IQWiG Reports – Commission No. A21-158

Ertugliflozin (type 2 diabetes mellitus) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ertugliflozin (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Ertugliflozin (type 2 diabetes mellitus) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
1 December 2021

Internal Commission No.
A21-158

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Wolfgang Kerner, Karlsburg Clinic, 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. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG employees involved in the dossier assessment

- Bent Müller
- Lars Beckmann
- Tatjana Hermanns
- Wiebke Hoffman-Eßer
- Sabine Ostlender
- Daniela Preukschat
- Min Ripoll
- Katharina Wölke

Keywords: Ertugliflozin, Diabetes Mellitus – Type 2, Benefit Assessment, NCT01999218, NCT01986881

Table of contents

Page

List of tables ..... **iv**
List of abbreviations ..... **v**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **8**
2.3 Information retrieval and study pool **11**
2.4 Results on added benefit **20**
2.5 Probability and extent of added benefit **20**
References for English extract **23**

List of tables[2]

Page

Table 2: Research questions of the benefit assessment of ertugliflozin 2
Table 3: Ertugliflozin – probability and extent of added benefit 6
Table 4: Research questions of the benefit assessment of ertugliflozin 9
Table 5: Characterization of the VETIS SU study included by the company – RCT, direct comparison: ertugliflozin + metformin vs. glimepiride + metformin 13
Table 6: Glimepiride titration scheme used in the VERTIS SU study included by the company 15
Table 7: Characterization of the VERTIS CV study included by the company – RCT, direct comparison: ertugliflozin vs. placebo 17
Table 8: Information on diabetes therapies in the comparator arm of the VERTIS CV study included by the company 19
Table 9: Ertugliflozin – probability and extent of added benefit 21

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like peptide-1
HbA1c	glycated haemoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NYHA	New York Heart Association
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SGLT2	sodium-glucose cotransporter-2
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 ertugliflozin. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 December 2021.

Research question

The aim of this report is to assess the added benefit of ertugliflozin as an adjunct to diet and exercise in the treatment of adults with inadequately controlled type 2 diabetes mellitus in comparison with the appropriate comparator therapy (ACT):

- in the form of monotherapy where metformin is unsuitable due to intolerance or contraindications
- as add-on therapy to other diabetes drugs

The research questions shown in Table 2 result from the ACT specified by the G-BA. The G-BA created no separate research question for ertugliflozin monotherapy based on the assumption that, compared to the overall population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin.

Table 2: Research questions of the benefit assessment of ertugliflozin (multipage table)

Research question	Therapeutic indication[a]	ACT[b]
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet	Individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis, and potential risk factors for hypoglycaemia, selecting from ▪ metformin + sulphonylurea (glibenclamide or glimepiride)[c] ▪ metformin + sitagliptin ▪ metformin + empagliflozin ▪ metformin + liraglutide
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	▪ Metformin + empagliflozin or ▪ Metformin + liraglutide or ▪ Metformin + dapagliflozin
3	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + sitagliptin or ▪ Metformin + empagliflozin + liraglutide[d]
4	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + liraglutide or ▪ Metformin + dapagliflozin + liraglutide[d]
5	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin[e]
6	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin + empagliflozin or ▪ Human insulin + metformin + dapagliflozin or ▪ Human insulin + metformin + liraglutide[e]
7	Insulin-pretreated adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (conventional therapy [CT], if necessary + metformin or dulaglutide or intensified insulin therapy [ICT])[e]
8	Insulin-pretreated adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (conventional therapy [CT], if necessary + metformin or empagliflozin or liraglutide or dapagliflozin or intensified insulin therapy [ICT])[e]

Table 2: Research questions of the benefit assessment of ertugliflozin (multipage table)

