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
Apixaban (new therapeutic indication)

From 19 February 2015

In its session on 19 February 2015, 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 19 February 2015 (Federal Gazette, AT 11 March 2015 B5) as follows:

I.

In appendix XII, the following information shall be added after number 4 to the details of the benefit assessment of apixaban in the therapeutic indication "To prevent venous thromboembolic events (VTE) in adults following an elective hip or knee replacement operation" in accordance with the resolutions of 7 June 2012 and 6 September 2012, and the details of the benefit assessment of apixaban in the therapeutic indication "To prevent stroke and systemic embolism in adults with non-valvular atrial fibrillation (NVAF) and one or more risk factors, such as having had a previous stroke or TIA (transient ischemic attack), being 75 years or over, high blood pressure, diabetes mellitus, symptomatic heart failure (NYHA classification II or higher)." of 20 Juni 2013:

Apixaban (new therapeutic indication)

Therapeutic indication authorized (new indication of 28 July 2014):

Eliquis® is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent
DVT and PE in adults. (See section 4.4 of the product information for haemodynamically unstable PE patients)

1. Additional benefit of the pharmaceutical over appropriate comparator

a) Initial treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) with concurrent administration of prophylaxis in adults (for treatment up to 6 months)

Appropriate comparator:

- Initial treatment (anticoagulation) of deep vein thrombosis (DVT) or pulmonary embolism (PE) in adults

  Low-molecular-weight heparins authorized for this indication (e.g. enoxaparin).

  The active ingredients shall be administered in the dosages authorized for the respective indication and optimized for each individual patient.

- (concurrent administration to initial treatment) secondary prophylaxis of recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE) in adults

  Vitamin K antagonists

Extent and probability of additional benefit over low-molecular-weight heparins (enoxaparin) authorized for this indication, and over vitamin K antagonists (warfarin):

Indication of a minor additional benefit.

b) Long-term prophylaxis of recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE) in adults (after completion of 6-month treatment of DVT or PE), for which an additional anticoagulation is indicated

Appropriate comparator:

Vitamin K antagonists

Extent and probability of additional benefit over vitamin K antagonists (warfarin):

An additional benefit is not considered proved.

For a)

Initial treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) with concurrent administration of prophylaxis in adults

Study results according to endpoints:

Comparison of the treatment regimen apixaban vs. enoxaparin/warfarin [AMPLIFY study (CV185056)][1]:

Endpoint category Endpoint	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value[a] Absolute risk reduction (ARR %)[2]
Mortality					
All-cause mortality	2,608	41 (1.6[b])	2,630	52 (2.0[b])	0.80 [0.53; 1.19] 0.296[c]
Morbidity					
Aggregate endpoint: Symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or all-cause mortality					
Overall	2,609	84 (3.2)	2,635	104 (3.9[b])	0.82 [0.61; 1.08] 0.155
Symptomatic non-fatal DVT					
Overall	2,608	22 (0.8)	2,633	35 (1.3)	0.63 [0.37; 1.08] 0.090
Symptomatic non-fatal PE					
Overall	2,606	27 (1.0)	2,632	25 (0.9[b])	1.09 [0.63; 1.89] 0.746
Health-related quality of life					
Endpoint not ascertained					
Composite endpoint: severe bleeding or clinically relevant non-severe bleeding					
Overall	2,676	115 (4.3)	2,689	261 (9.7)	0.44 [0.36; 0.55] < 0.001 4.3 vs. 9.7 (5.4 %)
Severe bleeding					
Overall	2,676	15 (0.6[b])	2,689	49 (1.8)	0.31 [0.17; 0.55] < 0.001 0.6 vs. 1.8 (1.2 %)
Clinically relevant non-severe bleeding					
Overall	2,676	103 (3.8[b])	2,689	215 (8.0)	0.48 [0.38; 0.60] < 0.001 3.8 vs. 8.0 (4.2 %)
AE[d]					
Overall	2,676	1,713 (64.0)	2,689	1,787 (66.5)	n. a.

[1] IQWiG dossier assessment A14-28; version 1.0, issued: 26 November 2014; dichotomous endpoints were considered.

[2] ARR figures shown for significant differences only.

Endpoint category Endpoint	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value[a] Absolute risk reduction (ARR %)[2]
SAE[d]					
Overall	2,676	343 (12.8)	2,689	308 (11.5)	1.11 [0.96; 1.29] 0.141
Withdrawal due to AE					
Overall	2,676	109 (4.1)	2,689	113 (4.2)	0.97 [0.74; 1.25] 0.796

Abbreviations used: ARR: absolute risk reduction; CI: confidence interval; PE: pulmonary embolism; N: number of patients evaluated; n: number of patients with event; PC: pharmaceutical company; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse events; DVT: deep vein thrombosis; AE: adverse events; VTE: venous thromboembolic events

[a] If not indicated otherwise, the RR and the respective 95% CI and p-value are results the pharmaceutical company ascertained using the Cochran-Mantel-Haenszel method. The stratification with regard to the index event (only DVT or PE with/without DVT) was considered.

[b] IQWiG calculation.

[c] Own calculation of RR, confidence interval, and p-value (exact Fisher test) due to different information on the number of patients evaluated between module 4 and the study report.

[d] Only endpoints evaluated individually by the pharmaceutical company.

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

   a) Initial treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) with concurrent administration of prophylaxis in adults

      approx. 114,000

   b) Long-term prophylaxis of recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE) in adults (after completion of 6-month treatment of DVT or PE), for which an additional anticoagulation is indicated

      approx. 127,000

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 contents of the product information for Eliquis® (active ingredient: apixaban) at the following public link (last accessed: 4 December 2014):

   http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf

   Eliquis® is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of apixaban have not been established in these clinical situations.

   In accordance with the requirements of the European regulatory authority (EMA) for additional steps for risk reduction, the pharmaceutical company shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use apixaban. The educational pack for physicians shall contain the summary of product characteristics, a prescriber guide, and a patient alert card.

   Patients with transient risk factors (e.g. recent surgery, trauma, immobilization), for whom shorter treatment with apixaban (at least 3 months) may be indicated, were not studied in the AMPLIFY trial. No data is available for this patient population.

   According to the Eliquis® 5 mg product information, lower body weight (< 60 kg) can correspond to an increased risk of bleeding.

   No antidote is available for apixaban.

   According to the product information, continued treatment with apixaban can be indicated for patients who, in the opinion of their physicians, are not candidates for conversion to vitamin K antagonists (in particular due to danger to the patient associated with the conversion), but who require further prophylaxis (longer than 6 months). To ensure the quality-assured administration of apixaban, the rationale for continued treatment must be documented by the physician.

4. Costs of treatment

a) Initial treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) with concurrent administration of prophylaxis in adults[3]

Duration of treatment:

Description of therapy	Mode of treatment	Duration per treatment (days)	Number of treatment days per patient per year
Initial treatment of DVT or PE			
Pharmaceutical evaluated			
Apixaban First treatment week	ongoing, 2 × daily	7	7
Appropriate comparator (low-molecular-weight heparins, e.g. enoxaparin)			
Enoxaparin-sodium[4]	ongoing, 2 × daily	5	5
Secondary prophylaxis of recurrent DVT or PE			
Pharmaceutical evaluated			
Apixaban 2nd – 26th treatment weeks	ongoing, 2 × daily	183	183
Appropriate comparator (vitamin K antagonist; therapy to be initiated concurrent to first treatment)			
Phenprocoumon[5]	ongoing	182	182
Warfarin[5]	ongoing	182	182

Consumption:

Description of therapy	Strength (mg)	Dosage scheme	Quantity per pack (tablets, pre-filled syringes)	Average annual consumption (tablets (tbl.), pre-filled syringes)
Initial treatment of DVT or PE				
Pharmaceutical evaluated				
Apixaban	5 mg	2 × daily 10 mg	200 tbl.	28 tbl.
Appropriate comparator (low-molecular-weight heparins, e.g. enoxaparin)				
Enoxaparin-sodium	80 mg	2 x daily 1 mg per kg BW[6] s.c.	12 pre-filled syringes	10 pre-filled syringes
Secondary prophylaxis of recurrent DVT or PE				
Pharmaceutical evaluated				
Apixaban	5 mg	2 × daily 5 mg	200 tbl.	366 tbl.
Appropriate comparator (vitamin K antagonist; therapy to be initiated simultaneously with first treatment[5])				
Phenprocoumon	3 mg	1. Day 1 x daily 6 – 9 mg; 2. Day 1 x daily 6 mg; from day	100 tbl.	Initially 4 – 5 tbl. From day 3: 90 – 270 tbl.
Warfarin	5 mg	Initially 1 x daily 2.5 – 5 mg From day 3: 1 x daily 2.5 – 10	100 tbl.	Initially 1 – 2 tbl. From day 3: 90 – 360 tbl.

[3] A 6-month treatment time up to recommended start of indicated prophylactic therapy was observed. Patients with transient risk factors (e.g. recent surgery, trauma, immobilization), for whom shorter treatment with apixaban (at least 3 months) may be indicated, are not shown separately.

[4] Minimum treatment duration 5 days. Potential continued treatment until INR score of 2 or 3 is achieved (see Clexane® product information).

[5] Start of therapy concurrent to initial treatment within 2 to 3 days at the latest after start of therapy with NMH (here enoxaparin). The costs of treatment shown here follow the assumption that therapy with VKA is started on day 2 after the start of therapy with NMH.

[6] The basis for body weight (BW) dependent dosages is 76.3 kg, the average weight of the German population 18 years and older. Federal Statistical Office. Microcensus 2013: health questions; 2013 body dimensions of the population (online). 5 November 2014 (accessed: 8 December 2014). URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003139004_pdf?__blob=publicationFile.

