Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Dapagliflozin (new therapeutic indication: type 2 diabetes mellitus, ≥ 10 years)

of 16 June 2022

Contents

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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 active ingredient dapagliflozin (Forxiga) was listed for the first time on 15 December 2012 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 15 November 2021, dapagliflozin received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 10 December 2021, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in

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conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dapagliflozin with the new therapeutic indication (type 2 diabetes mellitus, ≥ 10 years).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 March 2022 on the website of the G-BA (www.g-ba.de), 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 dapagliflozin compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. 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 dapagliflozin.

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 dapagliflozin (Forxiga) according to product information

Forxiga is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

Therapeutic indication of the resolution (resolution of 16.06.2022):

For the treatment of children and adolescents aged 10 to 17 years with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Insulin-naïve children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least 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.

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Appropriate comparator therapy for dapagliflozin:

- Human insulin + metformin

b) Insulin-experienced children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous insulin regime in addition to diet and exercise

Appropriate comparator therapy for dapagliflozin:

- Escalation of insulin therapy (conventional therapy (CT) if necessary + metformin 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. If a non-medicinal treatment is considered as a comparator therapy, this 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. Only metformin, the GLP-1 RA liraglutide, the SGLT-2 inhibitor dapagliflozin and insulin (human insulin, insulin analogues) have been approved so far for the treatment of type 2 diabetes mellitus in children and adolescents aged 10 years and older.

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

on 3. At present, there are no resolutions on the early benefit assessment for children and adolescents with type 2 diabetes mellitus, apart from the resolution on insulin degludec of 20 August 2015.

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".

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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.

The currently available evidence for the treatment of type 2 diabetes mellitus in children and adolescents is limited overall. Three guidelines were considered, including one from the UK National Institute for Health and Care Excellence (NICE), one from the American Diabetes Association (ADA) and one from the Australasian Paediatric Endocrine Group (APEG). According to the recommendations, metformin is the first choice for the treatment of children and adolescents with type 2 diabetes mellitus. In addition to metformin, the guidelines recommend insulin in combination with metformin as initial therapy in case of signs of ketoacidosis or ketonuria, inadequate glycaemic control under metformin therapy or severe hyperglycaemia in a very extensive-stage of the disease.

Accordingly, taking into account the recommendations, the combination of human insulin with metformin is determined as the appropriate comparator therapy in insulin-naïve patients aged 10 to 17 years with inadequate glycaemic control according to patient population a).

It is assumed that metformin contraindications, which according to the product information of metformin exist, for example in severe renal failure, metabolic acidoses, diabetic precoma or liver failure, occur less frequently in children and adolescents.

Metformin intolerances, for example gastrointestinal intolerances can also occur in children and adolescents with type 2 diabetes mellitus, especially at the start of treatment. Clinical experience shows that metformin intolerance occurs with a comparable frequency in children and adolescents with type 2 diabetes mellitus as in adult patients. According to the product information of metformin for use in children and adolescents, a gradual increase in the dosage has a positive effect on the gastrointestinal tolerance of metformin. Consequently, it is assumed that only a small percentage of children and adolescents with type 2 diabetes mellitus have persistent metformin intolerance even at lower doses.

Overall, it is assumed that only a smaller percentage of children and adolescents have a metformin contraindication or permanent intolerance compared to the total population. Therefore, the patient population with metformin intolerance is not named separately.

In the antidiabetic treatment setting in insulin-experienced patients in patient population b), who do not achieve sufficient glycaemic control despite insulin therapy, the escalation of insulin therapy is determined as the appropriate comparator therapy. The escalation of the insulin therapy should take place in the form of a conventional insulin therapy (CT, mixed insulin, if necessary + metformin) or an intensified conventional insulin therapy (ICT), taking into account the individual life situation of the patient. In the context of ICT, the administration of an additional hypoglycaemic agent is not usually considered indicated. In addition to CT, metformin may be administered, if necessary.

For the GLP-1 RA liraglutide, which has been approved since August 2019 for the treatment of children aged 10 years and older with type 2 diabetes mellitus, there is no explicit recommendation for use with liraglutide in the current guidelines, so that

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liraglutide is currently not considered as an appropriate comparator therapy for the treatment of children aged 10 years and older with type 2 diabetes mellitus.

The continuation of an inadequate therapy (regimen) for the treatment of type 2 diabetes mellitus, if there are still possibilities of therapy escalation, does not correspond to the appropriate comparator therapy.

It is assumed that possible comorbidities or risk factors of type 2 diabetes mellitus (e.g., hypertension, dyslipidaemia, microvascular complications - nephropathy, neuropathy, retinopathy) are treated appropriately for the individual patient according to the current state of medical knowledge, in particular by antihypertensive agents and/or lipid-lowering agents.