Research question	Therapeutic indication[a]	ACT[b]
a. Subdivision of the therapeutic indication according to the G-BA. ▫ It is assumed that pharmacotherapy is initiated only after failure of basic treatment alone (nonpharmacological measures such as diet, exercise, etc.) and is always carried out in combination with said treatment. ▫ All guidelines relevant in the therapeutic indication cite metformin therapy as the standard of care for patients with type 2 diabetes mellitus. ▫ Initial diabetes treatment is assumed to be metformin monotherapy. ▫ In case of inadequate glycaemic control under metformin monotherapy, guidelines recommend continuing metformin administration and intensifying treatment by adding another drug. Treatment regimens without metformin therefore require an explanation as to why metformin was contraindicated for the patient. ▫ As per the current metformin dosing recommendations, metformin is an option for an expanded patient population, including patients with moderately reduced kidney function (GFR ≥ 30 mL/min). Because compared to the total population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin, patients with metformin contraindication were not designated as a separate group. ▫ For the treatment of comorbidities in patients with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of type 2 diabetes mellitus. ▫ Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to an ACT. b. Presented is the respective ACT specified by the G-BA. c. For research question 1, options are the sulphonylureas of glibenclamide or glimepiride, which the G-BA rated as equivalent in the determination of the ACT. In the group of sulphonylureas, glipizide is pharmacologically and therapeutically comparable to glimepiride; in accordance with existing decisions concerning type 2 diabetes mellitus, it is therefore accepted as a comparator in studies. d. An insulin-free combination of metformin and 1 of the other drugs designated as ACTs should be considered. Where a third drug is added, it should be determined whether doing so can achieve an adequate blood glucose-lowering effect or whether the initiation of insulin therapy should be contemplated. e. Patients on insulin should be regularly examined to determine whether insulin therapy remains indicated or whether de-escalation of insulin therapy might be possible and indicated. According to current medical knowledge, insulin analogues are neither superior nor inferior to human insulin, but no long-term data are available showing any advantages of insulin analogues regarding hard outcomes. This benefit assessment takes into account evidence from studies using insulin analogues, provided the results from studies with insulin analogues can be extrapolated to human insulin. The approval status of insulin analogues must be taken into account. While the insulin analogue of insulin glargine was not explicitly listed as an ACT, it was accepted as a suitable comparator in view of currently available data. ACT: appropriate comparator therapy; CT: conventional therapy; G-BA: Federal Joint Committee; GFR: glomerular filtration rate; ICT: intensified insulin therapy		

The company departed from the G-BA's specifications regarding the ACT as well as regarding the breakdown of the therapeutic indication into different patient groups. As commissioned by the G-BA, the present assessment was conducted using the patient groups and ACTs specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

The check of completeness of the study pool did not show any relevant studies for any of the research questions. The company's dossier discusses research questions departing from the G-BA's specification on the basis of the MK-8835-002 study (hereinafter referred to as "VERTIS SU") and the MK-8835-004 study (hereinafter referred to as "VERTIS CV"). However, both studies are unsuitable for assessing the added benefit of ertugliflozin as an adjunct to diet and exercise for the treatment of adults with inadequately controlled type 2 diabetes mellitus. The reasoning is provided below.

Suitability of the VERTIS SU study

The VERTIS SU study is a 3-arm, double-blind, randomized, parallel-group study comparing ertugliflozin versus glimepiride, each in combination with metformin. The study included adult patients with type 2 diabetes mellitus on prior therapy at a constant dose of ≥ 1500 mg/day metformin for ≥ 8 weeks who exhibited glycated haemoglobin (HbA1c) values of ≥ 7.0% and ≤ 9.0%. The study excluded patients with a history of myocardial infarction, unstable angina, arterial revascularization, stroke, transitory ischaemic attack, or New York Heart Association (NYHA) functional classes III through IV heart failure within 3 months after the screening visit.

Inadequate implementation of the ACT

The VERTIS SU study most closely fits the G-BA's research question 1. The ACT specified by the G-BA for this patient population is individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis, and potential risks of hypoglycaemia, selecting from 4 diabetes drugs or drug classes in combination with metformin.

However, the VERTIS SU study presented by the company is a single-comparator study in which all comparator arm patients were treated with glimepiride + metformin. The study did not offer individualized therapy, where a drug is selected by the investigator taking into account individualized treatment goals, nor did the company demonstrate that glimepiride + metformin represents the therapy best suited for all patients included in the comparator arm. Therefore, the VERTIS SU study did not adequately implement the ACT specified by the G-BA.

No individualized titration of glimepiride

In the VERTIS SU comparator arm, glimepiride was uptitrated to a maximum dose of 6 mg or 8 mg (according to local approval) based on defined target glucose values. However, this titration regimen deviates from the glimepiride Summary of Product Characteristics (SPC), according to which doses above 4 mg/day improve the effect only in isolated cases. Regular

titration up to a maximum dose of 6 mg or 8 mg is therefore not appropriate. Furthermore, titration with fixed glucose target values is inadequate. All patients in the VERTIS SU study received a glimepiride dose increase if their fasting blood glucose was ≥ 110 mg/dL, no hypoglycaemia had occurred since the last uptitration, and further uptitration did not risk hypoglycaemia. This titration regimen ignores individualized blood glucose targets as recommended by the National Disease Management Guideline Type 2 Diabetes.

In all, the VERTIS SU study is unsuitable for the benefit assessment because the company has not demonstrated that glimepiride represents the therapy best suited for each individual patient and because titration of glimepiride with fixed (rather than individualized) glucose targets is not appropriate.

Suitability of the cardiovascular outcome study VERTIS CV

The VERTIS CV study is a 3-arm, placebo-controlled, double-blind, randomized parallel-group study. It included adult patients ≥ 40 years of age with type 2 diabetes mellitus and an HbA1c of 7.0% to 10.5% as well as atherosclerosis involving the coronary, cerebral, or peripheral vascular system.

Inappropriate diabetes therapy in the comparator arm

For type 2 diabetes patients with simultaneous cardiovascular disease or high cardiovascular risk, the current National Disease Management Guideline Type 2 Diabetes calls for offering sodium-glucose cotransporter-2 (SGLT2) inhibitors (empagliflozin) or glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide). The ACT specified by the G-BA likewise calls for the use of SGLT2 inhibitors (empagliflozin or dapagliflozin) or GLP-1 receptor agonists (liraglutide) for insulin-naive patients with type 2 diabetes mellitus and manifest cardiovascular disease.

The VERTIS CV study, however, disallowed SGLT2 inhibitors. Accordingly, only 1 patient in the comparator arm received an SGLT inhibitor at study start, and 3.0% of patients received SGLT2 inhibitors at the final visit. GLP-1 receptor agonists were received by only 3.1% of comparator arm patients at study start and by 5.6% at the final visit. However, excluding SGLT2 inhibitors and/or GLP-1 receptor agonists from the treatment of patients with type 2 diabetes mellitus and cardiovascular disease, as done in the VERTIS CV study, is not appropriate and not in accordance with the ACT specified by the G-BA.

Overall, the VERTIS CV study is unsuitable for assessing the added benefit of ertugliflozin as an adjunct to diet and exercise in adults with inadequately controlled type 2 diabetes mellitus.

Since no suitable data are available, there is no proof of added benefit of ertugliflozin as an adjunct to diet and exercise in comparison with the ACT in adults with inadequately controlled type 2 diabetes mellitus for any of the 8 research questions.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of added benefit of ertugliflozin.

Table 3: Ertugliflozin – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet	Individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis, and potential risk factors for hypoglycaemia, selecting from ▪ metformin + sulphonylurea (glibenclamide or glimepiride) ▪ metformin + sitagliptin ▪ metformin + empagliflozin ▪ metformin + liraglutide	Added benefit not proven
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	▪ Metformin + empagliflozin or ▪ Metformin + liraglutide or ▪ Metformin + dapagliflozin	Added benefit not proven
3	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + sitagliptin or ▪ Metformin + empagliflozin + liraglutide	Added benefit not proven

[3] 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 to 3 cannot be drawn from the available data). 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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Ertugliflozin – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
4	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + liraglutide or ▪ Metformin + dapagliflozin + liraglutide	Added benefit not proven
5	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	Human insulin + metformin	Added benefit not proven
6	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin + empagliflozin or ▪ Human insulin + metformin + dapagliflozin or ▪ Human insulin + metformin + liraglutide	Added benefit not proven
7	Insulin-pretreated adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	Escalation of insulin therapy (conventional therapy [CT], possibly + metformin or dulaglutide or intensified insulin therapy [ICT])	Added benefit not proven
8	Insulin-pretreated adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	Escalation of insulin therapy (conventional therapy [CT], possibly + metformin or empagliflozin or liraglutide or dapagliflozin or intensified insulin therapy [ICT])	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; CT: conventional therapy; G-BA: Federal Joint Committee; ICT: intensified insulin therapy

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of ertugliflozin as an adjunct to diet and exercise in the treatment of adults with inadequately controlled type 2 diabetes mellitus in comparison with the ACT.

- in the form of monotherapy where metformin is unsuitable due to intolerance or contraindications
- as add-on therapy to other diabetes drugs

The research questions shown in Table 4 result from the ACT specified by the G-BA. The G-BA created no separate research question for ertugliflozin monotherapy based on the assumption that, compared to the overall population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin.

Table 4: Research questions of the benefit assessment of ertugliflozin (multipage table)

Research question	Therapeutic indication[a]	ACT[b]
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet	Individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis, and potential risk factors for hypoglycaemia, selecting from ▪ metformin + sulphonylurea (glibenclamide or glimepiride)[c] ▪ metformin + sitagliptin ▪ metformin + empagliflozin ▪ metformin + liraglutide
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	▪ Metformin + empagliflozin or ▪ Metformin + liraglutide or ▪ Metformin + dapagliflozin
3	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + sitagliptin or ▪ Metformin + empagliflozin + liraglutide[d]
4	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved sufficient glycaemic control with their current drug treatment consisting of 2 blood-glucose lowering drugs in addition to diet and exercise and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + liraglutide or ▪ Metformin + dapagliflozin + liraglutide[d]
5	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin[e]
6	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin + empagliflozin or ▪ Human insulin + metformin + dapagliflozin or ▪ Human insulin + metformin + liraglutide[e]
7	Insulin-pretreated adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (conventional therapy [CT], if necessary + metformin or dulaglutide or intensified insulin therapy [ICT])[e]
8	Insulin-pretreated adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (conventional therapy [CT], if necessary + metformin or empagliflozin or liraglutide or dapagliflozin or intensified insulin therapy [ICT])[e]

