Resolution

Gemeinsamer Bundesausschuss

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 Dupilumab (New Therapeutic Indication: Chronic Rhinosinusitis with Nasal Polyps)

of 14 May 2020

At its session on 14 May 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of dupilumab in accordance with the resolution of 20 February 2020:

Dupilumab

Resolution of: 14 May 2020
Entry into force on: 14 May 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 October 2019):

Dupixent is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

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

Adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control

Appropriate comparator therapy:

- A treatment with intranasal corticosteroids (budesonide or mometasone furoate)

Extent and probability of the additional benefit of dupilumab as an add-on therapy with intranasal corticosteroids compared with mometasone furoate:

Indication of a considerable additional benefit

Study results according to endpoints:[1]

Adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control

Data cut-off at week 24

Results of the SINUS-24 and SINUS-52 studies as well as the meta-analysis of both studies (dupilumab + mometasone furoate vs placebo + mometasone furoate) (data cut-off at week 24)

[1] Data from the dossier assessment of the IQWiG (A19-96) unless otherwise indicated.

Mortality

Endpoint Study	Dupilumab + mometasone furoate[a]		Placebo + mometasone furoate		Dupilumab + mometasone vs Placebo + mometasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[b]
Overall mortality					
SINUS-24	143	0 (0)	132	0 (0)	-
SINUS-52	297	0 (0)	150	0 (0)	-

Morbidity

Endpoint/scale Study	Dupilumab + mometasone furoate[a]		Placebo + mometasone furoate		Dupilumab + mometasone vs Placebo + mometasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[b]
SNOT-22 total score (improvement ≥ 8.9 points)[c]					
SINUS-24	143	116 (81.1)	133	71 (53.4)	1.53 [1.28; 1.82]; < 0.001
SINUS-52	295	233 (79.0)	153	82 (53.6)	1.48 [1.26; 1.73]; < 0.001
Total					1.50 [1.33; 1.69]; < 0.001

Endpoint/scale Study	Dupilumab + mometasone furoate[a]			Placebo + mometasone furoate			Dupilumab + mometasone vs Placebo + mometasone
	N[d]	Values at start of study MV (SD)	Change at the end of study MV (SE)	N[d]	Values at start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI]; p value[e]
Nasal congestion/obstruction[f]							
SINUS-24	140	2.26 (0.57)	−1.38 (0.07)	128	2.45 (0.55)	−0.56 (0.07)	−0.82 [−1.00; −0.65]; < 0.001
SINUS-52	289	2.46 (0.61)	−1.28 (0.06)	144	2.38 (0.54)	−0.48 (0.07)	−0.80 [−0.95; −0.64]; < 0.001

Endpoint/scale Study	Dupilumab + mometasone furoate[a]			Placebo + mometasone furoate			Dupilumab + mometasone vs Placebo + mometasone
	N[d]	Values at start of study MV (SD)	Change at the end of study MV (SE)	N[d]	Values at start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI]; p value[e]
Total							−0.81 [−0.93; −0.70]; < 0.001 Hedges' g: −1.05 [−1.20; −0.90]
Loss of the sense of smell[f]							
SINUS-24	140	2.70 (0.57)	−1.44 (0.07)	128	2.73 (0.51)	−0.37 (0.08)	−1.07 [−1.26; −0.88]; < 0.001
SINUS-52	289	2.77 (0.53)	−1.24 (0.06)	144	2.72 (0.52)	−0.27 (0.08)	−0.98 [−1.15; −0.81]; < 0.001
Total							−1.02 [−1.15, −0.89]; < 0.001 Hedges' g: −1.20 [−1.35; −1.05]
Rhinorrhoea (anterior/posterior)[f]							
SINUS-24	140	1.87 (0.62)	−1.07 (0.06)	126	2.10 (0.67)	−0.49 (0.06)	−0.58 [−0.74; −0.42]; < 0.001
SINUS-52	289	2.07 (0.74)	−1.03 (0.05)	141	1.98 (0.72)	−0.49 (0.07)	−0.54 [−0.69; −0.39]; < 0.001
Total							−0.57 [−0.67; −0.46]; < 0.001 Hedges' g: −0.80 [−0.95; −0.65]
Rhinosinusitis VAS[f]							
SINUS-24	134	7.42 (2.01)	−4.67 (0.23)	123	7.96 (2.06)	−1.59 (0.24)	−3.08 [−3.68; −2.47]; < 0.001
SINUS-52	277	8.01 (2.01)	−4.43 (0.18)	139	7.98 (2.22)	−1.88 (0.24)	−2.55 [−3.07; −2.03]; < 0.001