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 part of the appropriate comparator therapy, but it is nevertheless accepted as a suitable comparator in view of the current data basis.

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 dapagliflozin is assessed as follows:

a) <u>Insulin-naïve children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least one hypoglycaemic agent in addition to diet and exercise</u>

   An additional benefit is not proven.

b) <u>Insulin-experienced children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous insulin regime in addition to diet and exercise</u>

   An additional benefit is not proven.

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Justification:

For the assessment of the additional benefit of dapagliflozin for the treatment of children and adolescents aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus, the pharmaceutical company submitted the D1690C00017 study and transferred the results from adults to children and adolescents.

D1690C00017 study

In the double-blind, multicentre, randomised phase III D1690C00017 study, dapagliflozin was compared to placebo in patients with type 2 diabetes mellitus aged 10 to 24 years, in each case in addition to background therapy. Background therapy consisted of diet and exercise and a stable dose of metformin, insulin or metformin + insulin. During the 24-week treatment phase, adjustments to the existing, stable anti-diabetic therapy were only allowed in exceptional cases, such as multiple or severe hypoglycaemic events. If hyperglycaemia persisted, insulin could be given as part of rescue therapy. For the derivation of the additional benefit, the pharmaceutical company uses the sub-population of patients aged 10 to 17 years (intervention arm: n = 29, comparator arm: n = 24).

In accordance with the therapeutic indication of dapagliflozin, the therapy should be intensified in children and adolescents, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least one hypoglycaemic agent in addition to diet and exercise. Therefore, therapy with metformin and human insulin was determined as the appropriate comparator therapy for insulin-naïve patients. In insulin-experienced patients who do not achieve sufficient glycaemic control despite insulin therapy, the escalation of insulin therapy was defined as the appropriate comparator therapy. The escalation of the insulin therapy should take place in the form of a conventional insulin therapy (mixed insulin, if necessary + metformin) or an intensified conventional insulin therapy (ICT), taking into account the individual life situation of the patient. This therapy escalation would have been indicated and, in principle possible in the majority of patients in the comparator arm of the D1690C00017 study, since here a mean HbA1c value of approx. 8.1% was present at the start of the study. However, in the comparator arm of the D1690C00017 study, 58% of patients received metformin monotherapy and there was no treatment escalation. Consequently, the appropriate comparator therapy was not implemented in the D1690C00017 study.

In addition, the pharmaceutical company considers the included patients as a total population and does not subdivide them into the two patient groups defined by the G-BA. It is not possible to assign the children and adolescents to the specified patient groups.

Against this background, an assessment of the additional benefit of dapagliflozin compared with the respective appropriate comparator therapy is not possible for either patient group on the basis of the D1690C00017 study.

Transfer of results from adults to children and adolescents not appropriate

In addition to the D1690C00017 study, the pharmaceutical company proposes a transfer of the results from adults to children and adolescents for the assessment of the additional benefit of dapagliflozin. The pharmaceutical company refers to results from the phase III DECLARE-TIMI 58 study, data on the pharmacokinetic-pharmacodynamic profile of dapagliflozin from the phase I D1690C00016 study and the phase III D1690C00017 study.

There is insufficient similarity between the patient population of children and adolescents and adults, so that the results of the DECLARE-TIMI 58 study cannot be transferred to children and

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adolescents with type 2 diabetes mellitus. The DECLARE-TIMI 58 study investigated the effect of dapagliflozin versus standard therapy in adult patients with type 2 diabetes mellitus and high cardiovascular risk. In children and adolescents with type 2 diabetes mellitus, a high cardiovascular risk exists only in exceptional cases, which is why transferability of the results is not considered appropriate. Furthermore, the data on the pharmacokinetic-pharmacodynamic profile of dapagliflozin from the D1690C00016 and D1690C00017 studies are not relevant for the assessment of additional benefit.

All in all, in the present benefit assessment procedure, no transfer of additional benefit from adults to children can be made because the conditions are not met that would justify recognition of additional benefit for children adolescents aged 10 to 17 years based on results of the adults.

Conclusion

In the overall assessment, no conclusions can be made on the additional benefit of dapagliflozin compared to the appropriate comparator therapy on the basis of the study presented. An additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient dapagliflozin. Forxiga (active ingredient dapagliflozin) is used to treat insufficiently controlled type 2 diabetes mellitus in adults and children aged 10 years and older. Only patients aged between 10 and 17 years are considered here.

Two groups of patients were distinguished:

a) Insulin-naïve children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least one hypoglycaemic agent in addition to diet and exercise, and

b) Insulin-experienced children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous insulin regime in addition to diet and exercise

on patient group a)

The G-BA determined human insulin and metformin as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the D1690C00017 study and transfers the results of dapagliflozin from adults to children and adolescents.

