Gemeinsamer Bundesausschuss

Semaglutide

Resolution of: 15 April 2021/ 5 August 2021 Valid until: unlimited
Entry into force on: 15 April 2021/ 5 August 2021
BAnz AT 02.06.2021 B5 / 22.10.2021 B3

Therapeutic indication (according to the marketing authorisation of 8 February 2018 and 3 April 2020):

Ozempic is indicated for the treatment of adults with insufficiently controlled diabetes mellitus type 2 as an addition to diet and exercise

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

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and populations studied, see sections 4.4, 4.5, and 5.1.

Rybelsus s is indicated for the treatment of adults with insufficiently controlled diabetes mellitus type 2 to improve glycaemic control as an addition to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in combination with other medicinal products for treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and populations studied, see sections 4.4, 4.5, and 5.1.

Therapeutic indication of the resolution (resolution from the 15/04/2021):

see therapeutic indication according to marketing authorisation

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

a) Adult patients with diabetes mellitus type 2 for whom diet and exercise alone do not adequately control blood glucose and for whom the use of metformin is not appropriate due to intolerance

a1) in patients without established cardiovascular disease[1]

[1] established cardiovascular disease can be determined in the present case on the basis of the SUSTAIN 6 and PIONEER 6 studies (see study protocols, Marso et. al. Semaglutide and Cardiovascular Outcomes in Patients with Diabetes Type 2. N Engl J Med 2016; 375:1834-1844. DOI: 10.1056/NEJMoa1607141 or Husain, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019; 381(9): 841-851. https://dx.doi.org/10.1056/NEJMoa1901118.) defined and summarized here approximately as ≥ 50 years of age with at least one cardiovascular disorder (previous myocardial infarction; Stroke or transient ischemic attack; revascularisation; > 50% stenosis; previous symptomatic coronary artery disease or unstable angina; asymptomatic cardiac ischemia, chronic heart failure (NYHA class II-III) or chronic renal failure) or ≥ 60 years of age with at least one risk factor for cardiovascular disease (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or Ankle Brachial Index < 0.9).

Appropriate comparator therapy:

- Sulfonylureas (glibenclamide or glimepiride)

Extent and probability of the additional benefit of semaglutide compared to the appropriate comparator therapy:

An additional benefit is not proven.

a2) in patients with established cardiovascular disease[1] in combination with further medication for the treatment of cardiovascular risk factors[2]

Appropriate comparator therapy:

- Sulfonylureas (glibenclamide or glimepiride)

Extent and probability of the additional benefit of semaglutide compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment <u>with one</u> hypoglycaemic agent (other than insulin) do not adequately control blood glucose

b1) in patients without established cardiovascular disease[1]

Appropriate comparator therapy:

- Metformin + sulfonylureas (glibenclamide or glimepiride) *or*
- Metformin + empagliflozin

Extent and probability of additional benefit of semaglutide + metformin versus empagliflozin + metformin:

An additional benefit is not proven.

b2) in patients with established cardiovascular disease[1] in combination with further medication for the treatment of cardiovascular risk factors[2]

Appropriate comparator therapy:

- Metformin + sulfonylureas (glibenclamide or glimepiride) *or*
- Metformin + empagliflozin *or*
- Metformin + liraglutide[3]

Extent and probability of the additional benefit of semaglutide compared to the appropriate comparator therapy:

An additional benefit is not proven.

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[2] In particular, anti-hypertensive drugs, anticoagulants and/or lipid-lowering agents.

[3] Empagliflozin or liraglutide only for patients with established cardiovascular disease who are receiving additional medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants and/or lipid-lowering agents (for operationalisation see study protocols: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117-28. DOI 10.1056/NEJMoa1504720 or Marso, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

c) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose

c1) in patients without established cardiovascular disease[1]

Appropriate comparator therapy:

- Human insulin + metformin *or*
- only human insulin if metformin is intolerable or contraindicated according to the product information or is not sufficiently effective due to advanced diabetes mellitus type 2

Extent and probability of the additional benefit of semaglutide compared to the appropriate comparator therapy:

An additional benefit is not proven.

c2) in patients with established cardiovascular disease[1] in combination with further medication for the treatment of cardiovascular risk factors[2]

Appropriate comparator therapy:

- Human insulin + metformin *or*
- Human insulin + empagliflozin[3] *or*
- Human insulin + liraglutide[3] *or*
- Human insulin, if the specific combination partners are intolerable or contraindicated according to the product information or are not sufficiently effective due to advanced diabetes mellitus type 2

Extent and probability of the additional benefit of semaglutide compared to the appropriate comparator therapy:

An additional benefit is not proven.

d) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose

d1) in patients without established cardiovascular disease[1]

Appropriate comparator therapy:

- The optimisation of the human insulin regime (+ metformin, if necessary)

Extent and probability of the additional benefit of semaglutide compared to the appropriate comparator therapy:

An additional benefit is not proven.

d2) in patients with established cardiovascular disease[1] in combination with further medication for the treatment of cardiovascular risk factors[2]

Appropriate comparator therapy:

- The optimisation of the human insulin regime (if necessary + metformin *or* empagliflozin[3] *or* liraglutide[3])

Extent and probability of the additional benefit of semaglutide compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[4]

a) Adult patients with diabetes mellitus type 2 for whom diet and exercise alone do not adequately control blood glucose and for whom the use of metformin is not appropriate due to intolerance

a1) in patients without established cardiovascular disease[1] *and*

a2) in patients with established cardiovascular disease[1] in combination with further medication for the treatment of cardiovascular risk factors[2] *and*

c1) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose - in patients without established cardiovascular disease[1] *and*

d1) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose - in patients without established cardiovascular disease[1]

There is no usable data for the benefit assessment.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	There are no usable data for the benefit assessment.
Morbidity	∅	There are no usable data for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	∅	There are no usable data for the benefit assessment.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

[4] Data from the dossier assessment of the IQWiG (A20-93) and from the addendum (A21-30), unless otherwise indicated.

b) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do not adequately control blood glucose

b1) in patients without established cardiovascular disease[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No statistically significant difference between treatment groups.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↓	Disadvantage in the endpoint "therapy discontinuation due to AE". Advantage in detail for specific AE "genital infections"; disadvantage in detail for "gastrointestinal disorders".
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

PIONEER 2 study: Semaglutide + metformin vs empagliflozin + metformin

Mortality and morbidity

Endpoint	Intervention Semaglutide + Metformin		control Empagliflozin + metformin		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a] p value AD
Mortality					
Overall mortality	410	0 (0)	409	1 (0.2)	0.33 [0.01; 8.14]; 0.371
Morbidity					
acute coronary syndrome[b]	no usable data available[c]				

Endpoint	Intervention Semaglutide + Metformin		control Empagliflozin + metformin		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a] p value AD
cerebrovascular event[d]	411	0 (0)	410	4 (1.0)	0.11 [0.01; 2.05] 0.046 AD = 1,0 %
Hospitalisations due to cardiac insufficiency	411	2 (0.5)	410	1 (0.2)	2.00 [0.18; 21.92] 0.683
Kidney disease[e,f]	411	0 (0)	409	1 (0.2)	1.00 [0.06; 15.89][g]; > 0.999[h]
diabetic retinopathies	no usable data available[c]				

a) unless otherwise stated, unconditional exact test (Barnard's test). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. In the case of 0 events in one study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI.
b) includes the following adjudicated events: acute myocardial infarction (STEMI or NSTEMI), silent myocardial infarction, or hospitalisation for unstable angina.
c) for justification see section 2.4.2.1 of the present IQWiG dossier assessment.
d) includes the following adjudicated events: ischaemic or haemorrhagic stroke, stroke with unexplained cause or TIA
e) The following events are considered (coded according to MedDRA): "Acute kidney injury (PT, SAEs)".
f) Only data on events that occurred during the treatment phase are available. Events after discontinuation of study medication were not recorded.
g) IQWiG calculation of RR and CI (asymptotic). In the case of 0 events in one study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI.
h) IQWiG calculation, unconditional exact test (CSZ method according to Andrés et al, 1994).

Abbreviations:
AD: Absolute difference: KI: Confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of patients evaluated; NSTEMI: Non-ST-stretch elevation myocardial infarction; PT: preferred term; RR: Relative Risk; STEMI: ST-segment elevation myocardial infarction; SAE: serious adverse event; TIA: transient ischemic attack; AE: adverse event

Health-related quality of life

Endpoint	Intervention Semaglutide + Metformin		control Empagliflozin + metformin		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
SF-36v2[b:] Improvement of 15 % of the scale range					
physical sum score (PCS)[c]	386	27 (7.0)	382	33 (8.6)	0,81 [0,50; 1,32]; 0,530

Endpoint	Intervention Semaglutide + Metformin		control Empagliflozin + metformin		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
mental sum score (MCS)[c]	386	39 (10.1)	382	44 (11.5)	0,88 [0,58; 1,32]; 0,544
physical functionality[c]	386	59 (15.3)	383	58 (15.1)	1,01 [0,72; 1,41]
physical role function	386	56 (14.5)	382	83 (21.7)	0,67 [0,49; 0,91]
physical pain[c]	386	99 (25.6)	383	108 (28.2)	0,91 [0,72; 1,15]
general health status[c]	386	111 (28.8)	383	89 (23.2)	1,24 [0,97; 1,57]
Vitality[c]	386	78 (20.2)	383	77 (20.1)	1,01 [0,76; 1,33]
social functioning[c]	386	58 (15.0)	383	55 (14.4)	1.05 [0.74; 1.47]
emotional role function[c]	386	85 (22.0)	382	83 (21.7)	1,01 [0,78; 1,32]
mental well-being[c]	386	51 (13.2)	383	59 (15.4)	0,86 [0,61; 1,21]

a) IQWiG calculation, unconditional exact test (CSZ method according to Andrés et al, 1994).

b) In the PIONEER 2 study, the acute version of the questionnaire was used with a recall time of 1 week. Higher (increasing) values mean better quality of life; positive effects (intervention minus control) mean an advantage for the intervention.

c) Patients with an improvement of ≥ 15% of the scale range determined using the empirical minima and maxima from a 2009 norm sample, see information in Table 7.1 of the Manual of the SF-36 (Maruish, 2011); this corresponds to an improvement of the following values: PCS: ≥ 9.7 points, MCS: ≥ 9.6 points, physical functionality: ≥ 5.8 points, physical role function: ≥ 5.3 points, physical pain: ≥ 5.9 points, general health perception: ≥ 6.6 points, vitality: ≥ 6.5 points, social functioning: ≥ 5.9 points, emotional role function: ≥ 6.9 points, psychological well-being: ≥ 7.4 points.

Abbreviations:

n. d.: no data; CI: Confidence interval; MCS: Mental Component Score; MD: mean difference; MV: mean value; N: number of patients with (at least 1) event; N: Number of patients evaluated; PCS: Physical Component Score; RR: Relative Risk; SD: Standard deviation; SE: Standard error; SF 36v2: Short Form-36 Health Survey Version 2; SMD: Standardised MD

Side effects

Endpoint	Intervention Semaglutide + Metformin		control Empagliflozin + metformin		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value AD
AE (presented additionally)	410	292 (71.2)	409	284 (69.4)	–
SAE	410	28 (6.8)	409	37 (9.0)	0.75 [0.47; 1.21] 0.248[d]
Therapy discontinuation due to AE	410	44 (10.7)	409	18 (4.4)	2.44 [1.43; 4.15]; < 0.001[d] AD = 6,3%
confirmed symptomatic hypoglycaemia (blood glucose < 56 mg/dl)	410	8 (2.0)	409	7 (1.7)	1.14 [0.42; 3.11] 0.865[d]
confirmed symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dl)	no data available[a]				
severe hypoglycaemia[b]	410	0 (0)	409	0 (0)	-
Acute pancreatitis[e]	410	1 (0.2)	409	1 (0.2)	1.00 [0.06; 15.89][c]; > 0.999[d]
Genital Infection[f]	410	4 (1.0)[g]	409	31 (7.6)[g]	0.13 [0.05; 0.36][c]; < 0.001[d] AD = 6.6%
Urinary tract infection (PT, AE)	410	11 (2.7)	409	13 (3.2)	0.84 [0.38; 1.86]; 0,753[d]
diabetic ketoacidosis (PT, SAE)[b]	410	0 (0)	409	1 (0.2)	0.33 [0.01; 8.14][c]; 0.371[d]
Gastrointestinal disorders (SOC, AEs)	410	167 (40.7)	409	58 (14.2)	2.87 [2.20; 3.75]; < 0.001[d] AD = 26,5%
included therein: nausea (PT, AE)	410	81 (19.8)	409	10 (2.4)	8.08 [4.25; 15.36]; < 0.001[d] AD = 17,4%

a) For the endpoint "symptomatic hypoglycaemia (blood glucose < 70 mg/dl)", no data are available in the dossier. The pharmaceutical company submits these with the written statement: in both study arms, 5.4% of patients had symptomatic hypoglycaemia (blood glucose < 70 mg/dl).

b) Only data on events that occurred during the treatment phase are available. Events after discontinuation of study medication were not recorded.

Endpoint	Intervention Semaglutide + Metformin		control Empagliflozin + metformin		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value AD

c) IQWiG calculation of RR and CI (asymptotic). In the case of 0 events in one study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI.

d) IQWiG calculation, unconditional exact test (CSZ method according to Andrés et al, 1994).

e) adjudicated events based on 2 of 3 of the following criteria: 1. Abdominal pain characteristic of acute pancreatitis, 2. 3-fold increase in serum amylase and/or serum lipase, and 3. characteristic signs of acute pancreatitis by imaging.

f) Post-hoc analysis on mycotic infections based on a PT / LLT collection compiled by the pU using the FDA approval of empagliflozin (for details see Table 12 of the benefit assessment).

g) IQWiG calculation from separate data by sex.

Abbreviations:
AD: Absolute difference: FDA: Food and Drug Administration; CI: Confidence interval; LLT: Lowest Level Term; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of patients evaluated; NSTEMI: Non ST-Route Elevation Infarction; PG: Plasma glucose; PT: preferred term; pU: pharmaceutical company; RR: Relative Risk; SOC: System organ class; STEMI: ST-segment elevation myocardial infarction; SAE: serious adverse event; TIA: transient ischemic attack; AE: adverse event

Additionally presented endpoints

Endpoint	Intervention Semaglutide + Metformin			control Empagliflozin + metformin			Intervention vs control
	N[a]	Values at the start of the study MV (SD)	Change week 52 MV (SE)[b]	N[a]	Values at the start of the study MV (SD)	Change week 52 MV (SE)[b]	MD [95% CI] p value[b]
HbA1c [%]	411	8.14 (0.9)	-1.30 (0.0)	410	8.14 (0.9)	-0.89 (0.0)	-0.40 [-0.54; -0.27] < 0.001
Weight [kg]	411	91.93 (20.5)	-3.79 (0.3)	410	91.30 (20.1)	-3.62 (0.3)	-0.18 [-0.88; 0.53] 0.623

a) Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at the start of the study (possibly at other times) can be based on other patient numbers.

b) MW and SE (change to week 52 per treatment group) and MD, CI and p-value (group comparison): ANCOVA with region and the corresponding value at baseline as variables. Replacement of missing values by means of multiple imputation.

