ARK Diagnostics, Inc.

For Export Only – Not For Sale in USA

ARK™ *Apixaban Assay*

This ARK Diagnostics, Inc. package insert for the ARK Apixaban Assay must be read carefully prior to use. Package insert instructions must be followed accordingly. Reliability of the assay results cannot be guaranteed if there are any deviations from the instructions in this package insert. The ARK Apixaban Assay test system includes separately provided test kits for the ARK Apixaban Assay, ARK Apixaban Calibrator and ARK Apixaban Control.

Report any serious incident that has occurred in relation to the device to the manufacturer and the appropriate competent authority as applicable. A Summary of Safety and Performance is available through Eudamed (European database on medical devices), SRN: US-MF-000023925

Customer Service

CE
2797

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Key to Symbols Used

LOT	Batch code	YYYY-MM-DD	Use by/Expiration date
REF	Catalog Number		Manufacturer
EC REP	Authorized Representative	CE 2797	CE Mark with notified body number
IVD	In Vitro Diagnostic Medical Device		Temperature limitation
	Consult Instructions for Use	R1 R2	Reagent 1/ Reagent 2
Rx Only	For Prescription Use Only		

Reagent Kit REF 5047-0001-00

1 Name

ARK™ *Apixaban Assay*

2 Intended Use

The ARK Apixaban Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of apixaban in 3.2% citrated human plasma on automated clinical chemistry analyzers. Apixaban concentrations can be used as an aid in management of patients on apixaban therapy in the following situations where measurement of apixaban levels could be useful to have as additional information:

- Patients at risk for major bleeding

- Patients experiencing a bleeding episode

The assay is not a stand-alone test and the results should be used in conjunction with other clinical and laboratory findings.

For use in adult population.

3 Summary and Explanation of the Test

Apixaban (*Eliquis*®, Bristol-Myers Squibb Pharma Company) 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide) is a direct oral anticoagulant indicated[1]

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy.

Measurement of apixaban concentration is recommended by the International Council for Standardization in Haematology (ICSH) consensus document providing guidance for laboratories on measuring direct oral anticoagulants (DOACs) in certain clinical scenarios including non-urgent situations (advanced age, severe renal failure or dependence on dialysis, prior interventions with high bleeding risk, body mass index >40 kg/m2, or drug interactions), urgent situations (acute bleeding or determination of appropriate reversal strategies), perioperative management involving high risk of bleeding, and suspicion of overdose.[2]

4 Principles of the Procedure

ARK Apixaban Assay is a homogeneous immunoassay based on competition between drug in the specimen and apixaban labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for binding to the antibody reagent. As the latter binds antibody, enzyme activity decreases. In the presence of drug from the specimen, enzyme activity increases and is directly related to the drug concentration. Active enzyme converts the coenzyme nicotinamide adenine dinucleotide (NAD) to NADH that is measured spectrophotometrically as a rate of change in absorbance. Endogenous serum G6PDH does not interfere with the results because the coenyzme NAD functions only with the bacterial enzyme used in the assay.

5 Reagents

REF	Product Description	Quantity/Volume
5047-0001-00	**ARK Apixaban Assay** **Reagent R1 – Antibody/Substrate** rabbit polyclonal antibodies to apixaban, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers	1 X 28 mL
	Reagent R2 – Enzyme Apixaban labeled with bacterial G6PDH, buffer, bovine serum albumin, sodium azide, and stabilizers	1 X 14 mL

Reagent Handling and Storage

ARK Apixaban Assay reagents are provided liquid, ready to use and may be used directly from the refrigerator. When not in use, reagents must be stored at 2–8°C (36–46°F), upright and with screw caps tightly closed. If stored as directed, reagents are stable until the expiration date printed on the label. Do not freeze reagents. Avoid prolonged exposure to temperatures above 32°C (90°F). **Improper storage of reagents can affect assay performance.** Reagents were stable up to 60 days when stored on-board the instrument based on supporting data.