Table 4: Research questions of the benefit assessment of ertugliflozin (multipage table)

Research question	Therapeutic indication[a]	ACT[b]
a. Subdivision of the therapeutic indication according to the G-BA. ▫ It is assumed that pharmacotherapy is initiated only after failure of basic treatment alone (nonpharmacological measures such as diet, exercise, etc.) and is always carried out in combination with said treatment. ▫ All guidelines relevant in the therapeutic indication cite metformin therapy as the standard of care for patients with type 2 diabetes mellitus. ▫ Initial diabetes treatment is assumed to be metformin monotherapy. ▫ In case of inadequate glycaemic control under metformin monotherapy, guidelines recommend continuing metformin administration and intensifying treatment by adding another drug. Treatment regimens without metformin therefore require an explanation as to why metformin was contraindicated for the patient. ▫ As per the current metformin dosing recommendation [3], metformin is an option for a broader patient population, including patients with moderate renal failure (GFR ≥ 30 mL/min). Because compared to the total population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin, patients with metformin contraindication were not designated as a separate group. ▫ For the treatment of comorbidities in patients with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of type 2 diabetes mellitus. ▫ Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to an ACT. b. Presented is the respective ACT specified by the G-BA. c. For research question 1, the options are the sulphonylureas of glibenclamide or glimepiride, which the G-BA rated as equivalent in the determination of the ACT. In the group of sulphonylureas, glipizide is pharmacologically and therapeutically comparable to glimepiride; in accordance with existing decisions concerning type 2 diabetes mellitus, it is therefore accepted as a comparator in studies. d. An insulin-free combination therapy of metformin and 1 of the other drugs designated as ACTs should be considered. Where a third drug is added, it should be determined whether doing so can achieve an adequate blood glucose-lowering effect or whether the initiation of insulin therapy should be contemplated. e. Patients on insulin should be regularly examined to determine whether insulin therapy remains indicated or whether de-escalation of insulin therapy might be possible and indicated. According to current medical knowledge, insulin analogues are neither superior nor inferior to human insulin, but no long-term data are available showing any advantages of insulin analogues regarding hard outcomes. This benefit assessment takes into account evidence from studies using insulin analogues, provided the results from studies with insulin analogues can be extrapolated to human insulin. The approval status of insulin analogues must be taken into account. While the insulin analogue of insulin glargine was not explicitly listed as an ACT, it was accepted as a suitable comparator in view of currently available data. ACT: appropriate comparator therapy; CT: conventional therapy; G-BA: Federal Joint Committee; GFR: glomerular filtration rate; ICT: intensified insulin therapy		

The company departed from the G-BA's specifications regarding the ACT as well as regarding the breakdown of the therapeutic indication into different patient groups. As commissioned by the G-BA, the present assessment was conducted using the patient groups and ACTs specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit.

Research questions by the company

Instead of the above 3 research questions posed by the G-BA, the company's dossier investigates the following research questions:

- A (ertugliflozin monotherapy): patients in whom diet and exercise alone do not achieve adequate glycaemic control and metformin is considered inappropriate due to intolerance or contraindications
- B (ertugliflozin in dual therapy): patients in whom diet and exercise and treatment with 1 blood-glucose lowering drug (except insulin) do not achieve adequate glycaemic control
- C (ertugliflozin in triple therapy): patients in whom diet and exercise and treatment with at least 2 blood-glucose lowering drugs (except insulin) do not achieve adequate glycaemic control
- D (ertugliflozin in combination with insulin): patients in whom diet and exercise and treatment with insulin (with or without another blood-glucose lowering drug) do not achieve adequate glycaemic control
- E: patients with type 2 diabetes mellitus and high cardiovascular risk

The company presents 1 study each for 2 of those 5 research questions (B and E). Both studies were checked to determine their suitability for answering 1 of the G-BA's research questions.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on ertugliflozin (status: 14 September 2021)
- bibliographical literature search on ertugliflozin (last search on 12 October 2021)
- search in trial registries/trial results databases for studies on ertugliflozin (last search on 20 October 2021)
- search on the G-BA website for ertugliflozin (last search on 25 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on ertugliflozin (last search on 17 December 2021); for search strategies, see Appendix A of the full dossier assessment

No relevant study was identified from the check.