Endpoint/scale Study	Dupilumab + mometasone furoate[a]			Placebo + mometasone furoate			Dupilumab + mometasone vs Placebo + mometasone
	N[d]	Values at start of study MV (SD)	Change at the end of study MV (SE)	N[d]	Values at start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI]; p value[e]
Total							−2.78 [−3.18; −2.39]; < 0.001 Hedges' g: −1.10 [−1.25; −0.94]
Health status (EQ-5D VAS)[g]							
SINUS-24	133	66.10 (19.39)	11.81 (1.53)	127	65.98 (21.32)	3.43 (1.60)	8.38 [4.36; 12.39]; < 0.001
SINUS-52	277	65.70 (20.72)	11.06 (1.17)	140	63.89 (19.99)	3.45 (1.51)	7.62 [4.32; 10.91]; < 0.001
Total							7.90 [5.35; 10.45]; < 0.001 Hedges' g: 0.48 [0.33; 0.64]

Health-related quality of life

not collected

Side effects

Endpoint Study	Dupilumab + mometasone furoate[a]		Placebo + Mometasone furoate		Dupilumab + mometasone vs placebo + mometasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[b]
AEs (additionally shown)					
SINUS-24	143	93 (65.0)	132	93 (70.5)	
SINUS-52	297	221 (74.4)	150	122 (81.3)	
SAEs					
SINUS-24	not usable[h]				
SINUS-52	not usable[h]				

Endpoint Study	Dupilumab + mometasone furoate[a]		Placebo + Mometasone furoate		Dupilumab + mometasone vs placebo + mometasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[b]
Discontinuation because of AEs					
SINUS-24	not usable[h]				
SINUS-52	not usable[h]				

a. For the analysis of the SINUS-52 study at Week 24, the treatment groups with dupilumab + mometasone furoate were pooled (Arm A + B).
b. RR, 95% CI, and p value from a generalised linear model with treatment arm, asthma/NSAID-ERD status, history of surgery, and region as covariates; for the meta-analysis, also study and study × treatment arm as covariates. Missing values after an emergency operation were replaced by WOCF.
c. Suitable data on individual scores are not available for responder analyses. The MID of 8.9 points is applicable and validated only for the total score. The individual scores are recorded on a scale of 0–5.
d. Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
e. MD, 95% CI, and p value from an ANCOVA for the change at start of study with treatment arm, value at the start of study, asthma/ NSAID-ERD status, history of surgery, and region as covariates; for the meta-analysis also study and study × treatment arm as covariates. Missing values after an emergency operation were replaced by WOCF.
f. Lower (decreasing) values mean an improvement; negative effects (dupilumab Q2W + mometasone furoate) − (placebo + mometasone furoate) mean an advantage for dupilumab Q2W + mometasone furoate.
g. Higher (increasing) values mean an improvement; positive effects (dupilumab Q2W + mometasone furoate) − (placebo + mometasone furoate) mean an advantage for dupilumab Q2W + mometasone furoate.
h. Data are not usable because they contain a large proportion of patients with events that can be both side effects and symptomatology of the disease.

ANCOVA: covariance analysis; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; IPD: individual patient data; CI: confidence interval; MD: mean difference; MID: Minimal important difference; MV: mean value; N: number of patients evaluated; n: number of patients with (at least 1) event; N: number of patients evaluated; NC: nasal congestion/obstruction; NSAID-ERD: analgesic intolerance syndrome; Q2W: 1 time every 2 weeks; RCT: randomised controlled study; RR: relative risk; SD: standard deviation; SE: standard error; SNOT-22: 22-Item Sino-nasal Outcome Test, SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus WOCF: Worst Observation carried forward

Data cut-off at week 52

Study SINUS-52: RCT dupilumab + mometasone furoate vs placebo + mometasone furoate

Mortality

Study SINUS-52 Endpoint	Dupilumab + mometasone furoate		Placebo + mometasone furoate		Dupilumab + mometasone vs placebo + mometasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall survival	149	0 (0)	150	0 (0)	---

Morbidity

Study SINUS-52 Endpoint	Dupilumab + mometasone furoate		Placebo + mometasone furoate		Dupilumab + mometasone vs placebo + mometasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
SNOT-22 total score (improvement ≥ 8.9 points)[b]	150	128 (85.3)	153	83 (54.2)	1.51 [1.28; 1.78]; < 0.001

