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

from 7 June 2012

In its session on 7 June 2012, 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 3 May 2012 (Federal Gazette, AT 18 June 2012 B2) as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient apixaban:

Apixaban

Therapeutic indication:

To prevent venous thromboembolic events (VTE) in adults following an elective hip or knee replacement operation.

1. Additional benefit of the pharmaceutical over appropriate comparative treatment

a) Patients with elective knee replacement operation

Appropriate comparator: the appropriate comparator for the primary peri- and post-operative prevention of deep vein thromboses following elective knee replacement operations are those low-molecular-weight heparins authorized for this indication (e.g. enoxaparin). The active ingredients shall be administered in the dosages authorized for the severity of the condition and optimized for each individual patient.

Extent and probability of additional benefit over low-molecular-weight heparins (enoxaparin): no proof of additional benefit of apixaban.

Study results according to endpoints:

Endpoint	Effect estimates[1] [95% CI] apixaban vs. enoxaparin	Incident rate, (absolute risk reduction (ARR[2])	p-value
Mortality			
Treatment period[3]	Peto OR 7.4 [0.46; 118.3]	0.13% vs. 0.00%	0.250
Aggregate period[4]	Peto OR 2.72 [0.38; 19.35]	0.2% vs. 0.07%	0.375
Morbidity			
Pulmonary embolism			
Treatment period[3]	Peto OR 7.41 [1.04; 52.64]	0.26% vs. 0.00%	0.062
Aggregate period[4]	Peto OR 4.5 [1.12; 18.02]	0.46% vs. 0.07% ARR = 0.39%	0.039

Endpoint	Effect estimates[1] [95% CI] apixaban vs. enoxaparin	Incident rate, (absolute risk reduction (ARR[2])	p-value
Symptomatic deep leg vein thrombosis			
Treatment period[3]	Peto OR 0.45 [0.13; 1.55]	0.20% vs. 0.46%	0.343
Aggregate period[4]	Peto OR 0.63 [0.21; 1.87]	0.33% vs. 0.52%	0.580
– Subgroup: symptomatic proximal deep leg vein thrombosis			
Treatment period[3]	Peto OR 1.0 [0.06; 16.01]	0.07% vs. 0.07%	1.000
Aggregate period[3]	Peto OR 1.49 [0.26; 8.63]	0.20% vs. 0.13%	0.687
– Subgroup: symptomatic distal deep leg vein thrombosis			
Treatment period[3]	Peto OR 0.45 [0.13; 1.55]	0.20% vs. 0.46%	0.343
Aggregate period[3]	Peto OR 0.45 [0.13; 1.55]	0.20% vs. 0.46%	0.343
Health-related quality of life			
Quality of life	No applicable data available		
Side effects			
Major bleeding or clinically relevant minor bleeding			
Treatment period[4]	RR 0.74 [0.52; 1.05]	3.53% vs. 4.77%	0.100
Aggregate period	– Unevaluable due to possible double counting of incidents		
Major bleeding			
Treatment period[4]	Peto OR 0.65 [0.29; 1.47]	0.60% vs. 0.93%	0.403
Aggregate period	– Unevaluable due to possible double counting of incidents		
Clinically relevant minor bleeding			
Treatment period[4]	RR 0.76 [0.52; 1.12]	2.93% vs. 3.85%	0.190
Aggregate period	– Unevaluable due to possible double counting of incidents		
Adverse events – bleeding			
Treatment period[4]	RR 0.81 [0.62; 1.06]	6.0% vs. 7.43%	0.126
Aggregate period	– Unevaluable due to possible double counting of incidents		
Severe adverse events – bleeding			
Treatment period	No data		
Aggregate period[4]	Peto OR 0.58 [0.25; 1.34]	0.53% vs. 0.93%	0.285
Adverse events – overall rate			
Treatment period[4]	RR 0.94 [0.88; 1.01]	52.37% vs. 55.44%	0.093
Aggregate period	– Unevaluable due to possible double counting of incidents		
Subgroup: DVT recorded as adverse event			
Treatment period[4]		6.6% vs. 9.81%	
Severe adverse events – overall rate			
Treatment period[4]	RR 0.82 [0.61; 1.11]	4.79% vs. 5.84%	0.223
Aggregate period	– Unevaluable due to possible double counting of incidents		
Subgroup: DVT recorded as adverse event			
Treatment period[4]		0.73% vs. 1.46%	
Termination due to adverse events			
Treatment period[4]	RR 0.91 [0.60; 1.39]	2.66% vs. 2.92%	0.740
Subgroup: DVT recorded as adverse event			
Treatment period[4]		0.67% vs. 0.73%	

[1] Figures given as Peto OR instead of RR for incident rates of less than 1% in at least one cell
[2] Figures given only in cases with significant differences; negative ARR figures are in favor of enoxaparin
[3] Data from the hearing procedure by the pharmaceutical company
[4] Data from the dossier evaluation A11-30 conducted by IQWiG on apixaban (p. 19 ff., results of ADVANCE-2 study)

Abbreviations used: OR = odds ratio, CI = confidence interval, RR = relative risk, ARR = absolute risk reduction, (S)AE = (serious) adverse event, DVT = deep leg vein thrombosis, vs. = versus

b) Patients with elective hip replacement operations

Appropriate comparator: the appropriate comparator for the primary peri- and post-operative prevention of deep vein thromboses following elective hip replacement operations are those low-molecular-weight heparins authorized for this indication (e.g. enoxaparin). The active ingredients shall be administered in the dosages authorized for the severity of the condition and optimized for each individual patient.

Extent and probability of additional benefit over low-molecular-weight heparins (enoxaparin): indication of a minor additional benefit of apixaban.

Study results according to endpoints:

Endpoint	Effect estimates[1] [95% CI] apixaban vs. enoxaparin	Incident rate, (absolute risk reduction (ARR[2])	p-value
Mortality			
Treatment period[3]	Peto OR 2.71 [0.38; 19.25]	0.11% vs. 0.04%	0.625
Aggregate period[4]	Peto OR 2.35 [0.53; 10.35]	0.18% vs. 0.07%	0.453
Morbidity			
Pulmonary embolism			
Treatment period[3]	Peto OR 0.6 [0.15; 2.42]	0.11% vs. 0.19%	0.507
Aggregate period[4]	Peto OR 0.37 [0.12; 1.14]	0.11% vs. 0.33%	0.091
Symptomatic deep leg vein thrombosis			
Treatment period[3]	Peto OR 0.26 [0.05; 1.3]	0.04% vs. 0.19%	0.124
Aggregate period[4]	Peto OR 0.21 [0.06; 0.78]	0.04% vs. 0.3% ARR = 0.26%	0.021
– Subgroup: symptomatic proximal deep leg vein thrombosis			
Treatment period[3]	Peto OR 0.3 [0.05; 1.73]	0.04% vs. 0.15%	0.218
Aggregate period[3]	Peto OR 0.22 [0.06; 0.89]	0.04% vs. 0.26% ARR = 0.22%	0.039
– Subgroup: symptomatic distal deep leg vein thrombosis			
Treatment period[3]	Peto OR 1.0 [0.06; 15.94]	0.04% vs. 0.04%	1.0
Aggregate period[3]	Peto OR 1.0 [0.06; 15.94]	0.04% vs. 0.04%	1.0
Health-related quality of life			
Quality of life	No applicable data available		
Side effects			
Major bleeding or clinically relevant minor bleeding			
Treatment period[4]	RR 0.96 [0.76; 1.21]	4.83% vs. 5.04%	0.752
Aggregate period	– Unevaluable due to possible double counting of incidents		
Major bleeding			
Treatment period[4]	Peto OR 1.22 [0.65; 2.27]	0.82% vs. 0.68%	0.635
Aggregate period	– Unevaluable due to possible double counting of incidents		
Clinically relevant minor bleeding			
Treatment period[4]	RR 0.9 [0.76; 1.16]	4.08% vs. 4.51%	0.458
Aggregate period	– Unevaluable due to possible double counting of incidents		
Adverse events – bleeding			
Treatment period[4]	RR 0.99 [0.85; 1.17]	10.03% vs. 10.08%	0.964
Aggregate period	– Unevaluable due to possible double counting of incidents		
Severe adverse events – bleeding			
Treatment period	No data		
Aggregate period[4]	Peto OR 2.56 [1.31; 5.03]	0.94% vs. 0.34% ARR = 0.6%	0.009
Adverse events – overall rate			
Treatment period[4]	RR 0.96 [0.93; 1.00]	65.54% vs. 68.11% ARR = 2.57%	0.048
Aggregate period	– Unevaluable due to possible double counting of incidents		
Subgroup: DVT recorded as adverse event			
Treatment period[4]		1.68% vs. 2.59%	

Endpoint	Effect estimates[1] [95% CI] apixaban vs. enoxaparin	Incident rate, (absolute risk reduction (ARR[2])	p-value
Adverse events – overall rate without DVT[a]			
From day 1 to day 35	RR 0.97 [0.93; 1.01]	65.2% vs. 67.3%	0.105
On day 35	RR 0.97 [0.93; 1.01]	65.3% vs. 67.4%	0.105
Severe adverse events – bleeding			
Treatment period[4]		6.88% vs. 6.47%	0.547
Aggregate period	– Unevaluable due to possible double counting of incidents		
Subgroup: DVT recorded as adverse event			
Treatment period		0.3% vs. 0.68%	
Termination due to adverse events			
Treatment period[4]	RR 0.82 [0.62; 1.07]	3.4% vs. 4.17%	0.151
Subgroup: DVT recorded as adverse event			
Treatment period[4]		0.22% vs. 0.26%	

[1] Figures given as Peto OR instead of RR for incident rates of less than 1% in at least one cell
[2] Figures given only in cases with significant differences; negative ARR figures are in favor of enoxaparin
[3] Data from the hearing procedure by the pharmaceutical company
[4] Data from the dossier evaluation A11-30 conducted by IQWiG on apixaban (p. 19 ff., results of ADVANCE-3 study)
[a] Number of patients experiencing DVT as only adverse event, as registered in patient data:

Apixaban:	from day 1 to day 35:	symptomatic: 1	unclear: 2	(N = 3)	1742/2673
	on day 35:	asymptomatic: 5	unclear: 2	(N = 7)	1745/2673
Enoxaparin:	from day 1 to day 35:	symptomatic: 1	unclear: 2	(N = 3)	1789/2659
	on day 35:	asymptomatic: 15	unclear: 4	(N = 19)	1792/2659

Abbreviations used: OR = odds ratio, CI = confidence interval, RR = relative risk, ARR = absolute risk reduction, (S)AE = (severe) adverse event, DVT = deep leg vein thrombosis, vs. = versus

2. Number of patients and criteria for defining patients eligible for treatment a) Patients with elective knee replacement operation

approx. 165,000[1]

b) Patients with elective hip replacement operation

approx. 225,000[1]

[1] DRG calculation 2010

3. Requirements for quality-assured administration

The specifications outlined in the product information are to be followed.

4. Costs of treatment

a) Patients with elective knee replacement operation

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per operation	Duration per treatment (days)	Treatment days per patient per operation
Pharmaceutical evaluated				
Apixaban (ELIQUIS®)	2 x daily 2.5 mg	1 episode	10 – 14[1]	10 – 14
appropriate comparator				
Enoxaparin	1 x daily (4000 IU anti-Xa)	1 episode	11 – 14[2]	11 – 14

[1] Duration of treatment according to product information
[2] Duration of treatment according to product information: "[…] as long as there is an increased risk of thromboembolic events, on average 7 – 10 days […]", here: figures identical to those from the pharmaceutical company (apixaban dossier, module 3, charts 3 – 11) and IQWiG benefit assessment A11–30, p. 64)

Consumption:

Description of therapy	Strength	Number/amount per pack[1]	Average consumption/operation
Pharmaceutical evaluated			
Apixaban (ELIQUIS®)	2.5 mg	10, 20 tablets	20 – 28 tablets
Appropriate comparator			
Enoxaparin	4000 IU anti-Xa	20 pre-filled syringes	11 – 14 pre-filled syringes

[1] Optimal pack size for treatment

Costs:

Cost of pharmaceutical:

Description of therapy	Cost/pack (pharmacy retail price)	Cost after legally mandated rebates[1,2]
Pharmaceutical evaluated		
Apixaban (ELIQUIS®)	€43.44 – €76.36	€37.22 – €65.97 (€2.05[1]; €4.17[2]; €8.34[2])
Appropriate comparator		
Enoxaparin	€110.53[3]	€100.57 (€2.05[1]; €7.91[2])

[1] Rebate in accordance with SGB V, section 130
[2] Rebate in accordance with SGB V, section 130a
[3] Reference price

"Lauer-Taxe", effective 15 April 2012

Costs for additional, necessary statutory health insurance (SHI) benefits: none

Annual treatment costs[a]:

Description of therapy	Cost of treatment per patient/operation
Pharmaceutical evaluated	
Apixaban (ELIQUIS®)	€65.97 – €103.19[1]
Appropriate comparator	
Enoxaparin	€100.57

[a] Not including stays in hospital or rehabilitation
[1] Optimal combination of pack sizes

b) Patients with elective hip replacement operations

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per operation	Duration per treatment (days)	Treatment days per patient per operation
Pharmaceutical evaluated				
Apixaban (ELIQUIS®)	2 x daily 2.5 mg	1 episode	32 – 38[1]	32 – 38
Appropriate comparator				
Enoxaparin	1 x daily (4000 IU anti-Xa)	1 episode	11 – 35[2]	11 – 35

[1] Duration of treatment according to product information
[2] Duration of treatment according to product information: "[…] as long as there is an increased risk of thromboembolic events, on average 7 – 10 days […]", here: Figures identical to those in the IQWiG benefit assessment A11-30, p. 64, minimum duration of treatment identical to that for knee replacement operations 11 days

Consumption:

Description of therapy	Strength	Number per pack[1]	Average consumption/ operation
Pharmaceutical evaluated			
Apixaban (ELIQUIS®)	2.5 mg	10, 20, 60 tablets	64 – 76 tablets
appropriate comparator			
Enoxaparin	4000 IU anti-Xa	20 pre-filled syringes	11 – 35 pre-filled syringes

[1] Optimal pack size for treatment

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)	Cost after legally mandated rebates[1,2]
Pharmaceutical evaluated		
Apixaban (ELIQUIS®)	€43.44 – €206.11	€37.22 – €179.05 (€2.05[1]; €4.17[2]; €8.34[2]; €25.01[2])
Appropriate comparator		
Enoxaparin	€110.53[3]	€100.57 (€2.05[1]; €7.91[2])

[1] Rebate in accordance with SGB V, section 130
[2] Rebate in accordance with SGB V, section 130a
[3] Reference price

"Lauer-Taxe", effective 15 April 2012

Costs for additional, necessary statutory health insurance (SHI) benefits: none

Annual treatment costs[a]:

Description of therapy	Cost of treatment per patient/operation
Pharmaceutical evaluated	
Apixaban (ELIQUIS®)	€216.27 – €245.02[1]
Appropriate comparator	
Enoxaparin	€100.57 – €201.14[1]

[a] Not including stays in hospital or rehabilitation
[1] Optimal combination of pack sizes

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 7 June 2012.

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

Berlin, 7 June 2012

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

The Chair
Hess

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

from 6 September 2012

In its session on 6 September 2012, 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 16 August 2012 (Federal Gazette AT 19 September 2012 B3), as follows:

I.

In appendix XII, the information on the benefit assessment of the active ingredients apixaban shall be amended in point "4. Costs of treatment" as follows:

1. In section a) Patients with elective knee replacement operation", the information on the active ingredient enoxaparin in the charts "Cost of pharmaceutical" and "Annual treatment costs" shall be amended as follows:
   a) In the chart "Cost of pharmaceutical"
      the figures "€100.57 (€2.05[1]; €7.91[2])" shall be replaced by the figures **"€108.48 (€2.05)"**, and the figure €2.05 shall be annotated with the footnote "[1] Rebate in accordance with SGB V, section 130".
   b) In the chart "Annual treatment costs"
      the figure "€100.57" shall be replaced by the figure **"€108.48"**.
2. In section b) Patients with elective hip replacement operation", the information on the active ingredient enoxaparin in the charts "Cost of pharmaceutical" and "Annual treatment costs" shall be amended as follows:
   a) In the chart "Cost of pharmaceutical"
      the figures "€100.57 (€2.05[1]; €7.91[2])" shall be replaced by the figures **"€108.48 (€2.05)"**, and the figure €2.05 shall be annotated with the footnote "[1] Rebate in accordance with SGB V, section 130".
   b) In the chart "Annual treatment costs"
      the figure "€100.57 – €201.14" shall be replaced by the figure **€108.48 – €216.96"**, and annotated with the footnote "[1] Optimal combination of pack sizes".

II.

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Berlin, 6 September 2012

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

The Chair
Hecken