The company's dossier analyses research questions other than those specified by the G-BA's (see Section 2.2), and for this purpose, it includes the MK-8835-002 study [4,5] (hereinafter referred to as VERTIS SU) for its research question B and the MK-8835-004 study [6] (hereinafter referred to as VERTIS CV) for its research question E. However, both studies are unsuitable for assessing the added benefit of ertugliflozin as an adjunct to diet and exercise for the treatment of adults with inadequately controlled type 2 diabetes mellitus. The reasoning is provided below.

Suitability of the VERTIS SU study

Table 5 characterizes the VERTIS SU study.

Table 5: Characterization of the VETIS SU study included by the company – RCT, direct comparison: ertugliflozin + metformin vs. glimepiride + metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
VERTIS SU	RCT, double-blind, parallel-group	Adult patients with type 2 diabetes mellitus and prior treatment with ▪ metformin ≥ 1500 mg at a constant dose for ≥ 8 weeks (or ≥ 10 weeks for wash-out of sulphonylureas) and ▪ HbA1c ≥ 7.0% and ≤ 9.0% prior to randomization[b]	Ertugliflozin 5 mg + metformin (N = 445) Ertugliflozin 15 mg + metformin (N = 436) Glimepiride + metformin (N = 435)	Screening: 1 week Run-in phase[c]: up to 13 weeks; single-blind placebo run-in phase: 2 weeks Treatment: 104 weeks Follow-up observation: 2 weeks	A total of 232 centres in Argentina, Canada, Czech Republic, Hungary, Lithuania, Mexico, Philippines, Poland, Romania, Russia, Slovakia, South Africa, South Korea, Taiwan, Ukraine, United States 12/2013–4/2017 Data cut-off: 30 May 2017 (final)[d]	Primary: change in HbA1c value Secondary: all-cause mortality, morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 B.
b. Patients exhibiting the following criteria were also eligible for inclusion at screening and were randomized if they met the above randomization criteria following a wash-out/titration/stabilization phase:
- metformin monotherapy
  - ≥ 1500 mg/day for < 8 weeks and HbA1c ≥ 7.0% and ≤ 9.0% or
  - < 1500 mg/day and HbA1c ≥ 7.5% and ≤ 9.5% or
- metformin in combination with a diabetes drug (e.g. sulphonylureas with < 50% of the maximum approved dosage in the respective country, DPP-4 inhibitors, or alpha-glucose inhibitors) and HbA1c ≥ 6.5% and 8.5%

c. Wash-out/titration/stabilization phase.
d. A 1st data cut-off was carried out after all patients had completed Week 52 (Phase A). The results were summarized in a separate study report generated for regulatory purposes.

AE: adverse event; DPP-4: dipeptidyl-peptidase 4, HbA1c: glycated haemoglobin A1c; N: number of randomized patients; RCT: randomized controlled trial

The VERTIS SU study is a 3-arm, double-blind, randomized, parallel-group study comparing ertugliflozin versus glimepiride, each in combination with metformin. The study included adult patients with type 2 diabetes mellitus on prior therapy at a constant dose of ≥ 1500 mg/day metformin for ≥ 8 weeks who exhibited HbA1c values of ≥ 7.0% and ≤ 9.0%. The study excluded patients with a history of myocardial infarction, unstable angina, arterial revascularization, stroke, transitory ischaemic attack, or NYHA functional class III through IV heart failure within 3 months after the screening visit.

A total of 1316 patients were randomly assigned in a 1:1:1 ratio to treatment with 5 mg ertugliflozin + metformin (N = 445), ertugliflozin + metformin (N = 436), or glimepiride + metformin (N = 435).

In the ertugliflozin arms, patients were treated with 5 mg and 15 mg ertugliflozin, respectively. In violation of approval [7], individualized dose adjustments were disallowed. All patients continued their metformin therapy at a constant dose of ≥ 1500 mg/day throughout the study.

Inadequate implementation of the ACT

The VERTIS SU study included patients with type 2 diabetes mellitus who exhibited an HbA1c of ≥ 7.0% and ≤ 9.0% despite being on metformin treatment and for whom cardiovascular disease was largely ruled out. This patient population most closely fits the G-BA's research question 1 (see Table 4). For adults with type 2 diabetes mellitus and no manifest cardiovascular disease who have not achieved adequate glycaemic control under their current pharmacological therapy consisting of 1 glucose-lowering drug in addition to diet, the ACT specified by the G-BA is individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis, and potential hypoglycaemia risk, selecting from

- metformin + sulphonylurea (glibenclamide or glimepiride)
- metformin + sitagliptin
- metformin + empagliflozin
- metformin + liraglutide

The VERTIS SU study presented by the company is a single-comparator study in which all comparator arm patients were treated with glimepiride + metformin. The study did not offer individualized therapy, where a drug is selected by the investigator taking into account individualized treatment goals, nor did the company demonstrate that glimepiride + metformin represents the therapy best suited for all patients included in the comparator arm. Therefore, the VERTIS SU study did not adequately implement the ACT specified by the G-BA.

