ 287.72	€ 1.77	€ 15.30	€ 270.65
Human insulin (NPH insulin) [17]	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95
Mixed insulin[17]	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95
Human insulin (bolus insulin)[17]	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95
Abbreviations: SD = single doses; FCT = film-coated tablets, I.U. = International Units; SFI = solution for injection; TAB = tablets					

LAUER-TAXE® last revised: 1 May 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Costs for additionally required SHI services:

Designation of the therapy	Designation	Cost/ pack[18]	Number	Consumption/ year
Appropriate comparator therapy				
Intensified conventional insulin therapy	Blood glucose test strips	€ 15.95	4 – 6 x daily	1,460 – 2,190

[18] Number of test strips/ pack = 50 pcs.; number of lancets/ pack = 200 pcs.; number of disposable needles/ pack = 100 pcs.; presentation of the lowest-priced pack according to LAUER-TAXE®, last revised: 1 May 2022

	Lancets	€ 4.20	4 – 6 x daily	1,460 – 2,190
	Disposable needles	€ 19.95	4 – 5 x daily	1,460 – 1,825
Liraglutide	Disposable needles	€ 19.95	1 x daily	365

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 12 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 December 2021, the pharmaceutical company submitted a dossier for the benefit assessment of ertugliflozin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 December 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient ertugliflozin.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2022. The deadline for submitting written statements was 22 March 2022.

The oral hearing was held on 11 April 2022.

By letter dated 12 April 2022, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 28 April 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 May 2022, and the proposed resolution was approved.

At its session on 19 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 October 2021	Determination of the appropriate comparator therapy
Working group Section 35a	5 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 April 2022 12 April 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	20 April 2022 3 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	10 May 2022	Concluding discussion of the draft resolution
Plenum	19 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 May 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken