

**Resolution
by the Federal Joint Committee
on an amendment to the Pharmaceutical Directive (AM-RL):
Appendix XII – Resolutions on the benefit assessment of pharmaceuticals
with new active ingredients, in accordance with the German Social Code,
Book Five (SGB V), section 35a
Canagliflozin**

from 4 September 2014

In its session on 4 September 2014, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 6 November 2014 (Federal Gazette, AT 15 December 2014 B4), as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient canagliflozin:

Canagliflozin

Therapeutic indication:

Invokana[®] is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

Add-on therapy

As add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies).

1. Additional benefit of the pharmaceutical over appropriate comparator

- a) In monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications.

Appropriate comparator:

A sulfonylurea (glibenclamide or glimepiride)

Extent and probability of additional benefit of canagliflozin over a sulfonylurea (glibenclamide or glimepiride)

An additional benefit has not been proved.

- b) In combination with other glucose-lowering medicinal products (except insulin), when these, together with diet and exercise, do not provide adequate glycaemic control (combination with metformin)

Appropriate comparator:

Metformin + a sulfonylurea (glibenclamide or glimepiride)

(Please note: if metformin is inappropriate when used according to product information, human insulin is to be used as a treatment option)

Extent and probability of additional benefit of canagliflozin in combination with metformin over metformin and a sulfonylurea (glibenclamide or glimepiride):

An additional benefit has not been proved.

- c) In combination with other glucose-lowering medicinal products (except insulin), when these, together with diet and exercise, do not provide adequate glycaemic control (combination with a sulfonylurea)

Appropriate comparator:

Metformin + sulfonylurea (glibenclamide or glimepiride)

(Please note: if metformin is inappropriate when used according to product information, human insulin is to be used as a treatment option)

Extent and probability of additional benefit of canagliflozin in combination with a sulfonylurea over metformin and a sulfonylurea (glibenclamide or glimepiride):

An additional benefit has not been proved.

- d) In combination with at least two other glucose-lowering medicinal products when these, together with diet and exercise, do not provide adequate glycaemic control

Appropriate comparator:

Metformin + human insulin

(Please note: therapy only with human insulin if metformin as used according to product information is insufficiently effective or not tolerated.)

Extent and probability of additional benefit of canagliflozin in combination with metformin and a sulfonylurea over metformin and human insulin:

An additional benefit has not been proved.

- e) In combination with insulin (with or without an oral anti-diabetic medication)

Appropriate comparator:

Metformin + human insulin

(Please note: therapy only with human insulin if metformin as used according to product information is insufficiently effective or not tolerated)

Extent and probability of additional benefit of canagliflozin in combination with insulin (with or without an oral anti-diabetic medication) over metformin and human insulin:

An additional benefit has not been proved.

2. Number of patients and criteria for defining patients eligible for treatment

- a) In monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications.

Number: approx. 221,400 patients

- b) In combination with other glucose-lowering medicinal products (except insulin)¹, when these, together with diet and exercise, do not provide adequate glycaemic control (combination with metformin)

Number: approx. 468,700 patients

- c) In combination with other glucose-lowering medicinal products (except insulin)², when these, together with diet and exercise, do not provide adequate glycaemic control (combination with a sulfonylurea)

Number: approx. 35,900 patients

- d) In combination with at least two other glucose-lowering medicinal products when these, together with diet and exercise, do not provide adequate glycaemic control

Number: approx. 77,400 patients

- e) In combination with insulin (with or without an oral anti-diabetic medication)

Number: approx. 450,000 – 650,000 patients

3. Requirements for quality-assured administration

The specifications outlined in the product information are to be followed. The European Medicines Agency (EMA), the European regulatory authority, provides the product information for Invokana[®] (active ingredient: canagliflozin) at the following public link (last accessed: 23 July 2014):

www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002649/WC500156456.pdf

4. Costs of treatment

- a) In monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications.

¹ Combination with sulfonylurea excluded (see population c).

² Combination with metformin excluded (see population c).

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Treatment days per patient per year
Pharmaceutical evaluated				
Canagliflozin	ongoing, 1 x daily	ongoing	365	365
Appropriate comparator glibenclamide or glimepiride				
Glibenclamide	ongoing, 1 – 2 x daily	ongoing	365	365
Glimepiride	ongoing, 1 x daily	ongoing	365	365

Consumption:

Description of therapy	Strength (mg)	Number/amount per pack (tablets) ³	Average annual consumption (tablets)
Pharmaceutical evaluated			
Canagliflozin	100 mg	100	365
	300 mg	100	365
Appropriate comparator glibenclamide or glimepiride			
Glibenclamide ⁴	3.5 mg	180	182.5 – 1,095
Glimepiride	1 mg – 6 mg	180	365

Costs:

Cost of pharmaceutical:

Description of therapy	Costs (pharmacy retail price)	Cost after legally mandated rebates
Pharmaceutical evaluated		
Canagliflozin	100 mg	€227.58 [€1.80 ⁵ ; €12.80 ⁶]
	300 mg	€336.77 [€1.80 ⁵ ; €19.20 ⁶]
Appropriate comparator glibenclamide or glimepiride		
Glibenclamide ⁷	€14.93	€12.82 [€1.80 ⁵ ; €0.31 ⁶]
Glimepiride ⁷	€16.87 – 82.53	€14.60 – 75.07 [€1.80 ⁵ ; €0.47 – €5.66 ⁶]

"Lauer-Steuer", effective: 15 August 2014

Costs for additional, necessary statutory health insurance (SHI) benefits: none

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated	
Canagliflozin	€330.67 – 1,229.21
Appropriate comparator glibenclamide or glimepiride	
Glibenclamide	€13.00 – 77.99
Glimepiride	€29.61 – 152.23

³ Largest pack.

⁴ Calculation is based on a strength of 3.5 mg. Dosage according to product information 1.75 – 10.5 mg.

⁵ Rebate in accordance with SGB V, section 130.

⁶ Rebate in accordance with SGB V, section 130a.

⁷ Reference price.

- c) In combination with other glucose-lowering medicinal products (except insulin), when these, together with diet and exercise, do not provide adequate glycaemic control (combination with metformin)

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Treatment days per patient per year
Pharmaceutical evaluated as combination therapy with metformin				
Canagliflozin	ongoing, 1 x daily	ongoing	365	365
Metformin	ongoing, 2 x daily	ongoing	365	365
Appropriate comparator glibenclamide or glimepiride, each with metformin				
Glibenclamide	ongoing, 1 – 2 x daily	ongoing	365	365
Glimepiride	ongoing, 1 x daily	ongoing	365	365
Metformin	ongoing, 2 – 3 x daily	ongoing	365	365

Consumption:

Description of therapy	Strength (mg)	Number/amount per pack (tablets) ³	Average annual consumption (tablets)
Pharmaceutical evaluated as combination therapy with metformin			
Canagliflozin	100 mg	100	365
	300 mg	100	365
Metformin ⁸	1,000 mg	180	365 – 1,095
Appropriate comparator glibenclamide or glimepiride, each with metformin			
Glibenclamide ⁴	3.5 mg	180	182.5 – 1,095
Glimepiride	1 mg – 6 mg	180	365
Metformin ⁸	1,000 mg	180	365 – 1,095

Costs:

Cost of pharmaceutical:

Description of therapy	Costs (pharmacy retail price)	Cost after legally mandated rebates
Pharmaceutical evaluated as combination therapy with metformin		
Canagliflozin 100 mg	€242.18	€227.58 [€1.80 ⁵ ; €12.80 ⁶]
	€357.77	€336.77 [€1.80 ⁵ ; €19.20 ⁶]
Metformin ⁷	€18.78	€16.36 [€1.80 ⁵ ; €0.62 ⁶]
Appropriate comparator glibenclamide or glimepiride, each with metformin		
Glibenclamide ⁷	€14.93	€12.82 [€1.80 ⁵ ; €0.31 ⁶]
Glimepiride ⁷	€16.87 – 82.53	€14.60 – €75.07 [€1.80 ⁵ ; €0.47 – €5.66 ⁶]
Metformin ⁷	€18.78	€16.36 [€1.80 ⁵ ; €0.62 ⁶]

"Lauer-Taxe", effective: 15 August 2014

Costs for additional, necessary SHI benefits: none

⁸ Calculation is based on a strength of 1,000 mg. Dosage according to product information 1,000 – 3,000 mg.

