Gemeinsamer Bundesausschuss

Nirmatrelvir/ Ritonavir (COVID-19)

Resolution of: 15 December 2022 valid until: unlimited
Entry into force on: 15 December 2022
Federal Gazette, BAnz AT 03 02 2023 B4

Therapeutic indication (according to the marketing authorisation of 28 January 2022):

Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

Therapeutic indication of the resolution (resolution of 15 December 2022):

See therapeutic indication according to marketing authorisation.

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

Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of nirmatrelvir/ ritonavir compared to therapy according to doctor's instructions:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-64) unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall mortality
Morbidity	↑	Advantages in the endpoints of severe COVID-19, need for intensive medical care due to any cause and relief of COVID-19 symptoms until day 28
Health-related quality of life	∅	No data available.
Side effects	n.c.	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.c.: not calculable		

EPIC-HR study: placebo-controlled, double-blind, randomised phase 2/3 study; direct comparison: Nirmatrelvir/ ritonavir vs placebo

Mortality

EPIC-HR study Endpoint	Nirmatrelvir/ ritonavir		Placebo		Nirmatrelvir/ ritonavir vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Overall mortality	944	0 (0)	964	15 (1.6)	0.03 [0.00; 0.55]; 0.017

Morbidity

EPIC-HR study Endpoint	Nirmatrelvir/ ritonavir		Placebo		Nirmatrelvir/ ritonavir vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Severe COVID-19	944	10 (1.1)	964	60 (6.2)	0.17 [0.09; 0.33]; < 0.001[a]
Need for intensive medical care due to any cause	944	0 (0)	964	9 (0.9)	0.05 [0.00; 0.92]; 0.044
COVID-19 symptoms at week 24	944	37 (3.9)	964	34 (3.5)	1.11 [0.70; 1.76]; 0.651
Activity impairment (WPAI)	No usable data available[b]				
Health status (EQ-5D VAS)	No usable data available[b]				
EPIC-HR study Endpoint	**Nirmatrelvir/ ritonavir**		**Placebo**		**Nirmatrelvir/ ritonavir vs placebo**
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI] p value[c]
Relief of COVID-19 symptoms until day 28	928	16 [15; 17] 588 (63.4)	955	20 [19; 22] 522 (54.7)	1.30 [1.16; 1.47]; < 0.001

Health-related quality of life

Not assessed

Side effects

EPIC-HR study Endpoint	Nirmatrelvir/ ritonavir		Placebo		Nirmatrelvir/ ritonavir vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
AEs (presented additionally)	No usable data available[d]				
SAEs	No usable data available[d]				
Severe AEs[e]	No usable data available[d]				
Discontinuation due to AEs	No usable data available[d]				

a. IQWiG calculation of RR, CI and p value (unconditional exact test, CSZ method)
b. No usable data due to inadequate return rates
c. HR, CI and p value: Cox proportional hazards model adjusted for treatment, viral load at baseline, serology status at baseline, region, treatment or planned treatment with monoclonal antibodies against COVID-19 at the start of the study, time between onset of symptoms and administration of first dose (≤ 3 days, > 3 days) and the interaction between treatment and covariates.
d. The pharmaceutical company does not provide any information on the events which it classifies as disease-related. Overall rates without disease-related events reported by the pharmaceutical company: SAEs: 6 (0.6%) [nirmatrelvir/ ritonavir] vs 8 (0.8%) [placebo]; severe AEs: 21 (2.2%) [nirmatrelvir/ ritonavir] vs 26 (2.7%) [placebo]; discontinuation due to AEs: 11 (1.2%) [nirmatrelvir/ ritonavir] vs 14 (1.5%) [placebo].
e. Severe AEs are operationalised as DAIDS grade ≥ 3.

Abbreviations used:
COVID-19: Coronavirus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; HR: hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; PC: pharmaceutical company; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

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

Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19

approx. 218,000 – 1,307,000 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 Paxlovid (combination of active ingredients: nirmatrelvir/ ritonavir) at the following publicly accessible link (last access: 29 September 2022):

https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Nirmatrelvir/ ritonavir	€ 1,084.39
Appropriate comparator therapy:	
Therapy according to doctor's instructions	Different from patient to patient

Costs after deduction of statutory rebates (information from the pharmaceutical company)

Costs for additionally required SHI services: not applicable

5. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Nirmatrelvir/ Ritonavir

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with nirmatrelvir/ ritonavir for the treatment of adults with COVID-19 on the basis of the marketing authorisation granted under Medicinal Products Act:

Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19

- No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.