No individualized titration of glimepiride

In the comparator arm of the VERTIS SU study, glimepiride was administered using a fixed titration scheme (see Table 6). Initially, patients received 1 mg/day of glimepiride. At blood

glucose values ≥ 110 mg/dL (6.1 mmol/L), this dose was to be increased in 1 mg steps up to a maximum dose of 6 mg or 8 mg (depending on approval).

Table 6: Glimepiride titration scheme used in the VERTIS SU study included by the company

Study	Glimepiride
VERTIS SU	▪ Starting dose: 1 mg/day Dose increase if all criteria listed below are met ▪ after 3 weeks: 1 mg twice daily ▪ after 6 weeks: 2 mg twice daily, followed by further up-titration in 1 mg steps up to the maximum dose of 6 or 8 mg/day (depending on approval) or up to the maximum tolerated dose if the last up-titration lies at least 1 week in the past Uptitration criteria: ▪ fasting blood glucose[a] ≥ 110 mg/dL (6.1 mmol/L) ▪ fasting blood glucose[a] (at least 2 measurements) and all preprandial blood glucose values[a] ≥ 110 mg/dL (6.1 mmol/L) in the week prior to uptitration ▪ no hypoglycaemic episodes since the last uptitration ▪ further dose increases not deemed by the investigator to risk hypoglycaemia Dose reduction or treatment discontinuation[b] in case of hypoglycaemia upon the investigator's discretion
a. Blood glucose fingerstick testing at the clinic or by patient. b. In the event of further hypoglycaemia occurring after dose reduction to 1 mg or the first hypoglycaemia occurring at a dosage of 1 mg/day. RCT: randomized controlled trial	

The titration scheme departs from approval. While the glimepiride SPC valid in Germany [8] lists 6 mg as the maximum recommended dose, it recommends titration in a stepwise manner up to a dose of 4 mg/day. According to the SPC, daily doses above 4 mg glimepiride improve the effect only in isolated cases. Regular titration up to a maximum dose of 6 mg or 8 mg is therefore not appropriate.

Furthermore, titration with fixed glucose target values is inadequate. All patients in the VERTIS SU study received a glimepiride dose increase if their fasting blood glucose was ≥ 110 mg/dL, no hypoglycaemia had occurred since the last uptitration, and further uptitration did not risk hypoglycaemia. This titration scheme ignores individualized glucose target values. The National Disease Management Guideline Type 2 Diabetes Mellitus [9] recommends establishing individualized blood glucose target values for each patient with type 2 diabetes mellitus based on age, physical condition, comorbidities, time since diabetes diagnosis, treatment adherence, therapy level, and the risk of adverse effects. Titration of the comparator therapy should be based on these individualized target glucose values.

In all, the VERTIS SU study is unsuitable for the benefit assessment because the company has not demonstrated that glimepiride represents the therapy best suited for each individual patient

and because titration of glimepiride with fixed (rather than individualized) glucose targets is not appropriate.

Suitability of the cardiovascular outcome study VERTIS CV

Table 7 characterizes the VERTIS CV study.

Table 7: Characterization of the VERTIS CV study included by the company – RCT, direct comparison: ertugliflozin vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
VERTIS CV	RCT, double-blind, parallel-group	Adult patients (> 40 years of age) with type 2 diabetes mellitus and ▪ HbA1c 7.0%–10.5% on a constant dose of glucose-lowering therapy or none at all > 8 weeks prior to screening and ▪ prior history of atherosclerosis involving the coronary, cerebral, or peripheral vascular system[b]	each as an add-on to concomitant diabetes medication: ▪ ertugliflozin 5 mg (N = 2752) ▪ ertugliflozin 15 mg (N = 2747) ▪ placebo (N = 2747)	Screening: 1–4 weeks Treatment: event-driven study, final analysis planned to occur after ▪ ≥ 939 confirmed primary MACE events Follow-up observation: 2 weeks	A total of 548 centres in Argentina, Australia, Bosnia and Herzegovina, Bulgaria, Canada, Columbia, Croatia, Czech Republic, Georgia, Greece, Hong Kong, Hungary, Israel, Italy, Latvia, Lithuania, Mexico, Netherlands, New Zealand, Philippines, Poland, Romania, Russia, Serbia, Slovakia, South Africa, South Korea, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States 11/2013–12/2019 Data cut-off: 16 March 2020 (final)	Primary: MACE Secondary: all-cause mortality, morbidity, AEs