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated as combination therapy with metformin	
Canagliflozin + metformin	€863.84 – 1,328.73
Appropriate comparator glibenclamide or glimepiride, each with metformin	
Glibenclamid + metformin or Glimepiride + metformin	€46.17 – 177.51 or €62.78 – €251.75

c) In combination with other glucose-lowering medicinal products (except insulin), when these, together with diet and exercise, do not provide adequate glycaemic control (combination with a sulfonylurea)

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Treatment days per patient per year
Pharmaceutical evaluated as combination therapy with a sulfonylurea				
Canagliflozin	ongoing, 1 x daily	ongoing	365	365
Glibenclamide	ongoing, 1 – 2 x daily	ongoing	365	365
Glimepiride	ongoing, 1 x daily	ongoing	365	365
Appropriate comparator glibenclamide or glimepiride, each with metformin				
Glibenclamide	ongoing, 1 – 2 x daily	ongoing	365	365
Glimepiride	ongoing, 1 x daily	ongoing	365	365
Metformin	ongoing, 2 – 3 x daily	ongoing	365	365

Consumption:

Description of therapy	Strength (mg)	Number/amount per pack (tablets) ³	Average annual consumption (tablets)
Pharmaceutical evaluated as combination therapy with a sulfonylurea			
Canagliflozin	100 mg	100	365
	300 mg	100	365
Glibenclamide ⁴	3.5 mg	180	182.5 – 1,095
Glimepiride	1 mg – 6 mg	180	365
Appropriate comparator glibenclamide or glimepiride, each with metformin			
Glibenclamide ⁴	3.5 mg	180	182.5 – 1,095
Glimepiride	1 mg – 6 mg	180	365
Metformin ⁸	1,000 mg	180	365 – 1,095

Costs:

Cost of pharmaceutical:

Description of therapy	Costs (pharmacy retail price)	Cost after legally mandated rebates
Pharmaceutical evaluated as combination therapy with a sulfonylurea		
Canagliflozin	100 mg	€242.18 €227.58 [€1.80 ⁵ ; €12.80 ⁶]
	300 mg	€357.77 €336.77 [€1.80 ⁵ ; €19.20 ⁶]

Description of therapy	Costs (pharmacy retail price)	Cost after legally mandated rebates
Glibenclamide ⁷	€14.93	€12.82 [€1.80 ⁵ ; €0.31 ⁶]
Glimepiride ⁷	€16.87 – 82.53	€14.60 – 75.07 [€1.80 ⁵ ; €0.47– €5.66 ⁶]
Appropriate comparator glibenclamide or glimepiride, each with metformin		
Glibenclamide ⁷	€14.93	€12.82 [€1.80 ⁵ ; €0.31 ⁶]
Glimepiride ⁷	€16.87 – 82.53	€14.60 – 75.07 [€1.80 ⁵ ; €0.47– €5.66 ⁶]
Metformin ⁷	€18.78	€16.36 [€1.80 ⁵ ; €0.62 ⁶]

"Lauer-Taxe", effective: 15 August 2014

Costs for additional, necessary statutory health insurance (SHI) benefits: none

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated as combination therapy with a sulfonylurea	
Canagliflozin + glibenclamide or canagliflozin + glimepiride	€843.67 – 1,307.20 or €860.27 – 1,381.44
Appropriate comparator glibenclamide or glimepiride, each with metformin	
Glibenclamide + metformin or glimepiride + metformin	€46.17 – 177.51 or €62.78 – 251.75

- d) In combination with at least two other glucose-lowering medicinal products when these, together with diet and exercise, do not provide adequate glycaemic control

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Treatment days per patient per year
Pharmaceutical evaluated as combination therapy with at least two other glucose-lowering medicinal products ⁹				
Canagliflozin	ongoing, 1 x daily	ongoing	365	365
Glibenclamide	ongoing, 1 – 2 x daily	ongoing	365	365
Glimepiride	ongoing, 1 x daily	ongoing	365	365
Metformin	ongoing, 2 x daily	ongoing	365	365
Appropriate comparator human insulin with metformin				
Human insulin (NPH insulin)	ongoing, 1 – 2 x daily	ongoing	365	365
Metformin	ongoing, 2 – 3 x daily	ongoing	365	365
Therapy only with human insulin if metformin is insufficiently effective or not tolerated				
Conventional insulin therapy (combination insulin)	ongoing, 1 – 2 x daily	ongoing	365	365

⁹ The combination with a sulfonylurea and metformin is shown as an example of combination therapy with at least two other glucose-lowering medicinal products.