The D1690C00017 study is unsuitable for the assessment of the additional benefit of dapagliflozin because the appropriate comparator therapy was not implemented. In addition, the pharmaceutical company considers all enrolled patients as a total population and does not subdivide them into the two patient groups defined by the G-BA.

A transfer of the results from adults to children and adolescents cannot be used for the assessment of the additional benefit due to the lack of similarity between the patient population of adults on the one hand and the patient population of children and adolescents on the other.

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Overall, no suitable studies were submitted by the pharmaceutical company for this patient population from which an additional benefit of dapagliflozin compared to the appropriate comparator therapy can be derived. An additional benefit is not proven.

on patient group b)

The G-BA determined an escalation of insulin therapy (conventional therapy (CT), if necessary + metformin or intensified insulin therapy (ICT)) as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the D1690C00017 study and transfers the results of dapagliflozin from adults to children and adolescents.

The D1690C00017 study is unsuitable for the assessment of the additional benefit of dapagliflozin because the appropriate comparator therapy was not implemented. In addition, the pharmaceutical company considers all enrolled patients as a total population and does not subdivide them into the two patient groups defined by the G-BA.

A transfer of the results from adults to children and adolescents cannot be used for the assessment of the additional benefit due to the lack of similarity between the patient population of adults on the one hand and the patient population of children and adolescents on the other.

Overall, no suitable studies were submitted by the pharmaceutical company for this patient population from which an additional benefit of dapagliflozin compared to the appropriate comparator therapy can be derived. 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 G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainty due to various methodological aspects. The data represent an overestimation because the pharmaceutical company did not restrict the target population to children and adolescents with insufficiently controlled type 2 diabetes mellitus in accordance with the marketing authorisation. Furthermore, no subdivision is made into patient populations a) and b), insulin-naïve and insulin-experienced patients.

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 Forxiga (active ingredient: dapagliflozin) at the following publicly accessible link (last access: 7 March 2022):
https://www.ema.europa.eu/en/documents/product-information/forxiga-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: 15 May 2022).

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Treatment duration and consumption

With regard to consumption, the average annual consumption was determined by indicating the number of tablets or international units. 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.

The recommended dose of dapagliflozin is 10 mg once daily for all patients 10 years and older.

For metformin, starting doses of 500 mg once daily are recommended for children 10 years and older. Dose increases up to 2,000 mg metformin daily are possible according to the product information; 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.

The daily starting dose of liraglutide for all patients 10 years and older 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).

A variety of different insulin dosing regimens 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.

The insulin dosages (I.U.) per patient are calculated based on the dosage requirement in the age group (children and adolescents from the age of 10 years). The consumption is calculated based on a dosage requirement of 0.7 to 2 I.U./ kg BW/ day for children and adolescents in puberty[2,3].

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. For body weight, a range between 37.6 kg for 10-year-olds and 67.0 kg for 17-year-olds is therefore assumed according to the official representative statistics "Microcensus 2017"[4].

[2] According to the WHO definition, adolescents aged 10 to 19 are in puberty. World Health Organisation. Maternal, Newborn, Child and Adolescent Health and Ageing Data portal [online] URL: https://platform.who.int/data/maternal-newborn-child-adolescent-ageing/adolescent-data

[3] Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T, Battelino T, Hanas R, Codner E. ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2018 Oct;19 Suppl 27:115-135. doi: 10.1111/pedi.12718.

[4] Information system of federal health reporting, average body measurements of the population (height in m, weight in kg). Characteristics of classification: Years, Germany, age, gender [online]. URL: https://www.gbe-bund.de/gbe/pkg_isgbe5.prc_menu_olap?p_uid=gast&p_aid=42472020&p_sprache=D&p_help=3&p_indnr=223&p_indsp=&p_ityp=H&p_fid=

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Consequently, weight differences between boys and girls as well as the fact that the bodyweight of patients with type 2 diabetes mellitus may be higher than the average values typical of the age are not taken into account for the cost calculation.

Treatment period:

a) Insulin-naïve children aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least 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				
Dapagliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[5]				
Metformin	continuously, 1-3 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	continuously, 1-3 x daily	365	1	365
Human insulin (NPH-insulin)	continuously, 1-2 x daily	365	1	365

b) Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient 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				
Dapagliflozin	continuously, 1 x daily	365	1	365
Concomitant active ingredient of the medicinal product to be assessed[6]				

[5] For the combination of dapagliflozin with a hypoglycaemic agent, metformin and liraglutide are presented as possible concomitant active ingredients.
[6] The combination with mixed insulin is shown as an example of the combination of dapagliflozin with an insulin in the context of escalation of insulin therapy, in this case with conventional insulin therapy.