ARK Apixaban products contain ≤0.09% sodium azide. As a precaution, affected plumbing including instrumentation should be flushed adequately with water to mitigate the potential accumulation of explosive metal azides. No special handling is required regarding other assay components.

6 Warnings and Precautions

- For **In Vitro Diagnostic Use.** Laboratory professional use only.
- For prescription use only. *Caution: U.S. Federal Law restricts this device to sale by or on the order of a licensed practitioner.*
- For use in adult population.

- The device is not intended for use in monitoring patients taking heparin or other direct oral factor Xa inhibitors.
- Reagents R1 and R2 are provided as a matched set and should not be interchanged with reagents from different lot numbers.
- Reagents contain ≤0.09% sodium azide.
- The assay should only be used in conjunction with information available from clinical evaluations and other diagnostic procedures.

7 Specimen Collection and Preparation for Analysis

- Each laboratory is responsible for supplying a valid specimen for analysis according to their quality procedures.
- Citrated plasma is required. Blood collection must be performed with 3.2% citrated plasma collection tubes. Whole blood cannot be used.
- Follow the collection tube manufacturer's recommendations for collection, processing and centrifugation.
- CLSI document GP44-A4 outlines procedures for minimizing artifacts due to specimen collection and handling for common laboratory tests.[3]
- Do not induce foaming and avoid repeated freezing and thawing to preserve the integrity of the specimen from the time it is collected until the time it is assayed.
- Fibrin, red blood cells, and other particulate matter may cause an erroneous result. Ensure adequate centrifugation.
- The presence of bubbles or foam on specimens can lead to short sample delivery and erroneous results.
- Each laboratory should consult available literature and internal data regarding specimen stability.
- Clarified specimens may be stored up to one week at 2 to 8°C based on supporting information. If testing will be delayed more than one week, specimens should be stored frozen (≤ -20°C) up to four weeks prior to being tested. Care should be taken to limit the number of freeze-thaw cycles.
- **Handle all patient specimens as if they were potentially infectious.**

8 Procedure

Materials Provided
ARK Apixaban Assay – **REF** 5047-0001-00

Materials Required – Provided Separately
ARK Apixaban Calibrator – **REF** 5047-0002-00
Quality Controls – ARK Apixaban Control – **REF** 5047-0003-00

Instruments
Reagents R1 and R2 may need to be transferred to analyzer-specific reagent containers prior to use. Avoid cross-contamination of R1 and R2.

Many automated clinical chemistry analyzers with photometric rate determination at 340 nm are suitable. Consult the analyzer-specific application sheet for programming the ARK Apixaban Assay, available from your distributor or ARK Customer Service. Application Protocol Sheets bearing the CE Mark have been verified by the manufacture. It is the responsibility of the laboratory to perform all appropriate validation for use of the assay with other settings or analyzers.

Refer to the instrument-specific operator's manual for daily maintenance.

Assay Sequence
To run or calibrate the assay, see the instrument-specific operator's manual.

Calibration
Perform a full calibration (6-point) procedure using the ARK Apixaban Calibrators A, B, C, D, E, and F; run calibrators in duplicate. Calibration is required with each new reagent kit lot number. Verify the calibration curve with at least two levels of quality controls according to the established laboratory quality assurance plan.

When to Re-Calibrate
- Whenever a new lot number of reagents is used
- Whenever indicated by quality control results
- Whenever required by standard laboratory protocols

Quality Control (QC)
Laboratories should establish QC procedures for the ARK Apixaban Assay. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations or accreditation requirements. Ensure that the quality control results meet the acceptance criteria before reporting patient results.

Good laboratory practice suggests that at least two levels (low and high medical decision points) of quality control be tested each day patient samples are assayed and each time a calibration is performed. Monitor the control values for any trends or shifts. If any trends or shifts are detected, or if the control does not recover within the specified range, review all operating parameters according to your clinical laboratory quality procedures. Contact Customer Service for further assistance.

Manual Dilution Protocol

To estimate drug levels in specimens exceeding the upper limit of quantitation, manually dilute the specimen with zero calibrator (CAL A). Multiply the assayed result by the dilution factor.

$$\text{Manual Dilution Factor} = \frac{\text{(Volume of Specimen + Volume of CAL A)}}{\text{Volume of Specimen}}$$

9 Results

Report result units as ng/mL or nmol/L. To convert results from ng/mL apixaban to nmol/L apixaban, multiply ng/mL by 2.176. The apixaban value from this assay should be used in conjunction with other clinical information. Refer to the instrument specific operator's manual for any result error codes.

10 Limitations of Procedure

This assay is designed for use with citrated plasma only; refer to the sections **Specimen Collection and Preparation for Analysis**. It is generally good practice to use the same method consistently for individual patient care due to the potential for method-to-method variabilities.

The assay is not a stand-alone test and the results should be used in conjunction with other clinical and laboratory findings.

11 Expected Values

The ARK Apixaban Assay is not intended to monitor patients on apixaban therapy. Currently, insufficient clinical evidence exists to warrant therapeutic drug monitoring; thus, there is no standard therapeutic range as the on-therapy range may be different for each individual patient.

Expected plasma levels (2021 ICSH Guidelines)[2]:

Condition	Dose (mg)	Trough ng/mL	Peak ng/mL
NVAF[a]	2.5	79 (34 – 162)[c]	123 (69 – 221)
	5	103 (41 – 230)	171 (91 – 321)
PE/VTE[b]	2.5	32 (11 – 90)	67 (30 – 153)
	5	63 (22 – 177)	132 (59 – 302)
	10	120 (41 – 335)	251 (111 – 572)

[a]Non-valvular atrial fibrillation
[b]Pulmonary embolism or venous thromboembolism
[c] 5 – 95th percentile
Drug levels lower than the 5th percentile trough concentration may be thought of as in the "below on-therapy" range, whereas those greater than the 95th percentile peak concentration may be considered to be "above on-therapy".[4]

The concentration of apixaban in human plasma in relation to clinical status has not been well-defined. Off-label dosing occurs, and factors associated with off-label dosing included advanced age, lower body mass index, decreased renal function, and hepatic impairment.[5,6]

Practical guidance on the use of laboratory testing in the management of bleeding in patients receiving direct oral anticoagulants should be consulted.[7,8] A number of factors can influence hemostasis. Other laboratory findings and clinical information should also be used to assess the hematological status of patients prior to medical decisions about dosage of apixaban.

12 Specific Performance Characteristics

Each laboratory is responsible for verification of performance using instrument parameters established for their analyzer. The following performance characteristics were obtained on the Beckman Coulter AU680® System.

Sensitivity

Limit of Quantitation (LOQ)

The following characteristics were determined according to CLSI EP17-A2 for the ARK Apixaban Assay. Analyzer-specific performance may vary.

Criterion	Apixaban (ng/mL)
Limit of Blank (LoB); N = 60 Average of 57th and 58th value in ascending order	0.65
Limit of Detection (LoD); N = 60 LoB + 1.652 SD, where SD = 0.5	1.5
Lower Limit of Quantitation (LLoQ); N = 40 LLoQ – 2 SD > LoD with acceptable recovery and linearity	3.0

Each laboratory is responsible for determining reporting criteria for apixaban concentrations. The following suggestion from CLSI EP17-A2 may be appropriate:

Result ≤ LoB	report “not detected; concentration < LoD”
LoB < Result < LoQ	report “analyte detected; concentration < LoQ”
Result ≥ LoQ	report the result as measured

Measurement Range

The measurement range of the ARK Apixaban Assay is 3.0 – 400.0 ng/mL. Specimens containing apixaban in higher concentrations (>400.0 ng/mL) may be assayed by dilution of the specimen into the measurement range for a quantitative result or otherwise reported as detected above the measurement range. Refer to **Section 8 Procedure - Manual Dilution Protocol.**

Recovery

Analytical recovery was assessed by adding concentrated apixaban drug into 3.2% citrated human plasma negative for apixaban. A stock concentrate of apixaban in methanol was added volumetrically to human citrated plasma negative for apixaban, representing drug concentrations across the assay range. Six replicates of each sample were assayed. The results were averaged and compared to the target concentration and percent recovery calculated.

$$\% \text{ Recovery} = \frac{100 \times \text{Mean recovered concentration}}{\text{Theoretical concentration}}$$

Theoretical Concentration (ng/mL)	Mean Recovered Concentration (ng/mL)	Percent Recovery (%)
3.0	3.4	111.7
16.0	17.2	107.4
40.0	41.3	103.3
80.0	83.4	104.3
160.0	172.9	108.1
300.0	294.8	98.3

Mean percent recovery: 105.5

Linearity

Linearity studies were performed as suggested in CLSI EP6-Ed2. A 500.0 ng/mL apixaban citrated plasma sample was prepared, and dilutions were made proportionally with human citrated plasma negative for apixaban. Linearity at specific dilutions was considered acceptable if the percent deviation was ≤10% from linearity. A linear relationship was demonstrated between 3.0 and 400.0 ng/mL.

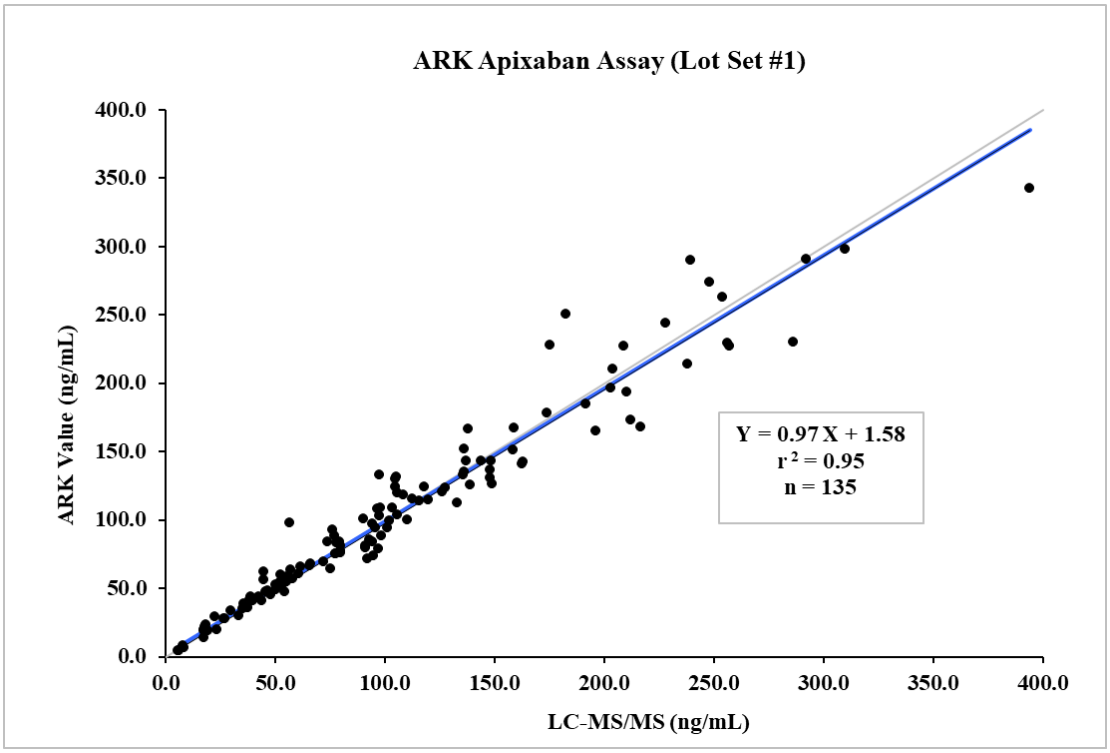
Nominal Value (ng/mL)	Results (ng/mL)	Predicted	% Recovery	Dev. from Linearity	% Deviation from Linearity (Acceptance Criteria: ≤ 10 %)
0.0	0.4	0.0	NA	NA	NA
3.0	3.3	3.0	109.4	0.23	7.7%
5.0	5.2	5.1	103.7	0.10	2.0%
12.5	13.0	12.7	104.0	0.30	2.3%
25.0	24.7	25.4	98.7	-0.74	-2.9%
50.0	48.4	50.8	96.8	-2.42	-4.8%
100.0	105.1	101.6	105.1	3.47	3.4%
150.0	155.2	152.4	103.5	2.75	1.8%
200.0	208.7	203.3	104.4	5.44	2.7%
250.0	250.1	254.1	100.0	-4.01	-1.6%
300.0	309.2	304.9	103.1	4.34	1.4%
350.0	330.2	355.7	94.3	-25.51	-7.2%
400.0	377.0	406.5	94.3	-29.51	-7.3%

Method Comparison

Method comparison studies were performed using CLSI Protocol EP09-A3 for three manufactured lots. Each lot is a separate set of assay reagents R1 & R2, calibrators and controls. Each lot was evaluated on a separate AU680 analyzer. Measurements of apixaban with the ARK Apixaban Assay were compared with determinations by liquid chromatography with tandem mass spectrometry (LC-MS/MS). Passing-Bablok[9] regression analysis was performed for 135 plasma specimens with apixaban concentrations by LC-MS/MS that ranged 5.4 ng/mL to 394.0 ng/mL. Passing-Bablok regression statistics are shown below (with 95% confidence limits).

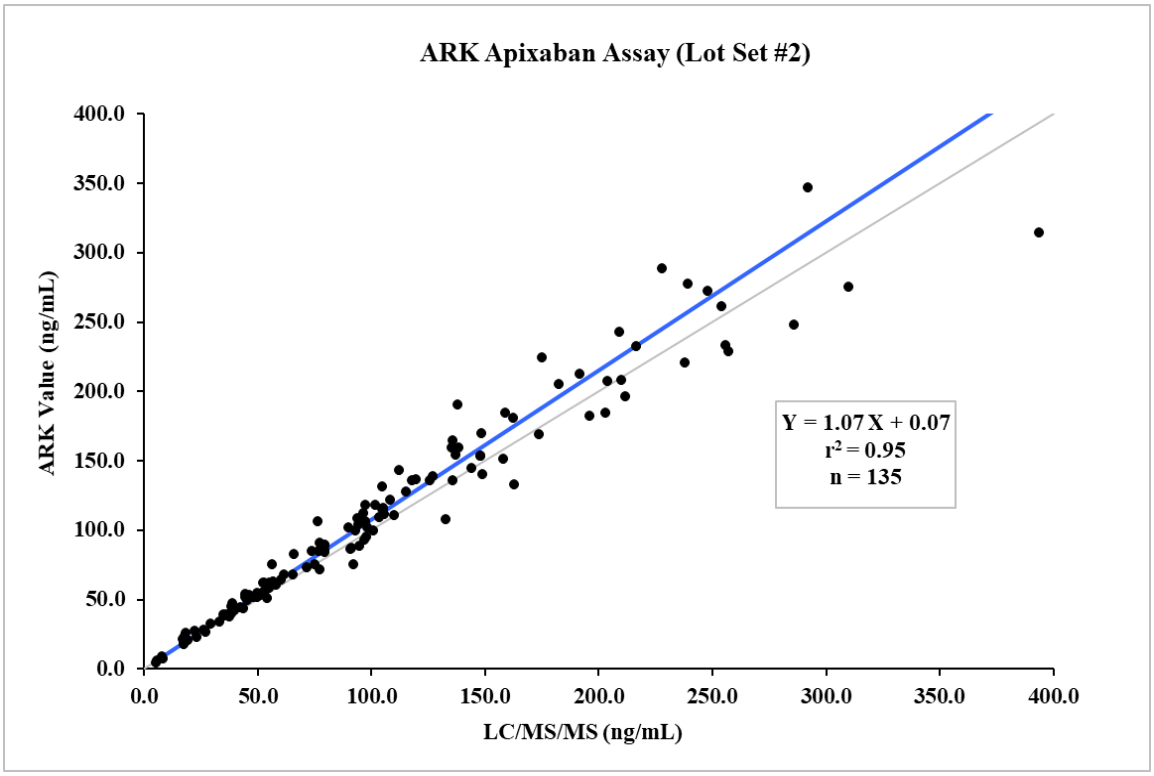
Lot #1

Slope	0.97	(0.94 to 1.01)
y-intercept	1.58	(-0.56 to 4.07)
Correlation Coefficient (r^2)	0.95	(0.93 to 0.96)
Number of Samples	135	



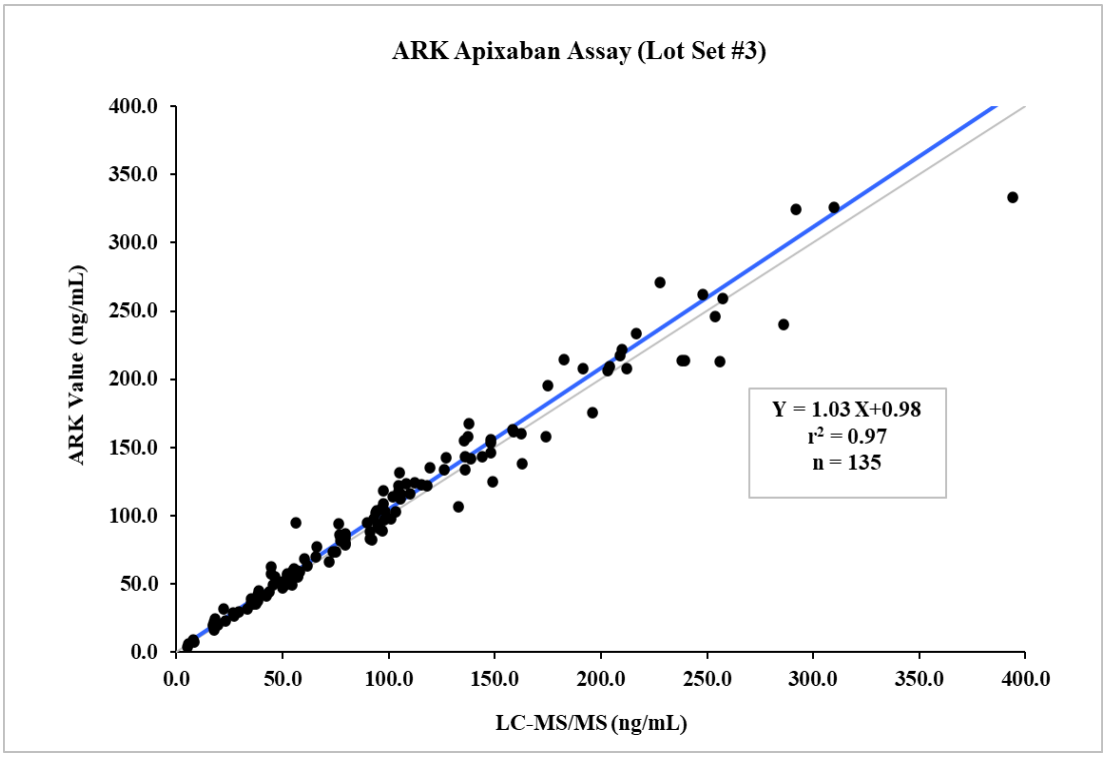
Lot #2

Slope	1.07	(1.03 to 1.11)
y-intercept	0.07	(-1.48 to 2.48)
Correlation Coefficient (r^2)	0.95	(0.96 to 0.98)
Number of Samples	135	



Lot #3

Slope	1.03	(1.01 to 1.06)
y-intercept	0.98	(-0.67 to 2.85)
Correlation Coefficient (r^2)	0.97	(0.95 to 0.98)
Number of Samples	135	



Precision

Precision was determined as described in CLSI EP05-A3 for three manufactured lots. Each lot is a separate set of assay reagents R1 & R2, calibrators and controls. Each lot was evaluated on a separate AU680 analyzer. Tri-level controls and three samples of apixaban in pooled 3.2% citrated human plasma were used in the study. Each level was assayed in quadruplicate twice a day for 20 days. Each of the runs per day was separated by at least two hours. The within run, between day, within lab total SD, and percent CVs were calculated. Results are shown below. Acceptance criteria: ≤10% within lab total CV.

Lot #1

Sample	N	Mean (ng/mL)	Repeatability Within Run		Between Day		Total Within Lab	
			SD	CV (%)	SD	CV (%)	SD	CV (%)
ARK Apixaban Control								
LOW	160	10.1	0.525	5.2	0.398	4.0	0.646	6.4
MID	160	29.2	0.944	3.2	0.662	2.3	1.241	4.3
HIGH	160	201.1	9.482	4.7	8.831	4.4	13.519	6.7
Human Plasma								
LOW	160	10.2	0.563	5.5	0.276	2.7	0.737	7.2
MID	160	29.7	1.221	4.1	0.441	1.5	1.407	4.7
HIGH	160	199.6	11.503	5.8	9.122	4.6	14.573	7.3

Lot #2

Sample	N	Mean (ng/mL)	Repeatability Within Run		Between Day		Total Within Lab	
			SD	CV (%)	SD	CV (%)	SD	CV (%)
ARK Apixaban Control								
LOW	160	10.0	0.25	2.5	0.212	2.1	0.32	3.2
MID	160	27.8	0.51	1.8	0.528	1.9	0.76	2.7
HIGH	160	206.7	6.06	2.9	6.266	3.0	8.84	4.3
Human Plasma								
LOW	160	9.3	0.20	2.1	0.158	1.7	0.27	2.9
MID	160	28.1	0.40	1.4	0.442	1.6	0.63	2.2
HIGH	160	199.6	5.03	2.5	5.112	2.6	7.58	3.8

Lot #3

Sample	N	Mean (ng/mL)	Repeatability Within Run		Between Day		Total Within Lab	
			SD	CV (%)	SD	CV (%)	SD	CV (%)
ARK Apixaban Control								
LOW	160	10.3	0.595	5.8	0.319	3.1	0.667	6.5
MID	160	28.6	0.971	3.4	0.488	1.7	1.382	4.8
HIGH	160	192.4	10.754	5.6	10.678	5.5	15.930	8.3
Human Plasma								
LOW	160	10.2	0.567	5.6	0.207	2.0	0.619	6.1
MID	160	29.2	0.845	2.9	0.704	2.4	1.242	4.3
HIGH	160	203.1	11.873	5.8	10.470	5.2	15.807	7.8

Endogenous Interfering Substances

Interference studies were conducted using CLSI EP7-A2 as a guideline. Clinically high concentrations of the following potentially interfering substances in citrated plasma with known levels of apixaban (10.0, 30.0, and 200.0 ng/mL) were evaluated. Each sample was assayed using the ARK Apixaban Assay, along with a citrated plasma control of apixaban. Measurement of apixaban resulted in ≤10% error in the presence of interfering substances at the levels tested.

		Percentage Recovery (%)		
Interfering Substance	**Interferent Concentration**	**10.0 ng/mL Apixaban**	**30.0 ng/mL Apixaban**	**200.0 ng/mL Apixaban**
Albumin	12 g/dL	93.6	92.2	94.6
Bilirubin - conjugated	70 mg/dL	107.1	106.9	102.5
Bilirubin - unconjugated	70 mg/dL	102.9	100.6	96.8
Cholesterol	620 mg/dL	102.3	97.8	106.2
Gamma-Globulin	12 g/dL	106.4	106.1	92.8
Hemoglobin	1000 mg/dL	103.4	99.3	95.9
Rheumatoid Factor	1000 IU/mL	107.5	100.5	98.1
Triglycerides	600 mg/dL	107.2	104.9	100
Uric Acid	30 mg/dL	106.8	99.2	98.4

Specificity

Crossreactivity to Other Anticoagulant Compounds

Other direct oral anticoagulants, heparins and warfarin did not interfere with the ARK Apixaban Assay when tested in the absence of apixaban. Levels tested were at or above maximum physiological or pharmacological concentrations. All measurements were less than the limit of the blank for apixaban (<0.6 ng/mL). Among the direct oral anticoagulants tested, heparins and warfarin tested, the ARK Apixaban Assay is specific for apixaban.

	Compound	Test Level (ng/mL)
1	Dabigatran	100,000
2	Edoxaban	1,000
3	Heparin (unfractionated)	330 units/dL
4	Heparin (low molecular weight)	330 units/dL
5	Rivaroxaban	3,000
6	Fondaparinux	1,000
7	Warfarin	75,000

Metabolism

Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. *O*-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.[1] However, *O*-demethyl apixaban sulfate, a stable and water-soluble metabolite, was the significant metabolite[10] and represented approximately 25% of the parent area under the time curve in human plasma.[11]

Metabolite

The crossreactivity of *O*-demethyl apixaban sulfate (10.0 ng/mL or 200.0 ng/mL) in the ARK Apixaban Assay was not clinically significant (≤ 5.0% crossreactivity). Apixaban (10.0 ng/mL or 200.0 ng/mL in human citrated plasma) was tested in the absence or presence of metabolite at higher-than-expected concentrations of metabolite.

O-Demethyl Apixaban (ng/mL)	Measured Apixaban in Absence/Presence of Metabolite (ng/mL)			
	Apixaban (10.0 ng/mL)		Apixaban (200.0 ng/mL)	
	Metabolite Absent	Metabolite Present	Metabolite Absent	Metabolite Present
10.0	9.9	10.4	Not Tested	
200.0	Not Tested		211.9	210.2

Crossreactivity

The compounds listed below did not interfere with the ARK Apixaban Assay when tested in the presence of apixaban (10.0 ng/mL and 200.0 ng/mL). Levels tested were at or above maximum physiological or pharmacological concentrations in plasma. Apixaban concentrations of samples containing interferent were within 10% of the apixaban level in a normal citrated plasma control.

Compound	Conc. Tested (µg/mL)	Compound	Conc. Tested (µg/mL)
Abacavir	15	Linezolid	48
Acetaminophen	200	Lopinavir	30
Acetylsalicylic acid	30	Lorazepam	1
Alprazolam	1	Maraviroc	10
Amikacin	150	Meropenem	200
Amiodarone (HCl)	50	Methotrexate	100
Amphotericin	100	Metronidazole	125
Amprenavir	30	Micafungin	100
Atazanavir	20	Morphine	10
Atorvastatin	1	Mycophenolic acid	40
Atovaquone	31.3	Nelfinavir	30
Bendamustine	150	Nevirapine	30
Bosutinib	50	Olanzapine	1
Carbamazepine	50	Penicillin V	100
Cefepime	500	Phenobarbital	500
Ceftazidime	600	Phenytoin	60
Ciprofloxacin	15	Piperacillin	500
Citalopram	10	Posaconazole	20
Clarithromycin	10	Prednisolone	2
Clonazepam	1	Quinidine	15
Codeine	2	Rifampicin	50
Colistimethate sodium	100	Ritonavir	30
Cyclosporin	2	Sirolimus (or) Rapamycin	10
Darunavir	20	Stavudine	30

Compound	Conc. Tested (µg/mL)	Compound	Conc. Tested (µg/mL)
Dasatinib	10	Sulfamethoxazole	400
Digoxin	0.5	Tacrolimus	1
Diltiazem	1	Tazobactam	15
Efavirenz	15	Tenofovir	1
Emtricitabine	10	Ticagrelor	1.9
Erythromycin	150	Tipranavir	30
Fluconazole	30	Tobramycin	35
Fosamprenavir	30	Trimethoprim	50
Gabapentin	30	Vancomycin	150
Gentamicin	30	Verapamil	2
Isosorbide dinitrate	6	Vincristine	100
Itraconazole	20	Voriconazole	20
Ketoconazole	20	Zolpidem	1
Lamivudine	15		

13 References

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14 Trademarks

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