Consumption:

Description of therapy	Strength (mg)	Number/amount per pack (tablets) ³	Average annual consumption (tablets)
Pharmaceutical evaluated as combination therapy with at least two other glucose-lowering medicinal products			
Canagliflozin	100 mg	100	365
	300 mg	100	365
Glibenclamide ⁴	3.5 mg	180	182.5 – 1,095
Glimepiride	1 mg – 6 mg	180	365
Metformin ⁸	1,000 mg	180	365 – 1,095
Appropriate comparator human insulin with metformin			
Human insulin (NPH insulin) ¹⁰	100 IU/mL	3,000 IU	13,797 IU – 27,594 IU
Metformin ⁸	1,000 mg	180	365 – 1,095
Therapy only with human insulin if metformin is insufficiently effective or not tolerated			
Conventional insulin therapy (combination insulin)	100 IU/mL	3,000 IU	13,797 IU – 27,594 IU

Costs:

Cost of pharmaceutical:

Description of therapy	Costs (pharmacy retail price)	Cost after legally mandated rebates
Pharmaceutical evaluated as combination therapy with at least two other glucose-lowering medicinal products		
Canagliflozin	100 mg	€242.18 €227.58 [€1.80 ⁵ ; €12.80 ⁶]
	300 mg	€357.77 €336.77 [€1.80 ⁵ ; €19.20 ⁶]
Glibenclamide ⁷	€14.93	€12.82 [€1.80 ⁵ ; €0.31 ⁶]
Glimepiride ⁷	€16.87 – 82.53	€14.60 – 75.07 [€1.80 ⁵ ; €0.47– €5.66 ⁶]
Metformin ⁷	€18.78	€16.36 [€1.80 ⁵ ; €0.62 ⁶]
Appropriate comparator human insulin with metformin		
Human insulin (NPH insulin) ⁷	€89.64	€81.62 [€1.80 ⁵ ; €6.22 ⁶]
Metformin ⁷	€18.78	€16.36 [€1.80 ⁵ ; €0.62 ⁶]
Therapy only with human insulin if metformin is insufficiently effective or not tolerated		
Conventional insulin therapy (Combination insulin) ⁷	€89.64	€81.62 [€1.80 ⁵ ; €6.22 ⁶]

“Lauer-Taxe”, effective: 15 August 2014

¹⁰ Average insulin need: 0.5 to 1 IU/kg BW/day; reference body weight: 75.6 kg BW (microcensus 2009).

Costs for additional, necessary statutory health insurance (SHI) benefits:

Description of therapy	Additional necessary SHI expense items				
	Description	Cost/pack ¹¹	Number/day	Consumption/year	Cost/year
Appropriate comparator – human insulin + metformin (or treatment only with human insulin, if applicable)	Blood sugar test strips	€12.00	1 – 3	365 – 1,095	€87.60 – 262.80
	Lancets	€3.80	1 – 3	365 – 1,095	€6.94 – 20.80
	Single-use needles	€22.80	1 – 2	365 – 730	€83.22 – 166.44

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated as combination therapy with at least two other glucose-lowering medicinal products	
Canagliflozin + metformin + glibenclamide or canagliflozin + metformin + glimepiride	€876.84 – 1,406.72 or €893.45 – 1,480.96
Appropriate comparator human insulin with metformin; or only with human insulin	
Human insulin (NPH insulin) + metformin	€408.54 – 850.26
Therapy only with human insulin, if metformin is not adequately effective or not tolerated	
Conventional insulin therapy (combination insulin)	€375.37 – 750.74
Costs of additional, necessary SHI benefits	
Blood sugar test strips	€87.60 – 262.80
Lancets	€6.94 – 20.80
Single-use needles	€83.22 – 166.44

e) In combination with insulin (with or without an oral anti-diabetic medication)