Abbreviations:
ANCOVA: Analysis of covariance; HbA1c: glycated haemoglobin; n. A.: not specified; CI: Confidence interval; MD: mean difference; MV: mean value; N: number of patients evaluated; SD: Standard deviation; SE: Standard error.

b2) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do not adequately control blood glucose - In

patients with established cardiovascular disease[1] in combination with other medication for the treatment of cardiovascular risk factors[2] *and*

c2) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose - In patients with established cardiovascular disease[1] in combination with other medication for the treatment of cardiovascular risk factors[2] *and*

d2) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose - In patients with established cardiovascular disease[1] in combination with other medication for the treatment of cardiovascular risk factors[2]

SUSTAIN 6 and PIONEER 6 study in patients with inadequately controlled diabetes mellitus type 2 and established cardiovascular disease[1] in combination with further medication for the treatment of cardiovascular risk factors[2]:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	Overall, no relevant difference between treatment groups. Advantage in the endpoint "all-cause mortality" in the PIONEER 6 study.
Morbidity	↔	Overall, no relevant difference between treatment groups. Advantage in the combined endpoint "MACE" as well as "nonfatal stroke" and disadvantage in the endpoint "retinal photocoagulation" in the study SUSTAIN 6.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↓	Disadvantage in the endpoint "therapy discontinuation due to AE" in the studies PIONEER 6 and SUSTAIN 6 as well as disadvantage in detail for specific AE "gastrointestinal disorders" in the study SUSTAIN 6.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

Mortality and morbidity

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI] p value[a] AD
Mortality					
Overall mortality					
PIONEER 6	1591	23 (1.4)	1592	45 (2.8)	0.51 [0.31; 0.84] 0.008 AD = 1,4%
SUSTAIN 6	1648	62 (3.8)	1649	60 (3.6)	1.05 [0.74; 1.50] 0.785
Total					qualitative evidence synthesis
Morbidity					
MACE					
PIONEER 6	Not interpretable[b]				
SUSTAIN 6	1648	108 (6.6)	1649	146 (8.9)	0.74 [0.58; 0.95] 0.017 AD = 2,3%
cardiovascular death					
SUSTAIN 6	1648	44 (2.7)	1649	46 (2.8)	0.98 [0.65; 1.48] 0.918
nonfatal myocardial infarction					
SUSTAIN 6	1648	47 (2.9)	1649	64 (3.9)	0.74 [0.51; 1.08] 0.119
nonfatal stroke					
SUSTAIN 6	1648	27 (1.6)	1649	44 (2.7)	0.61 [0.38; 0.99] 0.044 AD = 1,1%
Myocardial infarction (fatal and nonfatal)[d]					
PIONEER 6	1591	37 (2.3[e])	1592	35 (2.2[e])	1.04 [0.66; 1.66] 0.868[f]
SUSTAIN 6	1648	54 (3.3)	1649	67 (4.1)	0.80 [0.56; 1.15] 0.223

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI] p value[a] AD
Total					qualitative evidence synthesis
Stroke (fatal and nonfatal)					
PIONEER 6	1591	13 (0.8[e)]	1592	17 (1.1[e)]	0.76 [0,37; 1,56] 0,455[f]
SUSTAIN 6	1648	30 (1.8)	1649	46 (2.8)	0.65 [0.41; 1.02] 0.063
Total					qualitative evidence synthesis
Hospitalisations due to cardiac insufficiency					
PIONEER 6	1591	21 (1.3)	1592	24 (1.5)	0.86 [0.48; 1.55]; 0.623
SUSTAIN 6	1648	59 (3.6)	1649	54 (3.3)	1.11 [0.77; 1.61] 0.574
Total					qualitative evidence synthesis
TIA					
PIONEER 6	1591	5 (0.3)	1592	9 (0.6)	0.55 [0.18; 1.64] 0.284
SUSTAIN 6	1648	10 (0.6)	1649	13 (0.8)	0.77 [0.34; 1.75] 0.532
Total					qualitative evidence synthesis
Diabetic retinopathies					
retinal photocoagulation					
PIONEER 6	no usable data available [g]				
SUSTAIN 6	1648	38 (2.3)	1649	20 (1.2)	1.91 [1.11; 3.28] 0.019 AD = 1,1%
Vitreous haemorrhage					
PIONEER 6	no usable data available [g]				
SUSTAIN 6	1648	16 (1.0)	1649	7 (0.4)	2.29 [0.94; 5.57] 0.067