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)	Cost after legally mandated rebates
Pharmaceutical evaluated		
Apixaban	€282.80[7]	€281.03 [€1.77[8])
Appropriate comparator (vitamin K antagonist)		
Phenprocoumon	€18.03[9]	€15.70 [€1.77[8], €0.56[10]]
Warfarin	€18.03[9]	€16.26 [€1.77[8, 11]]
Appropriate comparator (low-molecular-weight heparins, e.g. enoxaparin)		
Enoxaparin-sodium	€122.03[9]	€120.26 [€1.77[8, 13]]

"Lauer-Taxe", effective: 1 January 2015

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

Description of therapy	Costs	Number of additional necessary SHI expense items per episode, cycle, etc.	Number of additional necessary SHI expense items per patient per year	Cost/year
Appropriate comparator (vitamin K antagonist)				
Examination of coagulation system, including PT, aPTT, thrombin time, and fibrinogen[12]	€1.55	Once before start of treatment; the maximum cost of the examinations according to the fee schedule items 32110 to 32116 is €1.55.	1	€1.55
Thromboplastin time test – from plasma (GOPa 32113)	€0.60	regularly at least every 3 – 4 weeks	6 – 8	€3.60 – €4.80
Appropriate comparator (enoxaparin)				
Thrombocyte count (32037)	€0.25	Before start of treatment On day 1 after start of treatment Then regularly every 3 to 4 days during the first 3 weeks and at the end of treatment	3[13]	€0.75

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated	
Apixaban[14]	€562.06
Appropriate comparator (vitamin K antagonist)	
Phenprocoumon	€15.70 – €47.10
Warfarin	€16.26 – €65.04
Costs for additional SHI expense items Examination of coagulation system, thromboplastin time test	€5.15 – €6.35

[7] Taxe sales price (consists of reimbursable price plus wholesale and pharmacy surcharges and VAT).

[8] Rebate in accordance with SGB V, section 130.

[9] Reference price.

[10] Rebate in accordance with SGB V, section 130a.

[11] The 10% discount on the ex-factory price in accordance with SGB V, section 130a, paragraph 3b does not apply.

[12] The maximum cost of the examinations according to the fee schedule items 32110 to 32116 is €1.55. (German Uniform Value Scale [EBM]; effective: 4th quarter 2014) (last accessed: 8 December 2014).

[13] A minimum treatment duration of 5 days was observed.

[14] Costs of both treatment phases are shown together.

Description of therapy	Annual treatment costs per patient
Appropriate comparator (low-molecular-weight heparins)	
Enoxaparin-sodium[15]	€100.22
Costs for additional SHI expense items Thrombocyte count	€0.75

b) Long-term prophylaxis of recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE) in adults (after completion of 6-month treatment of DVT or PE)[16], for which an additional anticoagulation is indicated

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient	Duration per treatment (days)	Number of treatment days per patient per year
Pharmaceutical evaluated				
Apixaban	ongoing, 2 × daily 2.5 mg	ongoing	365	365
Appropriate comparator (vitamin K antagonist)				
Phenprocoumon	ongoing, 1 × daily 1.5 mg – 4.5 mg[17]	ongoing	365	365
Warfarin	ongoing, 1 × daily 2.5 mg – 10 mg[17]	ongoing	365	365

Consumption:

Description of therapy	Strength (mg)	Quantity per pack (tablets)	Average annual consumption (tablets)
Pharmaceutical evaluated			
Apixaban	2.5 mg	200	730
Appropriate comparator (vitamin K antagonist)			
Phenprocoumon	3 mg	100	182.5 – 547.5
Warfarin	5 mg	100	182.5 – 730

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)	Cost after legally mandated rebates
Pharmaceutical evaluated		
Apixaban	€282.80[9]	€281.03 [€1.77[10]]
Appropriate comparator (vitamin K antagonist)		
Phenprocoumon	€18.03[11]	€15.70 [€1.77[8], €0.56[12]]
Warfarin	€18.03[9]	€16.26 [€1.77[8, 13]]

"Lauer-Taxe", effective: 1 January 2015

[15] Waste is included, as it can no longer be used after initial treatment is completed.

[16] The treatment period of an indicated prophylactic therapy in one calendar year following a prior 6-month initial treatment is considered.

[17] Possible daily dosage in maintenance therapy according to product information.

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

Description of therapy	Additional necessary SHI expense items				
	Designation	Costs	Number of additional necessary SHI expense items per episode, cycle, etc.	Number of additional necessary SHI expense items per patient per year	Cost/year
Appropriate comparator (vitamin K antagonist)	Thromboplastin time test – from plasma (GOPa 32113)	€0.60	Regularly, at least every 3 – 4 weeks	13 – 17	€7.80 – €10.20

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated	
Apixaban	€1,025.76
Appropriate comparator (vitamin K antagonist)	
Phenprocoumon	€28.65 – €85.96
Warfarin	€29.67 – €118.70
Additional necessary SHI expense items (thromboplastin time test)	€7.80 – €10.20

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 19 February 2015.

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

Berlin, 19 February 2015

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

The Chair
Prof. Hecken