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 20 June 2013

In its session on 20 June 2013, 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 20 June 2013 (Federal Gazette, AT 18 July 2013 B1), as follows:

I.

In appendix XII the following details shall be added after number 4 to the information on 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 with resolutions of 7 June 2012 and 6 September 2012:

Apixaban

Therapeutic indication authorized (new indication of 19 November 2012):

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).

1. Additional benefit of the pharmaceutical over appropriate comparator

Appropriate comparator: vitamin K antagonists

Extent and probability of additional benefit over vitamin K antagonists:

Indication of a minor additional benefit.

Chart 1: ARISTOTLE study overall population results (VKA population)[1]

	Effect estimates1 [95% CI] apixaban vs. warfarin	Results proportion apixaban vs. warfarin absolute risk reduction (ARR)	p-value
Mortality			
Overall mortality	HR 0.89 [0.80; 1.00]	6.6% vs. 7.4% (ARR = 0.8%)	p = 0.047
Morbidity			
Stroke (ischaemic, haemorrhagic, or unknown cause)	HR 0.79 [0.65; 0.95]	2.2% vs. 2.8% ARR = 0.6%	p = 0.012
Stroke (ischaemic or unknown cause)	HR 0.92 [0.74; 1.13]	1.8% vs. 1.9%	p = 0.422
Stroke (ischaemic)	HR 1.02 [0.81; 1.29]	1.5% vs. 1.5%	p = 0.871

[1] Data from the benefit assessment conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) (charts 10 and 26).

	Effect estimates1 [95% CI] apixaban vs. warfarin	Results proportion apixaban vs. warfarin	p-value
Stroke (haemorrhagic)	HR 0.51 [0.35; 0.75]	0.4% vs. 0.9% ARR = 0.5%	p < 0.001
Stroke (unknown cause)	HR 0.65 [0.33; 1.28]	0.2% vs. 0.2%	p = 0.212
Stroke (leading to disability)	HR 0.84 [0.58; 1.20]	0.6% vs. 0.7%	p = 0.338
Systemic embolism	HR 0.87 [0.44; 1.75]	0.2% vs. 0.2%	p = 0.702
Myocardial infarction	HR 0.88 [0.66; 1.17]	1.0% vs. 1.1%	p = 0.372
TIA	RR 1.29 [0.91; 1.84]	0.8% vs. 0.6%	p = 0.176
Health-related quality of life			
Health-related quality of life	Endpoint not ascertained		
Side effects			
Major bleeding, clinically relevant minor bleeding (aggregate endpoint: side effects)	HR 0.68 [0.61; 0.753]	6.8% vs. 9.7% ARR = 2.9%	p < 0.001
Region: Europe[2]	HR 0.74 [0.62; 0.88]	5.9% vs. 7.8% ARR = 1.9%	n/a
Major bleeding	HR 0.69 [0.60; 0.80]	3.6% vs. 5.1% ARR = 1.5%	p < 0.001
Major intracranial bleeding	HR 0.42 [0.30; 0.58]	0.6% vs. 1.4% ARR = 0.8%	p < 0.001
Other major bleeding (extracranial, incl. gastro-intestinal)	HR 0.79 [0.68; 0.93]	3.0% vs. 3.8% ARR = 0.8%	p = 0.004
Clinically relevant minor bleeding	HR 0.70 [0.60; 0.804]	3.5% vs. 4.9% ARR = 1.4%	p < 0.001
Overall rate AE[3]	HR 0.959 [0.928; 0.991]	78.4% vs. 79.2% ARR = 0.8%	n/a
Overall rate SAE[3]	HR 0.968 [0.919; 1.02]	31.1% vs. 31.6%	n/a
Termination of treatment due to AE[3]	HR 0.910 [0.799; 1.036]	4.8% vs. 5.2%	n/a
Termination of treatment due to SAE[3]	HR 0.806 [0.684; 0.949]	2.9% vs. 3.5% ARR = 0.6%	n/a
Stroke, systemic embolism, major bleeding or mortality (aggregate endpoint: mortality, morbidity, and side effects)	HR 0.85 [0.78; 0.92]	11.1% vs. 12.9% ARR = 1.8%	p < 0.001

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

   Number: approx 926,000 to 1,093,000 patients

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: 19 April 2013):
   http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf

   Patients unsuitable for VKA therapy are not included in the market authorization. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002148/WC500136575.pdf

   No antidote is available for apixaban.

[2] Assessment-relevant sub-group results.

[3] Results from the written hearing statement by Bristol-Myers Squibb GmbH & Co. KGaA and Pfizer Deutschland GmbH.

4 Costs of treatment

Duration of treatment

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Number of treatment days per patient per year
Pharmaceutical evaluated				
Apixaban	ongoing, 2 x daily	ongoing	365	365
Appropriate comparator; vitamin K antagonist				
Phenprocoumon	ongoing, 1 × daily	ongoing	365	365
Warfarin	ongoing, 1 × daily	ongoing	365	365

Consumption:

Description of therapy	Strength	Number/amount per pack (tablets)	Average annual consumption (tablets)
Pharmaceutical evaluated			
Apixaban	2 x 5 mg	100	730
Appropriate comparator; vitamin K antagonist			
Phenprocoumon	0.75 mg – 4.5 mg[4]	100	91.25 – 547.5
Warfarin	2.5 mg – 10 mg[4]	100	182.5 – 730

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price[5])	Cost after legally mandated rebates
Pharmaceutical evaluated		
Apixaban	€177.05	€175.00 [€2.05[6]]
Appropriate comparator; vitamin K antagonist		
Phenprocoumon	€17.84[7]	€15.23 [€2.05[6]; €0.56[8]]
Warfarin	€17.84[7]	€15.79 [€2.05[6]]

"Lauer-Taxe", effective 1 May 2013

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

	Additional necessary SHI expense items				
Description of therapy	Description	Cost	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 antagonists)	Test of thromboplastin time – 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	€1,277.50
Appropriate comparator	
Vitamin K antagonists (warfarin, phenprocoumon)	€36.70 – €125.45 (warfarin) €21.70 – €93.58 (phenprocoumon)

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

[5] Largest pack.

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

[7] Reference price

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

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 20 June 2013.

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

Berlin, 20 June 2013

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

The Chair
Hecken