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI] p value[a] AD
diabetes-related blindness[c]					
PIONEER 6	no usable data available [g]				
SUSTAIN 6	1648	5 (0.3)	1649	1 (0.1)	5.01 [0.59; 42.88] 0.141
Kidney disease					
Acute kidney injury[h]					
PIONEER 6	1591	16 (1.0)	1592	15 (0.9)	1.05 [0.52; 2.13] 0.882
SUSTAIN 6	1648	24 (1.5)	1649	36 (2.2)	0.66 [0.40; 1.11] 0.119
Total					qualitative evidence synthesis
Kidney failure[i]					
PIONEER 6	no usable data available [g]				
SUSTAIN 6	1648	18 (1.1)	1649	14 (0.8)	1.28 [0.64; 2.58] 0.484
Start of permanent renal replacement therapy					
PIONEER 6	no usable data available [g]				
SUSTAIN 6	1648	11 (0.7)	1649	12 (0.7)	0.91 [0.40; 2.07] 0.827
Death from kidney disease[c]					
PIONEER 6	no usable data available [g]				
SUSTAIN 6	1648	0 (0)	1649	0 (0)	-

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI] p value[a] AD

a) HR, 95% CI and p value: Cox proportional hazards model
- PIONEER 6: stratified by cardiovascular disease at the time of screening
- SUSTAIN 6 (for the endpoints all-cause mortality, MACE, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, myocardial infarction (fatal and nonfatal), stroke (fatal and nonfatal), cardiac insufficiency hospitalisations): SUSTAIN 6.dal stroke, myocardial infarction (fatal and nonfatal), stroke (fatal and nonfatal), hospitalisations for heart failure): Stratified by the 9 possible combinations of the 3 factors cardiovascular disease (yes / risk factor for cardiovascular disease), insulin treatment (none / basal insulin / mixed insulin), and renal function impairment with GFR < 30 mL/min/1.73 m² per MDRD (yes / no)
- SUSTAIN 6 (for the remaining endpoints): unstratified

b) The effects of semaglutide on the individual components are not equidirectional (HR [95% CI]): Cardiovascular death: 0.49 [0.27; 0.92]; Non-fatal myocardial infarction: 1.18 [0.73; 1.90]; Non-fatal stroke: 0.74 [0.35; 1.57]

c) Consideration was given to the 1. event in this endpoint regardless of whether it is also the 1st event. Event in the combined endpoint was MACE.

d) The analysis also included 6 patients in the semaglutide arm and 1 patient in the placebo arm with silent myocardial infarction.

e) IQWiG calculations

f) IQWiG calculation of p-value based on HR and 95% CI.

g) no evaluation of this operationalisation.

h) The following events are considered (coded according to MedDRA): "Acute kidney injury (PT, SAEs)".

i) operationalised as persistent doubling of serum creatinine concentration and creatinine clearance ≤ 45 ml/min/1.73 m² calculated as MDRD.

Abbreviations:
AD: Absolute difference: GFR: Glomerular filtration rate; HR: hazard ratio; n. d.: no data; CI: Confidence interval; MACE: Major Adverse Cardiovascular Events; MDRD: Modification of Diet in Renal Disease; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients evaluated; n: Number of patients with (at least 1) event; PT: preferred term; SAE: serious adverse event; TIA: transient ischaemic attack; vs: versus.

Health-related quality of life

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value[b]
SF-36v2[c]: Improvement of 15% of the scale range					
PIONEER 6	Not surveyed				
SUSTAIN 6					
physical sum score (PCS)[d]	1466	192 (13.1)	1443	167 (11.6)	1.13 [0.93; 1.37]; 0.248
mental sum score (MCS)[d]	1466	233 (15.9)	1443	215 (14.9)	1.07 [0.90; 1.26]; 0.533

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value[b]
physical functionality[d]	1467	370 (25.2)	1443	344 (23.8)	1,06 [0,93; 1,20]
bodily role function[d]	1467	370 (25.2)	1443	334 (23.1)	1,09 [0,96; 1,24]
physical pain[d]	1467	426 (29.0)	1443	386 (26.7)	1,09 [0,97; 1,22]
general health perception[d]	1467	435 (29.7)	1443	365 (25.3)	1,17 [1,04; 1,32]
Vitality[d]	1467	302 (20.6)	1443	256 (17.7)	1,16 [1,00; 1,35]
social functioning[d]	1467	280 (19.1)	1443	264 (18.3)	1,04 [0,90; 1,21]
emotional role functioning[d]	1466	389 (26.5)	1443	379 (26.3)	1,01 [0,89; 1,14]
psychic well-being[d]	1467	337 (23.0)	1443	260 (18.0)	1,27 [1,10; 1,47]

a) At the time of evaluation week 104, surveys were available for 89% and 88% of the randomised patients, respectively.
b) IQWiG calculation, unconditional exact test (CSZ method according to Andrés et al, 1994).
c) Higher (increasing) values mean better health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention. In the SUSTAIN 6 study, the standard version of the questionnaire with a recall period of 4 weeks was used.
d) Patients with an improvement of ≥ 15% of the scale range determined using the empirical minima and maxima from a 2009 norm sample, see information in Table 7.1 of the Manual of the SF-36 (Maruish. 2011); this corresponds to an improvement of the following values: PCS: ≥ 9.4 points, MCS: ≥ 9.6 points, physical functionality: ≥ 5.7 points, physical role function: ≥ 5.4 points, physical pain: ≥ 6.1 points, general health perception: ≥ 7.1 points, vitality: ≥ 7.1 points, social functioning: ≥ 6.0 points, emotional role function: ≥ 6.3 points, psychological well-being: ≥ 7.9 points.

Abbreviations:
CI: Confidence interval; MCS: Mental Component Summary; MW: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; PCS: Physical Component Summary; RR: Relative Risk; SF-36v2: Short Form-36 Health Survey Version 2; vs

Side effects

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
AE (presented additionally)					

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
PIONEER 6	Not surveyed				
SUSTAIN 6	1648	1472 (89.3)	1649	1484 (90.0)	–
SAE[a]					
PIONEER 6	1591	255 (16.0)	1592	282 (17.7)	0.90 [0,78; 1,06] 0,248[b]
SUSTAIN 6	1648	492 (29.9)	1649	544 (33.0)	0.90 [0.82; 1.00] 0.054[b]
Total					qualitative evidence synthesis
Discontinuation because of AEs					
PIONEER 6	1591	184 (11.6)	1592	104 (6.5)	1/77 [1.41; 2.23] 0.001[b] AD = 5,1%
SUSTAIN 6	1648	215 (13.0)	1649	110 (6.7)	1.96 [1.57; 2.44]; < 0.001 AD = 6,3%
Total					qualitative evidence synthesis
Pancreatitis[e]					
PIONEER 6	1591	1 (0.1)	1592	3 (0.2)	0.33 [0.03; 3.20] 0.411[b]
SUSTAIN 6	1648	11 (0.7)	1649	14 (0.8)	0.79 [0.36; 1.73] 0.689
Total					Not applicable[e]
severe Hypoglycaemia[f]					
PIONEER 6	1591	17 (1.1)	1592	12 (0.8)	1.42 [0,68; 2,96] 0,529[b]
SUSTAIN 6	1648	17 (1,1)[g]	1649	15 (0.9)	1.13 [0,57; 2,26] 0,794[b]
Total					qualitative evidence synthesis
confirmed symptomatic hypoglycaemia (blood glucose < 56 mg/dl)					

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
PIONEER 6	Not surveyed				
SUSTAIN 6	no usable data available[h]				
confirmed symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dl)					
PIONEER 6	Not surveyed				
SUSTAIN 6	1648	579 (35.1)	1649	547 (33.2)	1.06 [0,96; 1,16] 0,249[b]
Therapy discontinuation due to gastrointestinal disorders (SOC)					
PIONEER 6	1591	108 (6.8)	1592	26 (1.6)	4.16 [2.72; 6.34] 0.001[b] AD = 5,2%
SUSTAIN 6	1642	130 (7.9)	1644	23 (1.4)	5.66 [3.65; 8.77] 0.001[b] AD = 6,5%
Total					qualitative evidence synthesis
Gastrointestinal disorders (SOC, AE)					
PIONEER 6	Not surveyed				
SUSTAIN 6	1648	849 (51.5)	1649	584 (35.4)	1.45 [1.34; 1.58]; < 0.001 AD = 16,1%
nausea (PT)					
PIONEER 6	Not surveyed				
SUSTAIN 6	1648	323 (19.6)	1649	129 (7.8)	2.51 [2.07; 3.04]; < 0.001 AD = 11,8%
Vomiting (PT)					
PIONEER 6	Not surveyed				
SUSTAIN 6	1648	209 (12.7)	1649	77 (4.7)	2.72 [2.11; 3.50]; < 0.001 AD = 8,0%
Diarrhoea (PT)					
PIONEER 6	Not surveyed				

Endpoint Study	**Intervention** **Semaglutide + SoC**		**control** **Placebo + SoC**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
SUSTAIN 6	1648	299 (18.1)	1649	185 (11.2)	1.62 [1.36; 1.92]; < 0.001 AD = 6,9%
Reactions at the Injection site[i]					
PIONEER 6	Not surveyed				
SUSTAIN 6	1648	17 (1.0)	1649	21 (1.3)	0.81 [0.43; 1.53] 0.625
decreased appetite (PT, AE)					
PIONEER 6	Not surveyed				
SUSTAIN 6	1648	161 (9.8)	1649	28 (1.7)	5.75 [3.87; 8.54]; < 0.001 AD = 8,1%

a) without recording diabetic secondary complications.
b) IQWiG calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to Andrés et al, 1994).
c) adjudicated events based on 2 of 3 of the following criteria: 1. Abdominal pain characteristic of acute pancreatitis, 2. ≥ 3-fold increase in the upper normal limit of serum lipase and / or serum amylase and 3. Detection by imaging techniques. Only serious events were recorded.
d) includes the following events (coded according to MedDRA): "Acute pancreatitis (SMQ [narrow scope], AE)" and "Acute and chronic pancreatitis (HLT, AE)".
e) Due to different operationalisations of the endpoint in the two studies, no qualitative evidence synthesis was performed.
f) Severe hypoglycaemias were those classified as SAE.
g) slightly discrepant data between the current dossier (17 patients) and the dossier of the pU dated 30.10.2018 (16 patients). The discrepancy has no qualitative effect on the result.
h) discrepant information between the current dossier and the dossier dated 30/10/2018:
   - Dossier of 30.10.2018: 502 (30.5%) vs 470 (28.5%); RR [95% CI]; p-value: 1.07 [0.96; 1.19] 0.222
   - Current assessment: 382 (23.2 %) vs 355 (21.5 %); RR [95% CI]; p-value: 1.08 [0.95; 1.22] 0.268
i) includes the following events (coded according to MedDRA version 18.0): "Administration site reactions (HLT, AE)", "Application and instillation site reactions (HLT, AE)", "Infusion site reactions (HLT, AE)" and "Injection site reactions (HLT, AE)".

Abbreviations:
HLT: High Level Term; MedDRA: Medical dictionary of drug approval activities; CI: Confidence interval; n: number of patients with (at least 1) event; N: Number of patients evaluated; PT: preferred term; RR: Relative Risk; SMQ: standardised MedDRA query; SOC: System organ class; SAE: serious adverse eventAE: adverse event; vs: versus.

Additionally presented endpoints

Endpoint Study	**Intervention** **Semaglutide + SoC**			**control** **Placebo + SoC**			**Intervention vs control**
	N[a]	Values at start of study MV (SD)	Change at time of analysis[b] MV (SE)[c]	N[a]	Values at start of study MV (SD)	Change at time of analysis[b] MV (SE)[c]	MD [95% CI] p value[b]
HbA1c [%]							
PIONEER 6	no data[d]	8.2 (1.6)	-1.0 (0.0)	no data[d]	8.2 (1.6)	-0.3 (0.0)	-0.7 [-0.7; -0.6] < 0.001
SUSTAIN 6	no data[d]	8.7 (1.5)[e]	-1.3 (0.0)	no data[d]	8.7 (1.5)[e]	-0.4 (0.0)	-0.9 [-1.0; -0.8] < 0.001
Weight [kg]							
PIONEER 6	no data[f]	91.0 (21.4)	-4.2 (0.1)	no data[f]	90.8 (21.0)	-0.8 (0.1)	-3.4 [-3.8; -3.0] < 0.001
SUSTAIN 6	no data[f]	92.3 (20.7)[e]	-4.2 (0.2)	no data[f]	91.9 (20.5)[e]	-0.6 (0.2)	-3.7 [-4.1; -3.2] < 0.001

a) Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at baseline (possibly at other times) can be based on other patient numbers.

b) PIONEER 6 End of treatment; SUSTAIN 6: Week 104

c) MW and SE (change at time of analysis per treatment group) as well as MD, CI and p-value (group comparison); ANCOVA with the stratification factor(s) belonging to the respective study and the value at baseline as variables

d) Information is available on how many patients had values at baseline or at the time of analysis, but not on how many were included in the analysis. In the PIONEER 6 study, 95% and 94% of patients in the semaglutide and placebo arms, respectively, had surveys available at the time of analysis; in the SUSTAIN 6 study, the figures were 90% and 88%.

e) Discrepant information between the current dossier and dossier dated 30/10/2018. The data shown are from the current dossier.

f) Information is available on how many patients had values at baseline or at the time of analysis, but not on how many were included in the analysis. In the PIONEER 6 study, 94% and 93% of patients in the semaglutide and placebo arms, respectively, had surveys available at the time of analysis; in the SUSTAIN 6 study, the figures were 89% and 88%.

Abbreviations:
ANCOVA: Analysis of covariance; HbA1c: glycated haemoglobin; n. s.: not specified; CI: Confidence interval; MD: mean difference; MV: mean value; N: number of patients evaluated; SD: Standard deviation; SE: Standard error; vs

2. Number of patients or demarcation of patient groups eligible for treatment

a) Adult patients with diabetes mellitus type 2 for whom diet and exercise alone do not adequately control blood glucose and for whom the use of metformin is not appropriate due to intolerance:

approx. 364 000 patients

b) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do not adequately control blood glucose

approx. 642 000 patients

c) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose

approx. 440 000 patients

d) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose

approx. 662 000 patients

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 rybelusus/ozempic (active ingredient: semaglutide) at the following publicly accessible link (last access: 19 January 2021):

https://www.ema.europa.eu/documents/product-information/rybelsus-epar-product-information_de.pdf

(last access: 6. Juli 2021):

https://www.ema.europa.eu/documents/product-information/ozempic-epar-product-information_de.pdf

The use of GLP-1 receptor agonists (including semaglutide) has been associated with a risk of developing acute pancreatitis. Patients should be informed about characteristic symptomatology of acute pancreatitis, and therapy should be changed if necessary.

4. Treatment costs

Annual treatment costs:

a) Adult patients with diabetes mellitus type 2 for whom diet and exercise alone do not adequately control blood glucose and for whom the use of metformin is not appropriate due to intolerance

Designation of the therapy	Annual treatment costs:
Medicinal product to be assessed	
Semaglutide	€ 1,183.39
Appropriate comparator therapy (sulfonylureas (glibenclamide or glimepiride))	
Glibenclamide or Glimepiride	€ 13.09 – € 78.54 € 29.79 – € 152.41

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 March 2021).

