Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	11356	NCT00361894
Study Phase:	III	
Official Study Title:	RECORD 3 Study: REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in subjects undergoing elective total knee replacement	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Rivaroxaban (Xarelto, BAY59-7939)	
Name of Active Ingredient:	Rivaroxaban	
Dose and Mode of Administration:	Rivaroxaban 10 mg once daily (od) administered as 10 mg tablets; oral administration with water. Intake of rivaroxaban or matching placebo started on the day of surgery (Day 1), 6 to 8 hours after wound closure, and continued once daily until Day 12 ± 2 (the day before venography).	
Reference Therapy/Placebo		
Reference Therapy:	For all participating countries, enoxaparin for injection was provided as Clexane® 0.4 mL prefilled syringes (Aventis Pharma; Frankfurt am Main, Germany) containing 40 mg enoxaparin sodium (corresponding to 4000 IU anti-Xa).	
Dose and Mode of Administration:	For enoxaparin 40 mg od subcutaneous injection or matching placebo, the first dose was administered 12 hours prior to surgery. Thereafter, enoxaparin active or placebo was administered on the day of surgery, at least 6 to 8 hours after wound closure, and on subsequent evenings until the final evening dose, administered on the evening of Day 12 ± 2 (the day prior to venography [Day 13 ± 2])	
Duration of Treatment:	12 ± 2 days	
Studied period:	Date of first subjects' first visit:	21 FEB 2006
	Date of last subjects' last visit:	18 JAN 2007
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	There were 4 amendments to the original protocol. Amendment no. 1 (dated 06 MAR 2006) was applicable to all participating countries. Changes enacted included: • Changed blood sampling from Day 7 ± 2 to Day 6 ± 2 • Adjusted liver enzyme monitoring and study drug discontinuation rules related to liver function test abnormality	

	• Added the incidence of surgical site bleeding associated with ≥2 g/dL fall in hemoglobin or leading to infusion of ≥2 units of whole blood or packed cells as an additional safety variable • Added exclusion of subjects with significant liver disease • Added retention samples to be taken (HIV-, hepatitis A, B, and C-serology) for those subjects who had provided additional consent • For missing or venographies that were not performed or evaluable, added measures to collect the reason for why the test was not done or not evaluable • Clarified statistical analysis plan concerning study objective for US submission • Removed the enoxaparin 30 mg bid arm Amendment no. 2 (dated 06 MAR 2006) was requested by the German Competent Authority. It clarified: • The definition of "adequate birth control" • The definition of treatment in case of (1) venous thromboembolism and (2) bleeding complications; and intervals of platelet counts (locally determined) Amendment no. 3 (dated 13 MAR 2006) was requested by the Competent Authority in France. It changed: • Time after the last dose of study drug preceding withdrawal of the epidural catheter (in case of planned neuraxial anesthesia) from at least 2 x the half-life to 20 hours Amendment no. 4 (dated 29 MAY 2006) which was requested according to the then currently approved Summary of Product Characteristics (SmPC) of Clexane® in Monaco changed: • Time after the last dose of study drug preceding withdrawal of the epidural catheter (in case of planned neuraxial anesthesia) from at least 2 x the half-life to 20 hours
Study Centre(s):	A total of 147 centers in the following countries participated in the conduct of this study: Germany (11), France (14), Poland (10), Italy (12), Spain (10), Canada (10), Belgium (8), The Netherlands (7), Mexico (3), Sweden (8), Denmark (5), Norway (5), South Africa (10), Czech Republic (8), Israel (9), Austria (4), Columbia (3), China (6), and Peru (4).
Methodology:	The study consisted of screening and randomization performed on Day 0 (or up to 14 days prior to surgery), Surgery (Day 1), a Treatment period (Days 0 through 12 ± 2), a bilateral ascending venography (Day 13 ± 2), and a follow-up period (30 days [+ 5 days] after the last treatment with study drug). The total duration of each subject's participation was up to 61 days. In addition to the venography, blood samples were drawn (prior to the venography), and a physical examination was performed. Clinical signs of deep vein thrombosis and pulmonary embolism were assessed, and adverse events and concomitant medications were recorded. During the follow-up visit, clinical signs of deep vein thrombosis and pulmonary embolism were assessed, and

