Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V:
Relugolix/ Estradiol/ Norethisterone acetate (uterine fibroid)

of 17 February 2022

At its session on 17 February 2022, the Federal Joint Committee (G-BA) resolved to amend the 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the combination of active ingredients Relugolix / Estradiol / Norethisterone acetate as follows:

Benefit assessment procedure comprises several resolutions.
Please note the current version of the Pharmaceuticals Directive/Annex XII.

Courtesy translation – only the German version is legally binding.

Relugolix / Estradiol / Norethisterone acetate

Resolution of: 17 February 2022
Entry into force on: 17 February 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 16 July 2021):

Ryeqo is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Therapeutic indication of the resolution (resolution of 17 February 2022):

see therapeutic indication according to marketing authorisation.

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

a) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited:

Appropriate comparator therapy:

- Monitoring wait-and-see approach

Extent and probability of the additional benefit of Relugolix / Estradiol / Norethisterone acetate compared to monitoring wait-and-see approach:

Hint of a considerable additional benefit

b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited:

Appropriate comparator therapy:

- Patient-individual therapy depending on the type and severity of the symptoms as well as the burden of the symptoms on the patient, selecting from:
  - a symptom-oriented treatment:
    - progestogens under consideration of the respective authorisation status (for patients for whom symptomatic treatment of prolonged and/or heavy menstruation (menorrhagia, hypermenorrhoea) is sufficient)
    - ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolisation and/or surgery are not suitable or have failed)
  - invasive treatment options

Extent and probability of the additional benefit of Relugolix / Estradiol / Norethisterone acetate compared to the appropriate comparator therapy:

An additional benefit is not proven.

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Study results according to endpoints:[1]

a) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantage for menstrual blood loss, symptomatology and pain
Health-related quality of life	↑	Advantage in health-related quality of life
Side effects	↔	No relevant difference 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

Benefit assessment procedure comprises several resolutions of Art. XII. Please note the current version of the Pharmaceuticals Directive/AM

[1] Data from the dossier assessment of the IQWiG (A21-112) and from the addendum (A21-112), unless otherwise indicated.

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LIBERTY-1 and LIBERTY-2 studies: randomised, double-blind studies over 24 weeks, relugolix + estradiol / norethisterone acetate vs placebo[a]

Mortality

Endpoint	Relugolix+E2/NETA		Placebo		Relugolix + E2/NETA vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Overall mortality					
LIBERTY 1	128	0 (0)	127	0 (0)	--
LIBERTY 2	126	0 (0)	129	0 (0)	--

Morbidity

Endpoint	Relugolix+E2/NETA		Placebo		Relugolix + E2/NETA vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Confirmed clinically relevant reduction in menstrual blood loss (MBL) volume (MBL volume < 80 ml and at least 50 % reduction of the MBL output volume) [b]					
LIBERTY 1	128	88 (68.8)	127	15 (11.8)	5.82 [3.57; 9.50]; <0.001
LIBERTY 2	125	87 (69.6)	129	6 (4.7)	14.96 [6.79; 32.97]; <0.001
Total					8.40 [5.53; 12.74]; <0.001
Confirmed amenorrhoea[c]					
LIBERTY 1	128	67 (52.3)	127	7 (5.5)	9.50 [4.54; 19.88]
LIBERTY 2	125	63 (50.4)	129	4 (3.1)	16.25 [6.10; 43.32]
Total					11.92 [6.61; 21.50]

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Symptomatology (Symptom Severity Scale of the Uterine Fibroid Symptom and Quality of Life (UFS-QoL) questionnaire)[d]					
LIBERTY 1	128	74 (57.8)	127	39 (30.7)	1.89 [1.39; 2.55]; <0.001
LIBERTY 2	125	79 (63.2)	129	42 (32.6)	1.96 [1.48; 2.59]; <0.001
Total					1.92 [1.56; 2.35] <0.001

Endpoint Study	**Relugolix + E2/NETA**			**Placebo**			**Relugolix + E2/NETA vs placebo**
	N[e]	**Values at the start of study MV (SD)**	**Change in the course of study MV[f] (SE)**	**N**	**Values at the start of study MV (SD)**	**Change in the course of study MV[f] (SE)**	**MD [95% CI]; p value**
Pain (numerical rating scale)[g]							
LIBERTY 1	127	5.4 (3.4)	-2.6 (0.2)	126	5.7 (3.1)	-1.2 (0.2)	-1.42 [-2.06; -0.78]; <0.001
LIBERTY 2	124	5.7 (3.2)	-2.8 (0.3)	128	5.7 (2.9)	-1.6 (0.3)	-1.24 [-1.92; -0.55]; <0.001
Total							-1.33 [-1.80; -0.86]; <0.001 SMD -0.43 [-0.61; -0.26]
Health status (EQ-5D VAS)[h]							
LIBERTY 1	99	75.9 (17.4)	5.1 (2.0)[i]	104	73.5 (18.5)	4.8 (2.0)[i]	0.34 [-5.07; 5.74]; 0.902[i]
LIBERTY 2	100	73.9 (19.3)	7.6 (2.1)[i]	97	75.8 (19.5)	3.2 (2.2)[i]	4.33 [-1.23; 9.90]; 0.126[i]
Total							2.29 [-1.59; 6.17]; 0.247[i]

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Health-related quality of life

Endpoint	Relugolix+E2/NETA		Placebo		Relugolix + E2/NETA vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Total score of the UFS-QoL[j]					
LIBERTY 1	128	70 (54.7)	127	37 (29.1)	1.88 [1.38; 2.58] <0.001
LIBERTY 2	125	80 (64.0)	129	41 (31.8)	2.02 [1.52; 2.69] <0.001
Total					1.95 [1.58; 2.41] <0.001