a. Primary outcomes include information without consideration of relevance for this benefit assessment. Secondary outcomes comprise exclusively data only the basis of the information provided by the company's Module 4.
b. One or more of the following criteria had to have been demonstrably met:
- coronary artery disease as indicated by a history of presumed spontaneous myocardial infarction ≥ 90 days prior to screening (excluding peri-procedural or definite secondary myocardial infarction [e.g. due to anaemia or hypertensive emergency; troponin increase in sepsis]) or
- coronary artery disease as indicated by a history of coronary revascularization (PCI or CABG) ≥ 90 days prior to screening or
- ischaemic cerebrovascular disease as indicated by a history of ischaemic stroke ≥ 90 days prior to screening or history of carotid revascularization ≥ 90 days prior to screening or
- peripheral arterial disease as indicated by angiographically documented peripheral vascular disease or ABI < 8.5 plus symptoms of claudication or amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischaemia ≥ 90 days prior to screening

ABI: ankle/brachial index; AE: adverse event; CABG: coronary artery bypass graft; HbA1c: glycated haemoglobin; MACE: Major Adverse Cardiovascular Events; N: number of randomized patients; PCI: percutaneous coronary intervention; RCT: randomized controlled trial

The VERTIS CV study is a 3-arm, placebo-controlled, double-blind, randomized parallel-group study. It included adult patients ≥ 40 years of age with type 2 diabetes mellitus and an HbA1c of 7.0% to 10.5% as well as atherosclerosis involving the coronary, cerebral, or peripheral vascular system. The study enrolled both treatment-naive and pretreated patients.

A total of 8246 patients were randomly assigned in a 1:1:1 ratio to treatment with 5 mg ertugliflozin (N = 2752), 15 mg ertugliflozin (N = 2747), or placebo (N = 2747). Ertugliflozin or placebo was administered as an adjunct to existing concomitant treatment of type 2 diabetes mellitus, cardiovascular risk factors, and comorbidities.

In the 2 ertugliflozin arms, patients were treated with 5 mg and 15 mg ertugliflozin, respectively. In violation of approval, the study did not provide for any individualized dose adjustments [7].

Inappropriate diabetes therapy in the comparator arm

Table 8 presents the diabetes therapies administered in the comparator arm for both baseline and the final visit.

Table 8: Information on diabetes therapies in the comparator arm of the VERTIS CV study included by the company

Study **Drug class**	**Patients with diabetes therapy n (%)**
	Comparator arm **N = 2745**
VERTIS CV study	
Start of study	
Alpha-glucosidase inhibitors	37 (1.3)
Biguanides	2122 (77.3)
Glinides	26 (0.9)
DPP-4 inhibitors	290 (10.6)
GLP-1 receptor agonists	86 (3.1)
SGLT-2 inhibitors	1 (0.0)
Insulin and analogues for injection	1344 (49.0)
Sulphonamides and urea derivatives	1121 (40.8)
Thiazolidinedione	59 (2.1)
Number of diabetes drugs	
0	29 (1.1)
1	847 (30.9)
2	1416 (51.6)
3 +	453 (16.5)
Final visit	
Alpha-glucosidase inhibitors	34 (1.2)
Biguanides	2095 (76.3)
DPP-4 inhibitors	392 (14.3)
GLP-1 receptor agonists	153 (5.6)
SGLT-2 inhibitors	81 (3.0)
Insulin and analogues for injection	1514 (55.2)
Glinides	29 (1.1)
Other diabetes drugs	1 (0.0)
Sulphonamides and urea derivatives	1078 (39.3)
Thiazolidinedione	93 (3.4)
Number of diabetes drugs	
0	30 (1.1)
1	754 (27.5)
2	1328 (48.4)
3 +	633 (23.1)

DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide 1; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; SGLT-2: sodium-glucose cotransporter 2

The VERTIS CV study included only patients with cardiovascular disease. In the comparator arm, 49% of patients received insulin or insulin analogues at baseline. The study included patients without diabetes therapy at baseline as well as patients with ≥ 3 diabetes therapies at baseline. On the basis of this information, the patient population of the VERTIS CV study cannot be allocated to any one of the individual research questions specified by the G-BA. Rather, the VERTIS CV study included patients who, based on their prior therapies, could be allocated to different research questions specified by the G-BA for patients with manifest cardiovascular disease (research questions 2, 4, 6, 8; see Table 4).

The current National Disease Management Guideline Type 2 Diabetes [9] calls for offering SGLT2 inhibitors (empagliflozin) and GLP-1 receptor agonists (liraglutide) to type 2 diabetes patients who simultaneously have cardiovascular disease or are at high cardiovascular risk. The ACT specified by the G-BA likewise calls for the use of SGLT2 inhibitors (empagliflozin or dapagliflozin) or GLP-1 receptor agonists (liraglutide) for insulin-naive patients with type 2 diabetes mellitus and manifest cardiovascular disease. As per the ACT specified by the G-BA, the option of foregoing SGLT-2 inhibitors or GLP-1 exists only for insulin-pretreated patients.