	adverse events, concomitant medication, and cardiovascular and bleeding events during the 30 days after end of treatment were recorded. Blood samples for clinical chemistry were taken and a physical examination with vital signs was performed.
Indication/ Main Inclusion Criteria:	Indication: Prevention of venous thromboembolism Main Inclusion Criteria: Male and female subjects ≥18 years of age undergoing elective total knee replacement
Study Objectives:	Overall: To assess the efficacy and safety of rivaroxaban (BAY 59-7939) 10 mg once daily dosing for the prevention of venous thromboembolic events in male and female subjects aged 18 years or above undergoing elective total knee replacement.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy endpoint was a composite endpoint of: • Any deep vein thrombosis (proximal and/or distal), • Non-fatal pulmonary embolism, and • Death from all causes. The analysis of the primary efficacy endpoint (and all secondary efficacy endpoints related to venous thromboembolic events) was based solely on the assessments made by the Independent Central Adjudication Committee (ICAC) and venous thromboembolic events Adjudication Committees (AC/venous thromboembolic events). Efficacy (Secondary): The major secondary efficacy endpoint was the incidence of the composite endpoint encompassing proximal deep vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolic events-related death (i.e., "major venous thromboembolic events"). Additional secondary endpoints were: • Incidence of deep vein thrombosis (total, proximal, distal) • Incidence of symptomatic venous thromboembolic events (deep vein thrombosis, pulmonary embolism) • Incidence of symptomatic venous thromboembolic events during follow-up (i.e., after the end of the time window for primary efficacy assessment) • Net clinical benefit, assessed by the composite endpoint comprising major venous thromboembolic events and treatment-emergent major bleeding • Incidence of the composite endpoint that results from the primary endpoint by substituting venous thromboembolic events-related death for all death (composite of any deep vein thrombosis [proximal and/or distal] and non-fatal pulmonary embolism and venous thromboembolic events-related death) • Incidence of the composite endpoint that results from major venous thromboembolic events by substituting all-cause mortality for venous thromboembolic events-related death (composite of proximal deep vein thrombosis and non-fatal pulmonary embolism and death from all causes)

	An additional study endpoint was healthcare utilization, assessed by duration of hospitalization, any re-hospitalization during the entire study period, and rehabilitation center stay following hospital discharge. Safety: The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after the last intake of study drug. Major bleeding observed after this period was assessed separately. The analysis of the primary safety endpoint was based solely on the assessment and classification made by the Bleeding Event Committee. Adverse events that started >2 days after the last intake of study drug were not considered to be "treatment-emergent". Other safety variables included: • Incidence of any treatment-emergent bleeding observed no later than 2 days after last intake of study drug • Incidence of non-major treatment-emergent bleeding observed no later than 2 days after last intake of study drug • Incidence of postoperative bleeding (i.e., any, non-major, major) • Incidence of surgical site bleedings associated with ≥2 g/dL fall in hemoglobin or leading to infusion of ≥2 units of whole blood or packed cells • Treatment-emergent adverse events • Treatment-emergent serious adverse events • Discontinuation due to adverse event • Deaths • Adverse events starting >2 days after stop of treatment • Adjudicated cardiovascular events (on treatment/off treatment) • Incidence of (prolonged) hospitalization • Transfusion requirements • Amount of intra-operative blood loss • Postoperative volume in drainage • Laboratory parameters
Statistical Methods:	Populations: The safety population comprised those subjects who received at least 1 dose of study drug. A subject was considered valid for the modified intent-to-treat (MITT) analysis if the subject was (1) valid for safety analysis, (2) had undergone the appropriate surgery, and (3) had an adequate assessment of thromboembolism. The per protocol (PP) population included subjects who were (1) valid for the MITT analysis; (2) had an adequate assessment of thromboembolism that, in case of a positive finding, was done not later than 36 hours after stop of study drug; and (3) had no major protocol deviations.

	Efficacy (Primary): For the primary efficacy variable, the PP population was the primary population used for the test for non-inferiority of rivaroxaban as compared to enoxaparin and the MITT population was the primary population used for the test for superiority of rivaroxaban as compared to enoxaparin. For the primary efficacy endpoint, the difference between treatments with respect to the incidence rate was estimated and the corresponding asymptotic 2-sided 95% confidence interval (CI) was calculated. For non-inferiority testing, the hypothesis of relevant inferiority was rejected in favor of non-inferiority if the upper limit of the 95% CI for the treatment difference was below the pre-specified non-inferiority limit of 4% (absolute). If non-inferiority had been met in the PP population, a superiority test was performed based on the MITT population; the hypothesis of equality was rejected in favor of superiority if the upper limit of the 95% CI determined for the treatment difference (with respect to the incidence) was below 0. Efficacy (Secondary): The incidence of the secondary efficacy endpoints was evaluated by estimating the difference in the incidence between treatment groups and calculating corresponding CIs. For major venous thromboembolic events, the major secondary endpoint, a superiority test was preceded by a non-inferiority test based on a non-inferiority limit of 1.5%. Safety: The safety analysis was performed in the population of subjects valid for safety analysis. For the incidence of major bleeding, between-treatment differences were estimated and the corresponding 2-sided 95% CI was calculated. The incidences of any bleeding, non-major bleeding, and treatment-emergent adverse events were tabulated and stratified by treatment group.
Number of Subjects:	A total of 2531 subjects were randomized at 147 centers. Of these, 2459 subjects were treated with study drug (safety population), 1702 were valid for the modified intent-to-treat (MITT) analysis, and 1631 were valid for the per protocol (PP) analysis.

Study Results

Results Summary — Subject Disposition and Baseline

A total of 282 randomized subjects discontinued treatment prematurely (127 rivaroxaban 10 mg od subjects; 155 enoxaparin 40 mg od subjects); the difference in the rates (10.1% rivaroxaban 10 mg od versus 12.1% enoxaparin 40 mg od) was not statistically significant (P=0.12). The most common reason for discontinuation in both treatments was withdrawal of consent (5.1%) followed by adverse events (3.1%). The rates were similar between treatments. It should be noted that 5 of 1254 (0.4%) rivaroxaban 10 mg od subjects versus 17 of 1277 (1.3%) enoxaparin 40 mg od subjects discontinued treatment prematurely due to reaching the clinical endpoint, which was either reporting of a deep vein thrombosis or pulmonary embolism. In total, 2249 subjects completed the scheduled 11 to 15 day treatment period.

All randomized subjects entered the follow-up period, whether or not completing the treatment phase of the study. Of 2307 subjects entering the follow-up period, 63 subjects prematurely terminated (29 of 1150 [2.5%] rivaroxaban 10 mg od subjects; 34 of 1157 [2.9%] enoxaparin 40 mg od subjects). The most common reason for premature

termination from the study during the follow-up period was lost to follow-up (17 of 1150 [1.5%]) rivaroxaban 10 mg od subjects; 15 of 1157 [1.3%] enoxaparin 40 mg od subjects).

The results for demographic characteristics were similar across the safety, MITT and PP populations. These are described here for the safety population: approximately two-thirds of the subjects were female and there was a slightly greater rate of females in the rivaroxaban group as compared to the enoxaparin group (70% versus 66%, respectively). The difference was statistically significant (P=0.033). The majority of subjects were White (81%). It should be noted that 6% of subjects were reported as having "Race" missing and the reason for all but one subject was that, for legal reasons, "Race" is not reported for subjects enrolled in France. Subjects had a mean age of 67.6 years (range: 28 - 91), a mean weight of 80.6 kg (range: 41 - 157), and a mean BMI of 29.7 kg/m^2 (range: 16.0 - 54.3).

Results Summary — Efficacy

Rivaroxaban 10 mg od was both clinically effective and statistically superior to subcutaneous enoxaparin 40 mg od in the prevention of venous thromboembolic events in subjects undergoing elective total knee replacement.

Rivaroxaban met the pre-specified primary (see Table 1) and secondary efficacy objectives:

- Efficacy data were collected from 1631 (PP) of the 2531 randomized subjects. Based on the non-inferiority margin of 4%, results for the composite primary efficacy endpoint demonstrated that the objective of non-inferiority against enoxaparin was met and that rivaroxaban was at least as effective as enoxaparin in preventing venous thromboembolic events.
- In 1702 MITT subjects, the composite primary endpoint outcome occurred in 79 subjects (9.6%) and 166 subjects (18.9%) randomized to rivaroxaban or enoxaparin, respectively; a statistically significant difference (probability [P] < 0.001). This finding indicated the superiority (95% CI: -12.40%, -5.89%) of rivaroxaban over enoxaparin in preventing venous thromboembolic events.
- All components of the primary composite endpoint were reduced in the presence of rivaroxaban compared with enoxaparin, including proximal deep vein thrombosis (1.1% versus 2.3%), distal deep vein thrombosis (9.0% versus 17.8%), non-fatal pulmonary embolism (0% versus 0.5%), and death (0% versus 0.2%), (MITT population).
- For the major secondary endpoint, major venous thromboembolic events, there was a lower incidence in subjects treated with rivaroxaban (1.0%) demonstrating superiority over enoxaparin (2.6%) (P = 0.010; MITT population).
- For symptomatic venous thromboembolic events, a statistically significantly lower incidence was observed in subjects treated with rivaroxaban (1.0%) when compared with enoxaparin (2.7%), (MITT population).
- In the PP and MITT analyses, rivaroxaban was statistically superior to enoxaparin in the incidences of Composite Endpoint II (deep vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolic events-related death) and Composite Endpoint IV (proximal deep vein thrombosis, non-fatal pulmonary embolisms, and all-cause death).
- Rivaroxaban was statistically superior to enoxaparin in the analysis of net clinical benefit (composite of major venous thromboembolic events and treatment-emergent major bleeding).
- The results of locally reported deep vein thrombosis and pulmonary embolisms were consistent with the results of the respective adjudicated events.
- Clotting parameters (e.g., PT, prothrombinase-induced clotting time [PiCT]) were affected as expected by the mode of action.

Table-1: Incidence of Primary Efficacy Endpoint and its Individual Components as Assessed by the Central Adjudication Committee (PP and MITT Populations)

PER PROTOCOL POPULATION		
Endpoint /component n (%)	**Rivaroxaban 10 mg od (N=793)**	**Enoxaparin 40 mg od (N=838)**
Primary efficacy endpoint		
Any event	74 (9.3)	152 (18.1)
Death (any cause)	0	2 (0.2)
Non-fatal PE	0	3 (0.4)
Proximal and/or distal DVT	74 (9.3)	147 (17.5)
Components		
Death (VTE-related)	0	0
Death (not VTE-related)	0	0
Death (unexplained)	0	2 (0.2)
DVT, proximal	9 (1.1)	19 (2.3)
DVT, distal	69 (8.7)	143 (17.1)
MITT POPULATION		
	Rivaroxaban 10 mg od (N=824)	**Enoxaparin 40 mg od (N=878)**
Primary efficacy endpoint		
Any event	79 (9.6)	166 (18.9)
Death (any cause)	0	2 (0.2)
Non-fatal PE	0	4 (0.5)
Proximal and/or distal DVT	79 (9.6)	160 (18.2)
Components		
Death (VTE-related)	0	0
Death (not VTE-related)	0	0
Death (unexplained)	0	2 (0.2)
DVT, proximal	9 (1.1)	20 (2.3)
DVT, distal	74 (9.0)	156 (17.8)

Abbreviations: DVT=deep vein thrombosis; MITT=modified intent to treat ; od=once daily; PE=pulmonary embolism; PP=per protocol; and VTE=venous thromboembolism events

Results Summary — Safety

Of the 2531 randomized subjects, 2459 were exposed to study drug. Results indicated a comparable safety profile of rivaroxaban to enoxaparin (see Table 2). This conclusion was based on the following findings:

- The incidence of treatment-emergent major bleeding events was low in both treatment groups (0.6% rivaroxaban versus 0.5% enoxaparin). There were no fatal bleeding events reported in either group.
- The incidence of treatment-emergent major and non-major clinically relevant bleeding events as well as all bleeding events was similar between the 2 treatment groups.
- There were no deaths in the rivaroxaban group versus 6 deaths in the enoxaparin group. One death occurred during the treatment portion of the study, 4 deaths occurred during follow-up and one death occurred after early treatment discontinuation.
- The incidence of treatment-emergent adverse events (64% rivaroxaban versus 68% enoxaparin), including those that were considered to be treatment-related (12% rivaroxaban versus 13% enoxaparin), was similar between the 2 treatment groups.
- The incidence of treatment-emergent serious adverse events was similar between the 2 treatment groups (7% rivaroxaban, 9% enoxaparin).
- The incidence of adverse events starting more than 2 days after stop of study drug was similar between the 2 treatment groups (11% rivaroxaban, 12% enoxaparin).
- The rates of bleeding leading to re-operation, and surgical site bleeding associated with a fall in hemoglobin ≥2 g/dL or leading to infusion of ≥2 units whole blood/packed cells, were comparable between treatment groups.

The alanine aminotransferase (ALT [SGPT]) elevations appeared to be transient, with results returning to normal prior to the end of the study for all except 1 of the rivaroxaban subjects who had elevations >3 x upper limits of normal (ULN). For one subject, the final ALT (SGPT) result was minimally elevated at the end of the study (53 U/L with a normal range of 0 to 45 U/L). The number of subjects in this study with significant post-operative abnormalities in liver function tests was too small to draw a conclusion regarding any potential effect of either study drug on hepatic function.

Table 2 Adverse Event Summary (Safety Population)

Adverse event type n (%)	Rivaroxaban 10 mg od (N=1220)	Enoxaparin 40 mg od (N=1239)
Any adverse event	803 (65.8)	882 (71.2)
Any serious adverse event	119 (9.8)	141 (11.4)
Any death	0 (0.0)	6 (0.5)
Any treatment-emergent event	776 (63.6)	844 (68.1)
Any treatment-emergent event, excluding bleeding, acute DVT and pulmonary embolism events (as assessed by the investigator)	725 (59.4)	757 (61.1)
Any treatment-emergent bleeding event (as assessed by the investigator)	63 (5.2)	63 (5.1)
Any treatment-emergent acute DVT or pulmonary embolism event (as assessed by the investigator)	122 (10.0)	200 (16.1)
Any drug-related treatment emergent event	146 (12.0)	161 (13.0)
Any drug-related treatment-emergent event, excluding bleeding, acute DVT and pulmonary embolism events (as assessed by the investigator)	115 (9.4)	138 (11.1)
Any drug-related treatment-emergent bleeding event (as assessed by the investigator)	40 (3.3)	34 (2.7)
Any drug-related treatment-emergent acute DVT or pulmonary embolism event (as assessed by the investigator)	0 (0.0)	5 (0.4)
Any adverse event starting more than 2 days after stop of study drug	129 (10.6)	148 (11.9)
Any serious treatment-emergent event	90 (7.4)	110 (8.9)
Any drug-related serious treatment emergent event	26 (2.1)	19 (1.5)
Any serious event starting more than 2 days after stop of study drug	36 (3.0)	37 (3.0)
Any adverse event resulting in permanent discontinuation of study drug	39 (3.2)	56 (4.5)
Any adverse event resulting in (prolonged) hospitalization	92 (7.5)	105 (8.5)

Abbreviations: DVT=deep vein thrombosis; and od=once daily

Conclusion(s)

In this large double-blind study, oral administration of rivaroxaban 10 mg od was both clinically effective and statistically superior to subcutaneous enoxaparin 40 mg od in the prevention of venous thromboembolic events in subjects undergoing elective total knee replacement. Rivaroxaban met the pre-specified primary and secondary efficacy objectives. The clinical benefit of rivaroxaban was accompanied by an acceptable safety profile, which was comparable to SC enoxaparin 40 mg od in terms of adverse event rates, treatment-emergent as well as during follow-up. The incidence of major and non-major clinically relevant bleeding events as well as all bleeding events was similar between the 2 treatment groups.

Publication(s):	Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty. N Engl J Med. 2008;358:2776-2786		
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Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Pharma AG
Postal Address	D-13342 Berlin, Germany
Sponsor in Germany (if applicable)	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Krankenhaus der Barmherzigen Schwestern Linz	Orthopädische Abteilung Seilerstätte 4	4010	Linz	AUSTRIA
2	Medizinische Universität Graz	Universitätsklinik f. Orthopädie Auenbruggerplatz5-7	8036	Graz	AUSTRIA
3	SMZ Baumgartner Höhe Otto Wagner Spital	Orthopädisches Zentrum Sanatoriumstraße 2	1140	Wien	AUSTRIA
4	Universitätsklinikum Innsbruck	Universitätsklinik f. Orthopädie Anichstraße 35	6020	Innsbruck	AUSTRIA
5	AZ H. Familie	s'Herenbaan 172	2840	REET	BELGIUM
6	CAZ Midden-Limburg ZH Salvator-St.-Ursula Campus Salvator	Salvatorstraat 20	3500	HASSELT	BELGIUM
7	CHR de la Citadelle	Boulevard du 12e de Ligne 1	4000	LIEGE	BELGIUM

8	Jan Palfijn Ziekenhuis	Lange Bremstraat 70	2170	MERKSEM	BELGIUM
9	Stedelijk Ziekenhuis	Brugsesteenweg 90	8800	ROESELARE	BELGIUM
10	UZ Leuven Pellenberg	Weligerveld 1	3212	PELLENBERG	BELGIUM
11	Virga Jesse Ziekenhuis	Stadsomvaart 11	3500	HASSELT	BELGIUM
12	ZNA Middelheim	Lindendreef 1	2020	ANTWERPEN	BELGIUM
13	Grand River Hospital	835 King Street West	N2G 1G3	Kitchener	CANADA
14	Hotel Dieu-Grace Hospital	1030 Ouellette Avenue	N9A 1E1	Windsor	CANADA
15	Joseph Brant Memorial Hospital	1230 North Shore Blvd.	L7R 4C4	Burlington	CANADA
16	Lakeridge Health-Oshawa	Hospital Court	L1G 2B9	Oshawa	CANADA
17	Medical Arts Health Research Group	626 Main Street Suite 3	V2A 5C8	Penticton	CANADA
18	Office of Dr. Paul Zalzal, MD	435 Reynolds Street Suite 208	L6J 3M5	Oakville	CANADA
19	Ottawa Hospital - Civic Campus	Room C2-020 1053 Carling Avenue	K1Y 4E9	Ottawa	CANADA
20	Peterborough Regional Health Centre	1 Hospital Drive	K9J 7C6	Peterborough	CANADA
21	Rouge Valley Health System	Ajax & Pickering Hospital 580 Harwood Ave. South	L1S 2J4	Ajax	CANADA
22	St. John Regional Hospital	400 University Avenue 5DN - Research Office	E2L 4L2	St. John	CANADA
23	Affiliated Ruijin Hosp. Shanghai Jiaotong Univ. Med School	Cardiology Dept. No.197 Ruijin Er Road,	200025	Shanghai	CHINA

24	Chinese PLA General Hosp.	No.28 Fuxing Road, Haidai District, 100853, Beijing	100853	Beijing	CHINA
25	Peking University Jishuitan Hospital	No.31 Xinjiekou East Street, Xicheng District,	100035	Beijing	CHINA
26	Peking Univ. People's Hosp.	No.11 South Avenue, Xizhimen, Xicheng District,	100044	Beijing	CHINA
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35	Hospital Chomutov	Department of Orthopaedics Kochova 1185	430 01	Chomutov	CZECH REPUBLIC
36	Hospital Jihlava	Department of Orthopaedic Vrchlickeho 59/4630	586 01	Jihlava	CZECH REPUBLIC
37	Hospital Kolin	Department of Orthopaedic Zizkova 146	280 00	Kolin	CZECH REPUBLIC
38	Regional Hospital Havlicuv Brod	Department of Othopaedics Husova 2624	580 01	Havlickuv Brod	CZECH REPUBLIC
39	Regional Hospital Pardubice	Department od Orthopaedic Kyjevska 44	530 03	Pardubice	CZECH REPUBLIC
40	Gentofte Hospital	Ortopædkirurgisk Afdeling T 102 Niels Andersens Vej 65	DK-2900	Hellerup	DENMARK
41	Herlev Hospital	Ortopædkirurgisk Afd. T120 Herlev Ringvej 75	2730	Herlev	DENMARK
42	H:S Frederiksberg Hospital	Ortopædkirurgisk Klinik Elektivt Kirurgisk Center Nordre Fasanvej 57-59 Skadestuevej Indgang 1	2000	Frederiksberg	DENMARK
43	Nordsjællands Hospital - Hørsholm	Usserød Kongevej 102	DK-2970	Hørsholm	DENMARK
44	Regionshospitalet Silkeborg	Ortopædkirurgisk afdeling Falkevej 1-3	8600	Silkeborg	DENMARK
45	Centre clinical - Soyaux	Centre Clinical Service d'Anesthésie	16800	SOYAUX	FRANCE

46	CHU STRASBOURG - Hôpital de Hautepierre	Hopitaux Universitaires Hopital de Hautepierre Service d'anesthésiologie 1, avenue Molière	67098	STRASBOURG	FRANCE
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48	Clinique Juge - Marseille	Clinique Juge Service d'Anesthésie 116 rue Jean Mermoz	13008	MARSEILLE	FRANCE
49	Clinique les Maussins-Nollet - Paris	Clinique les Maussins-Nollet Service Anesthésie 67, rue de Romainville	75019	PARIS CEDEX 19	FRANCE
50	Clinique Saint Georges Anesthésie - Nice	Clinique Saint Georges Consultations d'Anesthésie 7 avenue du Roi Albert 1er	06000	NICE	FRANCE
51	Cochin - Paris	Hôpital Cochin Service d'Anesthésie 27, rue du Faubourg Saint-Jacques	75014	PARIS	FRANCE
52	Diaconesses Croix Saint Simon - Paris	Groupe Hospitalier Diaconesses Croix Saint Simon Département d'Anesthésie et de Réanimation 125 rue d'Avron	75960	PARIS CEDEX 20	FRANCE

53	Hôpital Arche - Nice	Hôpital de l'Archet Service d'anesthésie 151, route de Saint Antoine de Ginestiere	06000	NICE	FRANCE
54	Institut Médical des Sciences et du Sport - Monaco	Institut Médical des Sciences et du Sport Service d'Anesthésie 11bis avenue d'Ostende	98000	MONACO	FRANCE
55	Institut Montsouris - Paris	Institut Mutualiste Montsouris Service de chirurgie orthopedique 42 boulevard Jourdan	75877	PARIS CEDEX 14	FRANCE
56	Nouvelles Cliniques Nantaises - Nantes	Nouvelles Cliniques Nantaises SELARL CONVERGENCE Service d'Anesthésie 4, rue Eric Tabarly	44277	NANTES CEDEX	FRANCE
57	Pôle Santé République - Clermont Ferrand	Pôle Santé République Service d'Anesthésie 105 avenue de la république	63050	CLERMONT FERRAND	FRANCE
58	Polyclinique de Riaumont - Lievin	Polyclinique de Riaumont Service d'Anesthésie-Réanimation rue Entre Deux Monts	62806	LIEVIN	FRANCE
59	Caritas Krankenhaus GmbH	Orthopädie Uhlandstr. 7	97980	Bad Mergentheim	GERMANY

60	Klinikum Bremen Mitte gGmbH	Institut für Klinische Pharmakologie St.-Jürgen-Strasse 1	28177	Bremen	GERMANY
61	Klinikum Fürth	Chirurgische Klinik II Jakob-Henle-Str. 1	90766	Fürth	GERMANY
62	Klinikum Garmisch-Partenkirchen	Orthopädie Auenstr. 60	82467	Garmisch-Partenkirchen	GERMANY
63	Kreiskrankenhaus Rheinfelden	Orthopädie Am Vogelsang 4	79618	Rheinfelden	GERMANY
64	Medizinische Einrichtungen der Heinrich-Heine-Universität	Orthopädische Klinik Moorenstr. 5	40225	Düsseldorf	GERMANY
65	Orthopädische Klinik König-Ludwig-Haus	Brettreichstrasse 11	97080	Würzburg	GERMANY
66	Orthopädische Universitätsklinik - Friedrichsheim	Allg. Orthopädie und Traumatologie Marienburgstr. 2	60528	Frankurt am Main	GERMANY
67	Sana Kliniken	Helmut-Ulrici-Kliniken Klinik für Endoprothetik Waldhausstrasse	16766	Sommerfeld	GERMANY
68	Städtische Kliniken Frankfurt am Main / Hoechst	Orthopädie Gotenstr. 6-8	65929	Frankfurt	GERMANY
69	Universität Witten/Herdecke	Zentrum für Klinische Forschung der Universität Witten/Herdecke Pferdebachstr. 30	58455	Witten	GERMANY

70	Assaf Harofeh Medical Center	Department Orthopedic A	70300	Zerifin	ISRAEL
71	Chaim Sheba Medical Center	The Israeli National Hemophilia Center	52621	Tel Hashomer	ISRAEL
72	Edith Wolfson Medical Center	Department of Orthopedic 62 Halohamin Street	58220	Holon	ISRAEL
73	Meir Medical Center	Department of Orthopedic 59 Tchernihovsky street	44281	Kfar-Saba	ISRAEL
74	Rambam Medical Center	Hematology Department 8, Haaliya Hashniya St. Bat Galim	31096	Haifa	ISRAEL
75	Soroka University Medical Center	Department of Orthopedic P.O.B. 151	84101	Beer Sheva	ISRAEL
76	Tel Aviv Sourasky Medical Center	Department of orthopedic Surgery B 6 Weizmann Street	64239	Tel Aviv	ISRAEL
77	Tel-Aviv Sourasky Medical Center	Department of Orthopedic A 6, Weizmann Street	64239	Tel Aviv	ISRAEL
78					ISRAEL
79	A.O. Osp Circolo e Fond.Macchi	Dip. Scienze Ortopediche e Traumatologiche Viale L.Borri, 57	21100	Varese	ITALY
80	A.O. Ospedale di Lecco	Ortopedia, Anestesia e Rianimazione Ospedale San Leopoldo Mandic Largo Mandic, 1	23900	Merate	ITALY

81	A.O.U. di Parma	Anestesia, Rianimazione e Terapia Antalgica Via Gramsci, 14	43100	Parma	ITALY
82	A.O.U. Santa Maria Misericordia UD	Anestesia e Rianimazione Piazzale Santa Maria della Misericordia, 15	33100	Udine	ITALY
83	AULSS 16 Padova - Veneto	Ortopedia e Traumatologia Ospedale Sant' Antonio di Padova Via Facciolati, 71	35127	Padova	ITALY
84	AUSL 1 Perugia - Umbria	Medicina Interna P.O. Alto Chiascio Largo San Francesco, 7/a - Località Branca	06024	Gubbio	ITALY
85	AUSL 1 SS Ospedale Marino	Ortopedia Ospedale Marino Regina Margherita Via Primo Maggio	07041	Alghero	ITALY
86	Casa di Cura Abano Terme	Anestesia e Rianimazione Piazza Cristoforo Colombo, 1	35031	Abano Terme	ITALY
87	C.T.O. Università degli Studi di Firenze	II Clinica Ortopedica Largo P. Palagi, 1	50139	Firenze	ITALY
88	Gruppo Ospedaliero San Donato Foundation	Anestesia Locoregionale e Terapia del Dolore Policlinico San Donato Via Morandi, 30	20097	San Donato Milanese	ITALY

89	IRCCS Ist Ortopedico Rizzoli	Anestesia, Rianimazione e Terapia Intensiva Istituto Ortopedico Rizzoli Via Pupilli, 1	40136	Bologna	ITALY
90	Università Cattolica Columbus	Malattie Emorragiche e Trombotiche Complesso Integrato Columbus Università Cattolica del Sacro Cuore Largo A. Gemelli, 8	00168	Roma	ITALY
91	Antiguo Hospital Civil de Guadalajara "Fray Antonio Alcalde"	Calle del Hospital No. 278 Col. El Retiro Sector Hidalgo	44280	Guadalajara	MEXICO
92	Centro Médico Ignacio Chávez ISSSTESON	Juárez y Aguscalientes S/N Col. Modelo	83000	Hermosillo	MEXICO
93	Hospital Clínica del Parque	Calle Dr. Pedro Leal Rodríguez 1802 Col. Centro	31000	Chihuahua, Chih.	MEXICO
94	Academisch Medisch Centrum Universiteit van Amsterdam	Afd. ORCA/Orthopedie, G4-221, Meibergdreef 9		Amsterdam	NETHERLANDS
95	Bernhoven Ziekenhuis	Afd. orthopedie, Joannes Zwijsenlaan 121	5342 BT	Oss	NETHERLANDS
96	Diaconessenhuis	Afd. Orthopedie, Houtlaan 55	2334 CK	LEIDEN	NETHERLANDS
97	Isala Klinieken, lokatie Weezenlanden	afd. Orthopedie, Groot Wezenland 20	8011 JW	Zwolle	NETHERLANDS

98	Spaarne Ziekenhuis	Afdeling Orthopedie, Spaarnepoort 1	2134 TM	HOOFDDORP	NETHERLANDS
99	St. Maartenskliniek	Secretariat of Anaesthesiology, Hengstdal 3	6522 JV	NIJMEGEN	NETHERLANDS
100	Tergooiziekenhuizen Hilversum	Afd. orthopedie, Van Riebeeckweg 212	1213 XZ	HILVERSUM	NETHERLANDS
101	Helse Nord-Tönderlag HF sykehuset Namsos	.	7800	Namsos	NORWAY
102	Sykehuset Innlandet HF Elverum	Kirurgisk avd. Sykehuset Innlandet HF Elverum	2409	Elverum	NORWAY
103	Sykehuset Innlandet HF Gjøvik	Kirurgisk avd. Sykehuset Innlandet HF Gjövik	2819	Gjövik	NORWAY
104	Sykehuset Innlandet HF Kongsvinger	Orto./Revmakir. avd. Sykehuset Innlandet HF Kongsvinger	2212	Kongsvinger	NORWAY
105	Sykehuset Innlandet HF Lillehammer	Ortopedisk avd. Sykehuset Innlandet HF Lillehammer	2609	Lillehammer	NORWAY
106	Centro Médico Naval	Av. Venezuela s/n	CALLAO 2	Callao	PERU
107	Hospital Alberto Sabogal Sologuren	Avenida Colina 1081	CALLAO 2	Callao	PERU
108	Hospital Edgardo Rebagliati Martins	Av. Edgardo Rebagliati Martins S/N JESUS MARIA	LIMA 11	Lima	PERU
109	Hospital Guillermo Almenara	Av. Grau 800	LIMA 1	Lima	PERU

110	Instytut Reumatologii	Klinika Reumoortopedii ul. Spartanska 1	02-637	Warszawa	POLAND
111	Samodzielny Publiczny Szpital Kliniczny nr 4	Katedra i Klinika Ortopedii, Traumatologii AM ul. Jaczewskiego 8	20-090	Lublin	POLAND
112	SP Szpital Kliniczny AM w Bialymstoku	Klinika Ortopedii i Traumatologii Akademia Medyczna w Bialymstoku ul. Marii Sklodowskiej-Curie 24 a	15-276	Bialystok	POLAND
113	SP Szpital Kliniczny nr 1 PAM	Klinika Ortopedii i Traumatologii ul. Unii Lubelskiej 1	71-252	Szczecin	POLAND
114	Szpital Uniwersytecki im. Antoniego Jurasza	Klinika Ortopedii i Traumatologii Narzadu Ruchu ul. M. Sklodowskiej-Curie 9	85-094	Bydgoszcz	POLAND
115	Wojew. Centrum Ortopedii i Rehabilitacji Narzadu Ruchu	II Katedra Ortopedii UM Klinika Ortopedii i Ortopedii Dzieciecej ul. Drewnowska 75	91-002	Lodz	POLAND
116	Wojewodzki Szpital Specjalistyczny im. M. Kopernika	Katedra i Klinika Ortopedii i Traumatologii Narzadu Ruchu AM ul. Nowe Ogrody 1/6	80-803	Gdansk	POLAND

117	Wojewodzki Szpital Specjalistyczny im. Rydygiera	Oddzial Ortopedii i Traumatologii Narzadu Ruchu Os. Zlotej Jesien 1	31-826	Krakow	POLAND
118	Wojewodzki Szpital Specjalistyczny im. S. Wyszynskiego SPZOZ	Oddzial Urazowo-Ortopedyczny al. Krasnicka 100	20-718	Lublin	POLAND
119	Wojskowy Instytut Medyczny	Klinika Ortopedii ul. Szaserow 128	04-141	Warszawa	POLAND
120	1 Military Hospital	.		Pretoria	SOUTH AFRICA
121	Chatsmed Medical Center	105 Chatsmed Hosptial 80 Woodhurst drive Chatsworth	4092	Durban	SOUTH AFRICA
122	Clinical Projects Research SA	42 Russell Street	6850	Worcester	SOUTH AFRICA
123	Olivedale Hospital	Kapano Clinical Trials Room C1 Windsor Way	2125	Randburg	SOUTH AFRICA
124	Pretoria Academic Hospital Ethics Committee	H.W. Snyman Building Level 2/34 Prinshof / Gazena	0084	Pretoria	SOUTH AFRICA
125	Private Practice Dr UK Dhanjee	11 van Schalkwyk Street	2940	Newcastle	SOUTH AFRICA
126	University of the Free State	Faculty of Health Nelson Mandela Ave	9301	Bloemfontein	SOUTH AFRICA

127	University of Witwatersrand	University of the Witwatersrand Charlotte Maxeke Johannesburg Academic Hospital Medical School 7 York Road Parktown	2132	Johannesburg	SOUTH AFRICA
128	Vergelegen Medi-Clinic	Dr. J.M. Engelbrect Block 1 Vergelegen MediClinic Main Road	7130	Somerset West	SOUTH AFRICA
129	Wilgers Hospital	DIE WILGERS HOSPITAL LYNWOOD ROAD		PRETORIA	SOUTH AFRICA
130	Ciutat Sanitària i Universitaria de la Vall d'Hebron	Servicio de Traumatología Passeig de la Vall d'Hebrón, 119-129	08035	Barcelona	SPAIN
131	Clínica Platón	Servicio de Traumatología	08006	C/ Plató, 21	SPAIN
132	Clínica Universitaria de Navarra	Servicio de Hematología Avda. Pio XII, 36	31008	Pamplona	SPAIN
133	Complejo Hospitalario de Jaén	Avda. Ejército Español, s/n	23007	Jaén	SPAIN
134	Fundación Hospital Alcorcón	Servicio de Traumatología	28922	Alcorcón	SPAIN
135	Hospital Clínic i Provincial de Barcelona	Servicio de Traumatología C/ Villarroel, 170	08036	Barcelona	SPAIN
136	Hospital Clínico Universitario de Valencia	Servicio de Traumatología Avda. Blasco Ibañez, 17 46910 Valencia	46010	Valencia	SPAIN

137	Hospital Clínico Universitario San Carlos	Servicio de Traumatología C/. Dr. Martín Lagos, s/n	28040	Madrid	SPAIN
138	Hospital General de Castelló	Servei de Traumatologia Avda. de Benicasim, s/n	12004	Castelló de la Plana	SPAIN
139	Hospital Universitari Germans Trias i Pujol	Servicio de Traumatología Ctra. del Canyet, s/n	08916	Badalona	SPAIN
140	Hässleholms Sjukhus	Ortopedkliniken	281 25	Hässleholm	SWEDEN
141	Kungälvs Sjukhus	Ortoped/Kirurgkliniken Avd 3	442 83	Kungälv	SWEDEN
142	Länssjukhuset	Ortopedkliniken	301 85	Halmstad	SWEDEN
143	Länssjukhuset Ryhov	Ortopedkliniken	551 85	Jönköping	SWEDEN
144	Sjukhuset i Varberg	Ortopedkliniken	432 81	Varberg	SWEDEN
145	Skaraborgs Sjukhus Falköping	Ortopedkliniken	521 85	Falköping	SWEDEN
146	Skaraborgs Sjukhus Lidköping	Ortopedkliniken	531 85	Lidköping	SWEDEN
147	SU/Östra	Ortopedkliniken	416 85	Göteborg	SWEDEN

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Xarelto
Brand/Trade Name(s) ex-US	Xarelto
Generic Name	rivaroxaban
Main Product Company Code	BAY59-7939
Other Company Code(s)	
Chemical Description	IUPAC Name: 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
Other Product Aliases	

Date of last Update/Change: 04 Mar 2013