Side effects

Endpoint	Relugolix+E2/NETA		Placebo[a]		Relugolix + E2/NETA vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Adverse events (presented additionally)					
LIBERTY 1	128	79 (61.7)	127	84 (66.1)	–
LIBERTY 2	126	76 (60.3)	129	76 (58.9)	–
Serious adverse events (SAE)					
LIBERTY 1	128	7 (5.5)	127	2 (1.6)	3.47 [0.74; 16.40]; 0.172
LIBERTY 2	126	1 (0.8)	129	4 (3.1)	0.26 [0.03; 2.26]; 0.370
Total					1.34 [0.47; 3.84]; 0.584
Severe adverse events (CTCAE grade ≥ 3)					
LIBERTY 1	128	7 (5.5)	127	11 (8.7)	0.63 [0.25; 1.58]; 0.341
LIBERTY 2	126	5 (4.0)	129	8 (6.2)	0.64 [0.22; 1.90]; 0.571
Total					0.63 [0.31; 1.28]; 0.200

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Endpoint	Relugolix+E2/NETA		Placebo[a]		Relugolix + E2/NETA vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Therapy discontinuation due to adverse events					
LIBERTY 1	128	7 (5.5)	127	5 (3.9)	1.39 [0.45; 4.26]; 0.769
LIBERTY 2	126	3 (2.4)	129	6 (4.7)	0.51 [0.13; 2.00]; 0.500
Total					0.91 [0.39; 2.12]; 0.834
Skeletal events (SAEs[k])					
LIBERTY 1	128	1 (0.8)	127	0 (0)	2.98 [0.12; 72.39]; > 0.999
LIBERTY 2	126	0 (0)	129	1 (0.8)	0.34 [0.01; 8.30]; > 0.999
Total					1.01 [0.14; 7.17]; 0.994
Vasomotor events (AEs[l])					
LIBERTY 1	128	19 (14.8)	127	12 (9.4)	1.57 [0.80; 3.10]; 0.250
LIBERTY 2	126	8 (6.3)	129	5 (3.9)	1.64 [0.55; 4.87]; 0.407
Total					1.59 [0.89; 2.83]; 0.112

a. This is considered, with limitations, to be a sufficient approximation to a wait-and-see approach as a possible therapy option within the appropriate comparator therapy (patient-individual therapy).
b. Measured by the alkaline haematin method, which existed at least since the previous evaluation time and up to week 24.
c. Definition of amenorrhoea: "no dispensing of menstrual hygiene products for two consecutive visits due to reported amenorrhoea" or "no dispensing of menstrual hygiene products due to absence of menstruation" or "dispensing of menstrual hygiene products with an MBL volume of less than 5 ml".
d. Evaluations of the percentage of patients with improvement, defined as a decrease in score of at least 15 points (equivalent to 15% on a scale range of 0 to 100) after 24 weeks of treatment.
e. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on higher patient numbers.
f. Effect represents the difference between the treatment groups regarding the changes averaged over the course of the study between the start of the study and the respective measurement time point.
g. Lower scores mean better symptomatology (scale range 0 to 10); negative effects (relugolix + E2/NETA vs placebo) mean an advantage for relugolix + E2/NETA.
h. Higher scores mean better health status / health-related quality of life (scale range 0 to 100 each); positive effects (relugolix + E2/NETA vs placebo) mean an advantage for relugolix + E2/NETA.
i. Changes on week 24
j. Evaluations of the proportion of patients with improvement, defined as an increase in score of at least 15 points (equivalent to 15% on a scale range of 0 to 100) after 24 weeks of treatment.

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k. Operationalised as SMQ “Osteoporosis / Osteopenia" (broad search) + user-defined PT compilation of fractures.
l. Operationalised via the following 5 PTs: Hyperhidrosis, feeling of warmth, hot flushes, night sweats, flushes

Abbreviations used:

CTCAE: Common Terminology Criteria for Adverse Events; E2: estradiol; CI: confidence interval; MBL: menstrual blood loss; MD: mean difference; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NETA: norethisterone acetate; NRS: numeric rating scale; PT preferred term; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SMD: standardised mean difference; SMQ: standardised MedDRA query; SAE: serious adverse event; AE: adverse event; UFS-QoL: Uterine Fibroid Symptom and Quality of Life; VAS: visual analogue scale; vs = versus

b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited

No data available.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

a) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited

and

b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited

approx. 20,160 – 100,840 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 Ryeqo (active ingredient: relugolix / estradiol / norethisterone acetate) at the following publicly accessible link (last access: 6 December 2021):
https://www.ema.europa.eu/en/documents/product-information/ryeqo-epar-product-information_en.pdf

4. Treatment costs

Annual treatment costs:

a) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Relugolix / estradiol / norethisterone acetate	€ 1,208,98
Appropriate comparator therapy:	
Monitoring wait-and-see approach	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2022)

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b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Relugolix / estradiol / norethisterone acetate	€ 1,208.98
Appropriate comparator therapy:	
Chlormadinone	€ 42.04 - € 84.08
Levonorgestrel	€ 111.84
Additionally required SHI services:	€ 6.99
Ulipristal acetate	€ 590.32
Invasive treatment options	
Hysterectomy	€ 3,827.88 - € 5,116.7
Myomectomy	€ 3,263.08 - € 4,571.57
Percutaneous transluminal angioplasty	€ 4,654.04

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2022)

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 17 February 2022.

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

Berlin, 17 February 2022

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

Prof. Hecken

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