Costs for additionally required SHI services: not applicable

b) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do not adequately control blood glucose

Designation of the therapy	Annual treatment costs:
Medicinal product to be assessed (semaglutide in combination with an hipoglycaemic agent[5] (other than insulin))	
Semaglutide	€ 1,183.39
Metformin	€ 33.36 – € 100.07
Glibenclamide or Glimepiride	€ 13.09 – € 78.54 € 29.79 – € 152.41
Semaglutide + metformin or Semaglutide + glibenclamide or Semaglutide + Glimepiride	Total: € 1,216.75 – € 1,283.46 € 1,196.48 – € 1,261.93 € 1,213.18 – € 1,335.80
Appropriate comparator therapy	
Metformin	€ 33.36 – € 100.07
Sulfonylureas Glibenclamide or Glimepiride	 € 13.09 – € 78.54 € 29.79 – € 152.41
Empagliflozin	€ 659.15
Liraglutide	€ 1,308.99 – € 1,963.48
	Total:

[5] Examples of combination therapy with a hypoglycaemic agent are the combination with metformin or with a sulfonylureas (glibenclamide or glimepiride).

Designation of the therapy	Annual treatment costs:
Metformin + glibenclamide or metformin + glimepiride	46,45 € – 178,61 € 63,15 € – 252,48 €
Metformin + empagliflozin	€ 692.51 – € 759.22
Metformin + liraglutide[3]	€ 1,342.35 – € 2,063.55

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 March 2021).

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Appropriate comparator therapy		
Liraglutide	Disposable needles	€ 83.22

c) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose

Designation of the therapy	Annual treatment costs:
Medicinal product to be assessed (semaglutide in combination with at least two hypoglycaemic agents [6] (other than insulin))	
Semaglutide	€ 1,183.39
Metformin	€ 33.36 – € 100.07
Glibenclamide or Glimepiride	€ 13.09 – € 78.54 € 29.79 – € 152.41
Semaglutide + metformin + glibenclamide or Semaglutide + metformin + glimepiride	Total: € 1,229.84 – € 1,362.00 € 1,246.54 – € 1,435.87
Appropriate comparator therapy	
Metformin	€ 33.36 – € 100.07
Empagliflozin	€ 659.15
Liraglutide	€ 1,308.99 – € 1,963.48
Human insulin (NPH insulin)	€ 382.74 – € 765.49
Human insulin (NPH insulin) + metformin	Total: € 416.10 – € 865.56 €

[6] An example of combination therapy with other hypoglycaemic agents is the combination with metformin and with sulfonylureas (glibenclamide or glimepiride).

Designation of the therapy	Annual treatment costs:
Human insulin (NPH insulin) + empagliflozin[3] Human insulin (NPH insulin) + liraglutide[3]	€ 1,041.89 – € 1,424.64 € 1,691.73 – € 2,728.97
If necessary, therapy with human insulin only, if metformin and empagliflozin[3]and liraglutide[3] are intolerable or contraindicated according to the product information or are not sufficiently effective due to advanced diabetes mellitus type 2	
Conventional insulin therapy (mixed insulin)	€ 382.74 – € 765.49

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 March 2021).

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Appropriate comparator therapy		
Human insulin (NPH insulin) and conventional insulin therapy (mixed insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 83.22 – € 166.44
Liraglutide	Disposable needles	€ 83.22

d) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose

Designation of the therapy	Annual treatment costs:
Medicinal product to be assessed (semaglutide in combination with insulin (with or without another hypoglycaemic agent[7]))	
Semaglutide	€ 1,183.39
Human insulin (NPH insulin)	€ 382.74 – € 765.49
metformin if necessary	€ 33.36 – € 100.07
Semaglutide + human insulin (NPH insulin) or semaglutide +human insulin (NPH insulin) + metformin	Total: € 1,566.13 – € 1,948.88 € 1,599.49 – € 2,048.95
Appropriate comparator therapy	
Empagliflozin	€ 659.15
Liraglutide	€ 1,308.99 – € 1,963.48
Metformin	€ 33.36 – € 100.07

[7] Metformin is listed as an example of the combination with another blood hypoglycaemic agent

Designation of the therapy	Annual treatment costs:
Intensified conventional insulin therapy Human insulin (NPH insulin) Human insulin (bolus insulin)	 € 153.10 – € 459.29 € 153.10 – € 459.29 Total: € 382.74 – € 765.49 €
Conventional insulin therapy (mixed insulin) Conventional insulin therapy (mixed insulin) if necessary + metformin or empagliflozin or liraglutide Conventional insulin therapy (mixed insulin) + empaglifozin[3] Conventional insulin therapy (mixed insulin) + liraglutide[3] Conventional insulin therapy (mixed insulin) + metformin	€ 382.74 – € 765.49 € Total: € 1,041.89 – € 1,424.64 € 1,691.73 – € 2,728.97 € 416.10 – € 865.56 €

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 March 2021).

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Medicinal product to be assessed (semaglutide in combination with insulin (with or without another hypoglycaemic agent))		
Human insulin (NPH insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 83.22 – € 166.44
Appropriate comparator therapy		
Conventional insulin therapy (mixed insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 83.22 – € 166.44
Intensified conventional insulin therapy	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 332.88 – € 416.10
Liraglutide	Disposable needles	€ 83.22