The VERTIS CV study, however, disallowed SGLT2 inhibitors. Accordingly, only 1 patient in the comparator arm received an SGLT inhibitor at study start, and 3.0% of patients received SGLT2 inhibitors at the final visit. GLP-1 receptor agonists were received by only 3.1% of comparator arm patients at study start and by 5.6% at the final visit. Foregoing the use of SGLT2 inhibitors or GLP-1 receptor agonists in the treatment of patients with type 2 diabetes mellitus and cardiovascular disease, as was done in the VERTIS CV study, is inappropriate according to the current National Disease Management Guideline Type 2 Diabetes Mellitus [9] and is likewise not in accordance with the ACT specified by the G-BA.

Overall, the VERTIS CV study is unsuitable for assessing the added benefit of ertugliflozin as an adjunct to diet and exercise in adults with inadequately controlled type 2 diabetes mellitus. No other aspects of the VERTIS CV study were investigated.

2.4 Results on added benefit

Overall, no suitable data are available for assessing the added benefit of ertugliflozin as an adjunct to diet and exercise versus the ACT in adults with inadequately controlled type 2 diabetes mellitus. For all 8 research questions, this results in no hint of added benefit of ertugliflozin in comparison with the ACT; an added benefit is therefore not proven for any of them.

2.5 Probability and extent of added benefit

Table 9 summarizes the result of the assessment of the added benefit of ertugliflozin in comparison with the ACT.

Table 9: Ertugliflozin – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet	Individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis, and potential risk factors for hypoglycaemia, selecting from ▪ metformin + sulphonylurea (glibenclamide or glimepiride) ▪ metformin + sitagliptin ▪ metformin + empagliflozin ▪ metformin + liraglutide	Added benefit not proven
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	▪ Metformin + empagliflozin or ▪ Metformin + liraglutide or ▪ Metformin + dapagliflozin	Added benefit not proven
3	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + sitagliptin or ▪ Metformin + empagliflozin + liraglutide	Added benefit not proven
4	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + liraglutide or ▪ Metformin + dapagliflozin + liraglutide	Added benefit not proven
5	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	Human insulin + metformin	Added benefit not proven

Table 9: Ertugliflozin – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
6	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin + empagliflozin or ▪ Human insulin + metformin + dapagliflozin or ▪ Human insulin + metformin + liraglutide	Added benefit not proven
7	Insulin-pretreated adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	Escalation of insulin therapy (conventional therapy [CT], possibly + metformin or dulaglutide or intensified insulin therapy [ICT])	Added benefit not proven
8	Insulin-pretreated adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved sufficient glycaemic control with their current insulin regimen in addition to diet and exercise	Escalation of insulin therapy (conventional therapy [CT], possibly + metformin or empagliflozin or liraglutide or dapagliflozin or intensified insulin therapy [ICT])	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; CT: conventional therapy; G-BA: Federal Joint Committee; ICT: intensified insulin therapy

The assessment described above deviates from the assessment by the company, which derived an indication of minor added benefit for its research question B on the basis of the results of the VERTIS SU study and proof of considerable added benefit for its research question E on the basis of the VERTIS CV study.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Bundesinstitut für Arzneimittel und Medizinprodukte. Metformin zur Behandlung des Typ-2-Diabetes: Umsetzung der Durchführungsbeschlüsse der EU [online]. 2017 [Accessed: 04.02.2022]. URL: https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RV_STP/m-r/metformin.html

4. Hollander P, Hill J, Johnson J et al. Results of VERTIS SU extension study: safety and efficacy of ertugliflozin treatment over 104 weeks compared to glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin. Current medical research and opinion 2019; 35(8): 1335-1343. https://dx.doi.org/10.1080/03007995.2019.1583450.

5. Hollander P, Liu J, Hill J et al. Ertugliflozin Compared with Glimepiride in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin: the VERTIS SU Randomized Study. Diabetes Ther 2018; 9(1): 193-207. https://dx.doi.org/10.1007/s13300-017-0354-4.

6. Cannon CP, Pratley R, Dagogo-Jack S et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med 2020; 383(15): 1425-1435. https://dx.doi.org/10.1056/NEJMoa2004967.

7. Merck Sharp Dohme. Fachinformation STEGLATRO, Stand: 2021. 2021.

8. Aristo Pharma. Fachinformation Glimepirid Aristo, Stand: März 2019. 2019.

9. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie (NVL); Typ-2-Diabetes; Teilpublikation der Langfassung [online]. 2021 [Accessed: 02.02.2022]. URL: https://www.leitlinien.de/mdb/downloads/nvl/diabetes-mellitus/diabetes-2aufl-vers1.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-158.html.