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Treatment days per patient per year
Pharmaceutical evaluated as combination therapy with insulin (with or without an oral anti-diabetic medication) ¹²				
Canagliflozin	ongoing, 1 x daily	ongoing	365	365
Human insulin (NPH insulin)	ongoing, 1 – 2 x daily	ongoing	365	365
Metformin	ongoing, 2 – 3 x daily	ongoing	365	365
Appropriate comparator human insulin with metformin				
Human insulin (NPH insulin)	ongoing, 1 – 2 x daily	ongoing	365	365
Metformin	ongoing, 2 – 3 x daily	ongoing	365	365
Therapy only with human insulin if metformin is insufficiently effective or not tolerated				
Conventional insulin therapy (combination insulin)	ongoing, 1 – 2 x daily	ongoing	365	365

¹¹ Number of test strips/pack = 50; Number of lancets/pack = 200, least expensive pack according to "Lauer-Taxe"; effective: 15 August 2014.

¹² Metformin is named as an example of an additional anti-diabetic medication.

Consumption:

Description of therapy	Strength (mg)	Number/amount per pack (tablets) ³	Average annual consumption (tablets)
Pharmaceutical evaluated as combination therapy with insulin (with or without an oral anti-diabetic medication)			
Canagliflozin	100 mg	100	365
	300 mg	100	365
Human insulin (NPH insulin) ¹⁰	100 IU/mL	3,000 IU	13,797 IU – 27,594 IU
Metformin ⁸	1,000 mg	180	365 – 1,095
Appropriate comparator human insulin with metformin			
Human insulin (NPH insulin) ¹⁰	100 IU/mL	3,000 IU	13,797 IU – 27,594 IU
Metformin ⁸	1,000 mg	180	365 – 1,095
Therapy only with human insulin if metformin is insufficiently effective or not tolerated			
Conventional insulin therapy (combination insulin)	100 IU/mL	3,000 IU	13,797 IU – 27,594 IU

Costs:

Cost of pharmaceutical:

Description of therapy	Costs (pharmacy retail price)	Cost after legally mandated rebates
Pharmaceutical evaluated as combination therapy with insulin (with or without an oral anti-diabetic medication)		
Canagliflozin 100 mg	€242.18	€227.58 [€1.80 ⁵ ; €12.80 ⁶]
	€357.77	€336.77 [€1.80 ⁵ ; €19.20 ⁶]
Human insulin (NPH insulin) ⁷	€89.64	€81.62 [€1.80 ⁵ ; €6.22 ⁶]
Metformin ⁷	€18.78	€16.36 [€1.80 ⁵ ; €0.62 ⁶]
Appropriate comparator human insulin with metformin		
Human insulin (NPH insulin) ⁷	€89.64	€81.62 [€1.80 ⁵ ; €6.22 ⁶]
Metformin ⁷	€18.78	€16.36 [€1.80 ⁵ ; €0.62 ⁶]
Therapy only with human insulin if metformin is insufficiently effective or not tolerated		
Conventional insulin therapy (Combination insulin) ⁷	€89.64	€81.62 [€1.80 ⁵ ; €6.22 ⁶]

"Lauer-Taxe", effective: 15 August 2014

Costs for additional, necessary statutory health insurance (SHI) benefits: none

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated as combination therapy with insulin (with or without oral anti-diabetic medication)	
Canagliflozin + human insulin (NPH insulin) or Canagliflozin + human insulin (NPH insulin) + metformin	€1,206.04 – 1,979.95 or €1,239.21 – 2,079.47
Appropriate comparator human insulin + metformin; only human insulin, if applicable	
Human insulin (NPH insulin) + metformin	€408.54 – €850.26

Description of therapy	Annual treatment costs per patient
Therapy only with human insulin if metformin is not adequately effective or not tolerated	
Conventional insulin therapy (combination insulin)	€375.37 – 750.74

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 4 September 2014.

The justification for this resolution will be published on the websites of the Federal Joint Committee at www.g-ba.de.

Berlin, 4 September 2014

The Federal Joint Committee in
accordance with SGB V,
section 91

The Chair
Hecken