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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, 1-3 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:

a) Insulin-naïve children aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least one hypoglycaemic agent 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					
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Concomitant active ingredient of the medicinal product to be assessed[7]					
Metformin	500 mg - 1000 mg	500 mg - 2000 mg	0.5 x 1000 mg - 2 x 1000 mg	365 365	182.5 x 1000 mg - 730 x 1000 mg
Liraglutide[8]	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					

[7] For the combination of dapagliflozin with a hypoglycaemic agent, metformin and liraglutide are presented as possible concomitant active ingredients.
[8] 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.

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Metformin	500 mg - 1000 mg	500 mg - 2000 mg	0.5 x 1000 mg - 2 x 1000 mg	365 365	182.5 x 1000 mg - 730 x 1000 mg
Human insulin (NPH-insulin)	0.7 - 2 I.U. / kg BW	26.32 - 134 I.U.	1 x 26.32 I.U. - 1 x 134 I.U.	365 365	9 x 606.8 I.U. - 48 x 910 I.U.

b) Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient 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					
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Concomitant active ingredient of the medicinal product to be assessed[9]					
Conventional insulin therapy (CT) Mixed insulin	0.7 - 2 I.U. / kg BW	26.32 - 134 I.U.	1 x 26.32 I.U. - 1 x 134 I.U.	365 365	9 x 606.8 I.U. - 48 x 910 I.U.
Appropriate comparator therapy					
Metformin	500 mg - 1000 mg	500 mg - 2000 mg	0.5 x 1000 mg - 2 x 1000 mg	365 365	182.5 x 1000 mg - 730 x 1000 mg
Conventional insulin therapy (CT) Mixed insulin	0.7 - 2 I.U. / kg BW	26.32 - 134 I.U.	1 x 26.32 I.U. - 1 x 134 I.U.	365 365	9 x 606.8 I.U. - 48 x 910 I.U.
Intensified insulin therapy (ICT)					

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

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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)	0.28 - 1.2 I.U./kg BW	10.53 - 80.4 I.U.	1 x 10.53 I.U. - 1 x 80.4 I.U.	365 365	3,842.72 I.U. - 29 x 346 I.U.
Human insulin (Bolus insulin)	0.28 - 1.2 I.U./kg BW	10.53 - 80.4 I.U.	1 x 10.53 I.U. - 1 x 80.4 I.U.	365 365	3,842.72 I.U. - 29 x 346 I.U.

Costs:

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, 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.

Costs of the medicinal products:

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					
Dapagliflozin 10 mg	98 FCT	€ 269.73	€ 1.77	€ 14.31	€ 253.65
If necessary + metformin[10] 1,000 mg	180 FCT	€ 19.08	€ 1.77	€ 0.62	€ 16.69
If necessary + liraglutide 18 mg	100 - 150 SD	€ 570.94	€ 1.77	€ 30.99	€ 538.18
If necessary + conventional insulin therapy (CT) Mixed insulin	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95

[10] Fixed reimbursement rate

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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
Appropriate comparator therapy					
Metformin[10] 1,000 mg	180 FCT	€ 19.08	€ 1.77	€ 0.62	€ 16.69
Human insulin (NPH insulin)[10]	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95
Mixed insulin[10]	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95
Human insulin (bolus insulin)[10]	3000 I.U.	€ 89.94	€ 1.77	€ 6.22	€ 81.95
Abbreviations: SD = single doses; FCT = film-coated tablets, I.U. = international units					

LAUER-TAXE® last revised: 15 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[11]	Number	Consumption/ year
Concomitant active ingredient of the medicinal product to be assessed				
Liraglutide	Disposable needles	€ 19.95	1 x daily	365
Appropriate comparator therapy				
Human insulin (NPH insulin)	Blood glucose test strips	€ 15.95	1 – 3 x daily	365 – 1,095
	Lancets	€ 4.20	1 – 3 x daily	365 – 1,095
	Disposable needles	€ 19.95	1 – 2 x daily	365 – 730

[11] 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: 15 May 2022

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Intensified conventional insulin therapy (ICT)	Blood glucose test strips	€ 15.95	4 – 6 x daily	1,460 – 2,190
	Lancets	€ 4.20	4 – 6 x daily	1,460 – 2,190
	Disposable needles	€ 19.95	4 – 5 x daily	1,460 – 1,825

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 27 April 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 11 January 2022.

On 10 December 2021, the pharmaceutical company submitted a dossier for the benefit assessment of dapagliflozin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 13 December 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 dapagliflozin.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 March 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2022. The deadline for submitting written statements was 5 April 2022.

The oral hearing was held on 25 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 24 May 2022, and the draft resolution was approved.

At its session on 16 June 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

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Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 April 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	11 January 2022	New determination of the appropriate comparator therapy
Working group Section 35a	20 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 April 2022	Conduct of the oral hearing
Working group Section 35a	3 May 2022; 17 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	24 May 2022	Concluding discussion of the draft resolution
Plenum	16 June 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 June 2022

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

Prof. Hecken

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