Study SINUS-52 Endpoint Scale	Dupilumab + mometasone			Placebo + mometasone			Dupilumab + mometasone vs placebo + mometasone
	N[c]	Values at start of study MV (SD)	Change at the end of study MV (SE)	N[c]	Values at start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI]; p value[d]
Nasal congestion/ obstruction[e]	145	2.48 (0.62)	−1.44 (0.07)	138	2.38 (0.54)	−0.52 (0.07)	−0.92 [−1.11; −0.74]; < 0.001 Hedges' g: −0.92 [−1.15; −0.70]
Loss of the sense of smell[e]	145	2.81 (0.46)	−1.37 (0.08)	138	2.72 (0.52)	−0.21 (0.08)	−1.15 [−1.36; −0.94]; < 0.001 Hedges' g: −1.04 [−1.27; −0.81]
Rhinorrhoea (anterior/ posterior)[e]	144	2.03 (0.76)	−1.25 (0.07)	137	1.98 (0.72)	−0.46 (0.07)	−0.79 [−0.96; −0.62]; < 0.001 Hedges' g: −0.73 [−0.96; −0.50]
Rhinosinusitis VAS[e]	138	8.24 (1.77)	−5.02 (0.25)	130	7.98 (2.22)	−1.79 (0.25)	−3.23 [−3.86; −2.61]; < 0.001 Hedges' g: −0.98 [−1.21; −0.74]

Study SINUS-52 Endpoint Scale	Dupilumab + mometasone			Placebo + mometasone			Dupilumab + mometasone vs placebo + mometasone
	N[c]	Values at start of study MV (SD)	Change at the end of study MV (SE)	N[c]	Values at start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI]; p value[d]
Health status (EQ-5D VAS)[f]	137	63.76 (21.76)	14.65 (1.66)	131	63.89 (19.99)	3.15 (1.72)	11.51 [7.19; 15.83]; < 0.001 Hedges' g: 0.58 [0.34; 0.81]

Health-related quality of life

not collected

Side effects

Study Endpoint	Dupilumab + mometasone		Placebo + mometasone		Dupilumab + mometasone vs placebo + mometasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
AEs (additionally shown)	149	125 (83.9)	150	138 (92.0)	---
SAEs	not usable[g]				
Discontinuation because of AEs	not usable[g]				

a. RR, 95% CI, and p value from a generalised linear model with treatment arm, asthma/NSAID-ERD status, history of surgery, and region as covariates; for the meta-analysis, also study and study × treatment arm as covariates. Missing values after an emergency operation were replaced by WOCF.
b. Suitable data on individual scores are not available for responder analyses. The MID of 8.9 points is applicable and validated only for the total score. The individual scores are recorded on a scale of 0–5.
c. Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
d. MD, 95% CI, and p value from an ANCOVA for the change at start of study with treatment arm, value at the start of study, asthma/ NSAID-ERD status, history of surgery, and region as covariates; for the meta-analysis also study and study × treatment arm as covariates. Missing values after an emergency operation were replaced by WOCF.
e. Lower (decreasing) values mean an improvement; negative effects (dupilumab Q2W + mometasone furoate) − (placebo + mometasone furoate) mean an advantage for dupilumab Q2W + mometasone furoate.
f. Higher (increasing) values mean an improvement; positive effects (dupilumab Q2W + mometasone furoate) − (placebo + mometasone furoate) mean an advantage for dupilumab Q2W + mometasone furoate.
g. Data are not usable because they contain a large proportion of patients with events that can be both side effects and symptomatology of the disease.

ANCOVA: covariance analysis; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; IPD: individual patient data; CI: confidence interval; MD: mean difference; MID: Minimal important difference; MV: mean value; N: number of patients evaluated; n: number of patients with (at least 1) event; N: number of patients evaluated; NC: nasal congestion/obstruction; NSAID-ERD: analgesic intolerance syndrome; Q2W: 1 time every 2 weeks; RCT: randomised controlled study; RR: relative risk; SD: standard deviation; SE: standard error; SNOT-22: 22-Item Sino-nasal Outcome Test, SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus WOCF: Worst Observation carried forward

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑↑	Improvement of symptomatology, advantage for loss of the sense of smell, advantage for rhinosinusitis, advantage for nasal congestion/obstruction, advantage for rhinorrhoea (anterior/posterior) and advantage for health status
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↔	Overall, there is no disadvantage for dupilumab.
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		

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

Adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control

approx. 10,500–12,600 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 Dupixent® (active ingredient: dupilumab) at the following publicly accessible link (last access: 3 April 2020):
https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf

For patients who do not respond to CRSwNP treatment after 24 weeks, discontinuation of treatment should be considered. Some patients with an initial partial response may benefit from continued treatment beyond 24 weeks.

4. Treatment costs

Annual treatment costs:

Adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Dupilumab	€ 19,058.35
Intranasal corticosteroids	€ 60.23 – 240.90
Total	€ 19,118.58 – 19,299.25
Appropriate comparator therapy:	
Intranasal corticosteroids	€ 60.23 – 240.90

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 14 May 2020.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 14 May 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken