# EU-RISK MANAGEMENT PLAN FOR GENERICS

# RIVAROXABAN

## Rivaroxaban 2.5 mg film-coated tablets
## Rivaroxaban 10 mg film-coated tablets
## Rivaroxaban 15 mg film-coated tablets
## Rivaroxaban 20 mg film-coated tablets

**DISTRIQUÍMICA, S.A.**

**DATE OF THIS REPORT:**

20 November 2017

**Version 2.0**

**CONFIDENTIAL**

[redacted]

# Table of contents

## *Part I: Product(s) Overview*

| | |
|---|---|
| Active substance(s) (INN or common name): | Rivaroxaban |
| Pharmaco-therapeutic group<br>(ATC Code): | B01AF01 Rivaroxaban |
| Name of Marketing Authorisation Holder or Applicant: | [redacted] |
| Number of medicinal products to which this RMP refers: | 4 |
| Product(s) concerned (brand name(s)): | Rivaroxaban 2.5 mg film-coated tablets<br>Rivaroxaban 10 mg film-coated tablets<br>Rivaroxaban 15 mg film-coated tablets<br>Rivaroxaban 20 mg film-coated tablets |

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| Data lock point for this RMP | 20 November 2017 | Version number | Version 2.0 |
| Date of final sign off | 27 November 2017 | | |

• RMP submitted in the scope of MA application

Administrative information on the RMP

| Part | Module/annex | Date last updated for submission (sign off date) | Version number of RMP when last submitted/ or Not Applicable |
|---|---|---|---|
| Part II<br>Safety Specification | SV Post authorisation experience | Not applicable | Not applicable |
| | SVIII<br>Summary of the safety concerns | Not applicable | Not applicable |
| Part III<br>Pharmacovigilance Plan | | Not applicable | Not applicable |
| Part IV<br>Plan for post-authorisation efficacy studies | | Not applicable | Not applicable |
| Part V<br>Risk Minimisation Measures | | Not applicable | Not applicable |
| Part VI<br>Summary of RMP | | Not applicable | Not applicable |
| Part VII<br>Annexes | ANNEX 2<br>Current or proposed SmPC/PIL | Not applicable | Not applicable |
| | ANNEX 3<br>Worldwide marketing status by country | Not applicable | Not applicable |
| | ANNEX 5<br>Synopsis of pharmacoepidemiological study programme | Not applicable | Not applicable |

| Part | Module/annex | Date last updated for submission (sign off date) | Version number of RMP when last submitted/ or Not Applicable |
|---|---|---|---|
| | ANNEX 6<br>Protocols for proposed and on-going studies in Part III | Not applicable | Not applicable |
| | ANNEX 7<br>Specific adverse event follow-up forms | Not applicable | Not applicable |
| | ANNEX 8<br>Protocols for studies in Part IV | Not applicable | Not applicable |
| | ANNEX 9<br>Synopsis of newly available study reports in Parts III-IV | Not applicable | Not applicable |
| | ANNEX 10<br>Details of proposed additional risk minimisation activities | Not applicable | Not applicable |
| | ANNEX 11<br>Mock up examples | Not applicable | Not applicable |
| | ANNEX 12<br>Other supporting data | Not applicable | Not applicable |

QPPV name: [redacted]

QPPV signature: [redacted]

Contact person for this RMP: [redacted]

E-mail address or telephone number of contact person: [redacted]

[redacted]

[redacted]

**Overview of versions:**

Version number of last agreed RMP: The present RMP is the first RMP of the aforementioned medicinal product submitted within a Marketing Authorisation Application (MAA) following the current Directive 2010/84/EU. Therefore there is no an existing RMP for such product and no previous versions are available.

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|---|---|
| Version number | Version 2.0 |
| Agreed within | Not applicable[a] |

**Current RMP versions under evaluation:**

| RMP Version number | Submitted on | Submitted within |
|---|---|---|
| Not applicable[a] | Not applicable[a] | Not applicable[a] |

[a] Not applicable, since this RMP (version 2.0) is submitted in the scope of MA application.

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| **Invented name(s) in the European Economic Area (EEA)** | Rivaroxaban 2.5 mg film-coated tablets<br>Rivaroxaban 10 mg film-coated tablets<br>Rivaroxaban 15 mg film-coated tablets<br>Rivaroxaban 20 mg film-coated tablets |
| **Authorisation procedure** | National procedure |
| **Brief description of the product including:**<br>• chemical class<br>• summary of mode of action<br>• important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines | • Rivaroxaban is a pure (S)-enantiomer. It is an odourless, non- hygroscopic, white-to-yellowish powder.<br>• Chemical name: 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholi nyl)phenyl]-1 ,3-oxazolidi n-5-yl}methyl)-thi ophen e- carboxamide<br>• Empirical formula: C19H1sCIN30sS<br>• Molecular weight: 435.85<br>• Dueto its direct inhibitory effect on clotting Factor Xa, rivaroxaban inhibits blood clotting in vitro and in vivo. Due to the pharmacokinetic properties of the molecule, the drug is suitable for oral administration.<br>• Excipients are as follows: microcrystalline cellulose, croscarmellose sodium, lactase monohydrate, hypromellose, sodium lauryl sulphate and magnesium stearate. In addition, the film coat contains the following: macrogol 3350, hypromellose, titanium dioxide (E171), iron oxide yellow (E172) (2.5 mg) and iron oxide red (E172) (1O mg, 15 mg, 20 mg). |
| **Indication(s) in the EEA**<br>Proposed (if applicable) | • Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.<br>• Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.<br>• Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age > 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.<br>• Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. |

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| **Posology and route of administration in the EEA**<br><br>Proposed (if applicable) | Posology<br><br>• Prevention of venous thromboembolism (VTE1 in adult Patients undergoing elective hip or knee replacement surgery<br><br>The recommended dose is 10 mg taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery provided that haemostasis has been established.<br><br>• Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.<br><br>Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE.<br><br>• Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age > 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.<br><br>The recommended dose is 20 mg once daily, which is also the recommended maximum dose.<br><br>For patients with moderate renal impairment (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) the recommended dose is 15 mg once daily.<br><br>• Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers<br><br>The recommended dose is 2.5 mg twice daily.<br><br>Patients should also take a daily dose of 75-100 mg ASA or a daily dose of 75-100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine.<br><br>Method of administration<br><br>For oral use. It can be taken with or without food. Patients should be instructed not to open the capsule as this may increase the risk of bleeding. |
| **Pharmaceutical form(s) and strengths**<br>Proposed (if applicable) | Film-coated tablet, 2.5 mg<br><br>Film-coated tablet, 10 mg<br><br>Film-coated tablet, 15 mg<br><br>Film-coated tablet, 20 mg |

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| Country and date of first authorisation worldwide | Not applicable |
| Country and date of first launch worldwide | Not applicable |
| Country and date of first authorisation in the EEA | Not applicable |

Is the product subject to additional monitoring in the EU? Yes **X** No ☐

## *Part II: Module SVIII - Summary of the safety concerns*

| | |
|---|---|
| Active substance | Rivaroxaban |
| Product(s) concerned<br>(brand name(s)): | Rivaroxaban 2.5 mg film-coated tablets<br>Rivaroxaban 10 mg film-coated tablets<br>Rivaroxaban 15 mg film-coated tablets<br>Rivaroxaban 20 mg film-coated tablets |
| MAH/Applicant name | [redacted] |

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|---|---|
| Data lock point for this module | 15 September 2016 |
| Version number of RMP when this module was last updated | Not applicable |

**Table 1.** Summary of safety concerns

| | |
|---|---|
| **Important identified risks** | Haemorrhage |
| **Important potential risks** | Embryo-fetal toxicity |
| **Missing information** | Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery |
| | Patients with severe renal impairment (CrCI < 30 Ml/lmin) |
| | Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) |
| | Remedial pro-coagulant therapy for excessive haemorrhage |
| | Pregnant or breast-feeding women |
| | Patients with atrial fibrillation (AF) and a prosthetic heart valve |
| | Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting |
| | Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) |
| | Patients < 18 years |

***Part III: Pharmacovigilance Plan***

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|---|---|
| Active substance | Rivaroxaban |
| Product(s) concerned<br>(brand name(s)): | Rivaroxaban 2.5 mg film-coated tablets<br>Rivaroxaban 10 mg film-coated tablets<br>Rivaroxaban 15 mg film-coated tablets<br>Rivaroxaban 20 mg film-coated tablets |
| MAH/Applicant name | [redacted] |

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|---|---|
| Data lock point for this module | 15 September 2016 |
| Version number of RMP when this module was last updated | Not applicable |

## III.1 Safety concerns and overview of planned pharmacovigilance actions

Routine pharmacovigilance will be conducted for rivaroxaban as detailed in corresponding pharmacovigilance procedures that are in place at Distriquímica, S.A. These routine practices include the collection, follow-up, evaluation and expedited reporting of individual case reports, ongoing monitoring and signal investigation, preparation of periodic safety update reports, and initiation of label changes as required, and are described in applicable Standard Operating Procedures.

## III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

As only routine pharmacovigilance activities have been proposed, additional activities to assess effectiveness are not necessary.

## III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

Not applicable, as this is the first RMP

## III.4 Details of outstanding additional pharmacovigilance activities

Not applicable.

### III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

Bayer Pharma AG, the MAH of the reference product, Xarelto®, has the obligation to conduct post-authorisation measures at the moment of preparing this document. Bayer shall complete, within the stated timeframe, the below measures: A post-authorisation study program that addresses the safety of rivaroxaban in the secondary prevention of Acute Coronary Syndrome outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all population and particularly in patients at increased risk of bleeding.

The due dates are the following:

• Interim analyses reports provided annually beginning Q4 2015 until completion of the study program. • Cumulative interim report by Q4 2017

• Final Study Reports submitted by Q4 2020

Distriquímica S.A will amend the labelling or implement any other additional pharmacovigilance activities according to the results of these studies.

### III.4.2 Mandatory additional PhV Activity (being a Specific Obligation)

Not applicable.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

Not applicable.

III.4.4 Stated additional pharmacovigilance activities

Not applicable.

## III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

There are no on-going or planned studies regarding Rivaroxaban

III.5.2 Table of completed studies/activities from the Pharmacovigilance Plan

There are no completed studies regarding Rivaroxaban

### *Part IV: Plans for post-authorisation efficacy studies*

Not applicable since post-authorisation efficacy studies has not been imposed to the reference product.

## *Part V: Risk minimisation measures*

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|---|---|
| Active substance | Rivaroxaban |
| Product(s) concerned<br>(brand name(s)): | Rivaroxaban 2.5 mg film-coated tablets<br>Rivaroxaban 10 mg film-coated tablets<br>Rivaroxaban 15 mg film-coated tablets<br>Rivaroxaban 20 mg film-coated tablets |
| MAH/Applicant name | [redacted] |

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|---|---|
| Data lock point for this module | 20 November 2017 |
| Version number of RMP when this module was last updated | Not applicable |

## V.1 Risk minimisation measures by safety concern

| Safety concern (important identified risk) | Haemorrhage |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>**4.3 Contraindications:**<br>• Active clinically significant bleeding.<br>• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.<br>• Lesion or condition, if considered to be a significant risk for majar bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or majar intraspinal or intracerebral vascular abnormalities.<br>• Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.<br>**Additional contraindication in the SmPC Section 4.3 only for 2.5 mg (ACS):**<br>• Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke ora transient ischaemic attack (TIA). |

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| | **4.4 Special warnings and precautions for use:**<br><br>Haemorrhagic risk<br><br>Several sub-groups of patients, as detailed below, are at increased risk of bleeding.<br><br>**Further text only for 2.5 mg (ACS):** Therefore, the use of Rivaroxaban in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment.<br><br>**Further text only for 10 mg (VTE-P):** These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4. 8). This m ay be done by regular physical examination ofthe patients, clase observation of the surgical wound drainage and periodic measurements of haemoglobin.<br><br>**Further text only for 15 mgl20 mg(VTET,SPAF):**<br><br>These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation oftreatment (see section 4.8).<br><br>Any unexplained fall in haemoglobin or blood pressure should lead toa search for a bleeding site.<br><br>Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.<br><br>**Additional warning text in the SmPC Section 4.4 only for 2.5 mg (ACS) and 15 mgl20 mg (VTE-T, SPAF):**<br><br>As with other anticoagulants, patients taking Rivaroxaban should be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban administration should be discontinued if severe haemorrhage occurs.<br><br>In the clinical studies mucosal bleedings (i.e. |

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| | epistaxis, gingival, gastrointestinal, genitourinary) and anaemia were seen more frequently during long-term rivaroxaban treatment on top of single or dual anti-platelet therapy. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.<br><br>**4.5 Interaction with other medicinal products and other forms of interaction**<br><br>• CYP3A4 and P-gp inhibitors<br>• Anticoagulants<br>• NSAIDs/platelet aggregation inhibitors<br>• Warfarin<br><br>**4.8 Undesirable effects**<br><br>The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings (>4%) were epistaxis (5.9%) and gastrointestinal tract haemorrhage (4.2%). […]<br><br>Haemorrhage is listed in different SOCs:<br><br>• *Nervous system disorders:* cerebral and intrachaemorrhage. (uncommon)<br>• *Eye disorders:* Eye haemorrhage (common)<br>• *Gastrointestinal disorders:* Gingival bleeding,<br>gastrointestinal tract haemorrhage (incl. rectal<br>haemorrhage) (common)<br>• *Skin and subcutaneous tissue disorders:* cutaneous and subcutaneous haemorrhage (common)<br>• *Musculoskeletal and connective tissue disorders:* Muscle haemorrahage (rare)<br>• *Renal and urinary disorders:* Urogenital tract haemorrhage (incl. haematuria and menorrhagia)[B] (common)<br><br>B: observed in treatment of DVT, PE and prevention of recurrence as very common in women <55 years<br><br>• *Injury, poisoning and procedural* |

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| | *complications:* postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage) (common) |
| | Other routine risk minimisation measures:<br>Routine pharmacovigilance<br>Prescription only medicine |
| Additional risk minimisation measure(s) | ➢ Patient alert cards are introduced to reinforce patient counselling about key safety reminders during treatment with rivaroxaban, and as a consequence to redude the risk of bleeding. Patient alert cards must contain the following information:<br>• Signs or symptoms of bleeding and when to seek attention from a health care provider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient Alert Card that is included in each pack, with them at all times<br>• The need to inform Health Care Professionals that they are taking Rivaroxaban if they need to have any surgery or invasive procedure.<br>A patient alert card will be part of the package insert and by this be included in every package of rivaroxaban. (see Part VII Annex 10)<br>➢ A prescriber guide for each indication will be prepared prior to launch of the medicinal product. The prescriber guide should contain the following key safety messages:<br>• Details of populations potentially at higher risk of bleeding<br>• Recommendations for dose reduction in at risk populations<br>• Guidance regarding switching from or to rivaroxaban treatment<br>➢ The need for intake of the 15 mg and 20 mg tablets with food<br>➢ Management of overdose situations<br>➢ The use of coagulation tests and their |

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| | interpretation<br>➢ That all patients should be provided with a Patient alert card and be counselled about:<br>• Signs or symptoms of bleeding and when to seek attention from a health careprovider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient alert card with them at all times<br>• The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure. |
| **Effectiveness of risk minimisation measures** | |
| How effectiveness of risk minimisation measures for the safety concern will be measured | None Proposed |
| Criteria for judging the success of the proposed risk minimisation measures | None Proposed |
| Planned dates for assessment | None Proposed |
| Results of effectiveness measurement | None Proposed |
| Impact of risk minimisation | None Proposed |
| Comment | None Proposed |

| **Safety concern (important potential risk)** | **Embryo-fetal toxicity** |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>**4.3 Contraindications:** |

| Safety concern (important potential risk) | Embryo-fetal toxicity |
|---|---|
| | Pregnancy and breast feeding (see section 4.6).<br>**4.6 Fertility, pregnancy and breast feeding**<br><u>Pregnancy</u><br>Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).<br>Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.<br><u>Fertility</u><br>No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).<br>**5.3 Preclinical safety data**<br>In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and postnatal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams. |
| | Other routine risk minimisation measures:<br>Routine pharmacovigilance<br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed |
| **Effectiveness of risk minimisation measures** | |
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |

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|---|---|
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| **Safety concern (missing information)** | **Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery** |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>**Current text in SmPC only for 10 mg (VTE-P)**<br>**4.1 Therapeutic indications:**<br>The indication is specific to "adult patients undergoing elective hip or knee replacement surgery".<br>**4.4 Special warnings and precautions for use:**<br><u>Hip fracture surgery</u><br>Rivaroxaban has not been studied in interventional clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety. |
| | Other routine risk minimisation measures:<br>Routine pharmacovigilance<br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed |
| **Effectiveness of risk minimisation measures** | |
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |

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|---|---|
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| **Safety concern (missing information)** | **Patients with severe renal impairment (CrCl < 30 mL/min)** |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>**4.2 Posology and method of administration:**<br><br>Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 mL/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 mL/min.<br><br>No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).<br><br>**4.4 Special warnings and precautions for use:**<br><br>***Renal impairment***<br><br>In patients with severe renal impairment (creatinine clearance < 30 mllmin) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15-29 mL/min. Use is not recommended in patients with creatinine clearance< 15 mL/min.<br><br>**Only for 2.5 mg (ACS) and 10 mg (VTE-P):**<br><br>Rivaroxaban is to be used with caution in patients |

| Safety concern (missing information) | Patients with severe renal impairment (CrCl < 30 mL/min) |
|---|---|
| | with moderate renal impairment (creatinine clearance 30-49 mllmin) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.<br>**Only for 15 mg /20 mg (VTE-T, SPAF):**<br>Rivaroxaban is to be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations. |
| | Other routine risk minimisation measures:<br>Routine Pharmacovigilance<br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed. |
| **Effectiveness of risk minimisation measures** | |
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| Safety concern (missing information) | Patients receiving systemic treatment with Cyp3A4 and P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>**4.4 Special warnings and precautions for use:** |

| Safety concern (missing information) | Patients receiving systemic treatment with Cyp3A4 and P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) |
|---|---|
| | ***Renal impairment***<br>**Only for 2.5 mg (ACS) and 10 mg (VTE-P):**<br>Rivaroxaban is to be used with caution in patients with moderate renal impairment (creatinine clearance 30-49 mllmin) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see below section 4.5).<br>**Only for 15 mg/20 mg (VTE-T, SPAF):**<br>Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5 below).<br>**Section 4.5 (Interaction with other medicinal products and other forms of interaction):**<br>**CYP3A4 and P-gp inhibitors**<br>Go-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold/1.6 fold increase in mean rivaroxaban Cmax, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp. Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in Cmax. This increase is not considered clinically relevant. Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and Cmax. This increase is not considered clinically relevant.<br>Fluconazole (400 mg once daily), considered as a |

| Safety concern (missing information) | **Patients receiving systemic treatment with Cyp3A4 and P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)** |
|---|---|
| | moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean Cmax. This increase is not considered clinically relevant. Given the limited clinical data available with dronedarone, eo-administration with rivaroxaban should be avoided. |
| | Other routine risk minimisation measures:<br>Routine Pharmacovigilance<br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed. |

| **Effectiveness of risk minimisation measures** | |
|---|---|
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| Safety concern (missing information) | **Remedial procoagulant therapy for excessive haemorrhage** |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is appropriately communicated through current labeling:<br>**4.9 Overdose**<br><u>Management of bleeding</u><br>Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban |

| Safety concern (missing information) | Remedial procoagulant therapy for excessive haemorrhage |
|---|---|
| | administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.<br><br>If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).<br><br>Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable. |
| | Other routine risk minimisation measures:<br><br>Routine Pharmacovigilance<br><br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed. |
| **Effectiveness of risk minimisation measures** | |

| | |
|---|---|
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| **Safety concern (missing information)** | **Pregnant or breast-feeding women** |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is mentioned in current labeling:<br>SPC Sections:<br>**4.3 Contraindications**<br>Pregnancy and breast feeding (see section 4.6).<br>**4.6 Fertility, pregnancy and breast feeding**<br><u>Pregnancy</u><br>Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).<br>Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.<br><u>Breast feeding</u><br>Safety and efficacy of Rivaroxaban have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rivaroxaban is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to |

| Safety concern (missing information) | Pregnant or breast-feeding women |
|---|---|
| | discontinue/abstain from therapy.<br><br>**5.3 Preclinical safety data**<br><br>Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post¬natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams. |
| | Other routine risk minimisation measures:<br><br>Routine Pharmacovigilance<br><br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed. |

| **Effectiveness of risk minimisation measures** | |
|---|---|
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| Safety concern (missing information) | Patients with atrial fibrillation (AF) and a prosthetic heart valve |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | **This item is mentioned only for 15mg/20mg (VTE-T, SPAF):** |

| Safety concern (missing information) | Patients with atrial fibrillation (AF) and a prosthetic heart valve |
|---|---|
| | SPC Sections:<br>**Section 4.4 Special warnings and precaution for use:**<br><u>Patients with prosthetic valves</u><br>Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients. |
| | Other routine risk minimisation measures:<br>Routine Pharmacovigilance<br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed. |

| **Effectiveness of risk minimisation measures** | |
|---|---|
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| Safety concern (missing information) | Long-term therapy for treatment of DVT, PE, SPAF and ACS in real-life setting |
|---|---|
| Objective(s) of the risk minimisation measures | No additional activities beyond routine risk minimisation measures are proposed. |
| Routine risk minimisation measures | No additional activities beyond routine risk minimisation measures are proposed. |

| Safety concern (missing information) | Long-term therapy for treatment of DVT, PE, SPAF and ACS in real-life setting |
|---|---|
| | Other routine risk minimisation measures:<br>Routine Pharmacovigilance<br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed. |
| **Effectiveness of risk minimisation measures** | |
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| Safety concern (missing information) | Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>**4.2 Posology and method of administration**<br>*Hepatic impairment*<br>Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).<br>**4.3 Contraindications**<br>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2). |

| Safety concern (missing information) | Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) |
|---|---|
| | **5.2 Pharmacokinetic properties**<br><br>*Hepatic impairment*<br>Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.<br>The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.<br>Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3). |
| | Other routine risk minimisation measures:<br><br>Routine Pharmacovigilance<br><br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed. |
| **Effectiveness of risk minimisation measures** | |
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

| **Safety concern (missing information)** | **Patients< 18 years** |
|---|---|
| Objective(s) of the risk minimisation measures | Patients and HCPs to understand the risk of occurrence and appropriate risk management. |
| Routine risk minimisation measures | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>4.2 Posology and method of administration:<br>*Paediatric population*<br>The safety and efficacy of Rivaroxaban in children aged 0 to 18 years have not been established. No data are available. Therefore, Rivaroxaban is not recommended for use in children below 18 years of age. |
| | Other routine risk minimisation measures:<br>Routine Pharmacovigilance<br>Prescription-only medicine |
| Additional risk minimisation measure(s) | None proposed. |

| **Effectiveness of risk minimisation measures** | |
|---|---|
| How effectiveness of risk minimisation measures for the safety concern will be measured | N/A |
| Criteria for judging the success of the proposed risk minimisation measures | N/A |
| Planned dates for assessment | N/A |
| Results of effectiveness measurement | N/A |
| Impact of risk minimisation | N/A |
| Comment | N/A |

The effectiveness of all risk minimisation measures above mentioned will be evaluated periodically from the post-marketing experience of the product (ADRs received) as well as recommendations from Authorities and literature sources.

The MAH will update such measures if the safety profile of the product changes and will proceed implementing additional measures if considered needed.

## V.2 Risk minimisation measure failure (if applicable)

Not applicable.

### V.2.1 Analysis of risk minimisation measure(s) failure

Not applicable.

### V.2.2 Revised proposal for risk minimisation

Not applicable.

## V.3 Summary table of risk minimisation measures

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| **Haemorrhage** | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>**4.3 Contraindications:**<br>• Active clinically significant bleeding.<br>• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.<br>• Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or majar | ➢ Patient alert cards are introduced to reinforce patient counselling about key safety reminders during treatment with rivaroxaban, and as a consequence to redude the risk of bleeding. Patient alert cards must contain the following information:<br>• Signs or symptoms of bleeding and when to seek attention from a health care provider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient Alert Card that is included in each pack, with them at all times<br>• The need to inform Health Care Professionals that they are taking Rivaroxaban if they need |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | intraspinal or intracerebral vascular abnormalities.<br>• Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.<br>Additional contraindication in the SmPC Section 4.3 only for 2.5 mg (ACS):<br>• Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke ora transient ischaemic attack (TIA).<br>**4.4 Special warnings and precautions for use:**<br><u>Haemorrhagic risk</u><br>Several sub-groups of patients, as detailed below, are at increased risk of bleeding.<br>**Further text only for 2.5 mg (ACS):** Therefore, the use of Rivaroxaban in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment.<br>**Further text only for 10 mg (VTE-P):** These patients are to be carefully | to have any surgery or invasive procedure.<br>A patient alert card will be part of the package insert and by this be included in every package of rivaroxaban. (see Part VII Annex 10)<br>➢ A prescriber guide for each indication will be prepared prior to launch of the medicinal product. The prescriber guide should contain the following key safety messages:<br>• Details of populations potentially at higher risk of bleeding<br>• Recommendations for dose reduction in at risk populations<br>• Guidance regarding switching from or to rivaroxaban treatment<br>➢ The need for intake of the 15 mg and 20 mg tablets with food<br>➢ Management of overdose situations<br>➢ The use of coagulation tests and their interpretation<br>➢ That all patients should be provided with a Patient alert card and be counselled about:<br>• Signs or symptoms of bleeding and when to seek attention from a health careprovider. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4. 8). This m ay be done by regular physical examination ofthe patients, clase observation of the surgical wound drainage and periodic measurements of haemoglobin.<br><br>**Further text only for 15 mgl20 mg(VTET,SPAF):**<br><br>These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation oftreatment (see section 4.8).<br><br>Any unexplained fall in haemoglobin or blood pressure should lead toa search for a bleeding site.<br><br>Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.<br><br>**Additional warning text in the SmPC Section 4.4 only for 2.5 mg (ACS) and 15 mgl20 mg (VTE-T, SPAF):**<br><br>As with other anticoagulants, patients taking Rivaroxaban should be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban administration should be discontinued if severe haemorrhage occurs.<br><br>In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genitourinary) and anaemia were seen more frequently during long-term rivaroxaban treatment on top of single or | • Importance of treatment compliance<br><br>• The need for intake of the 15 mg and 20 mg tablets with food<br><br>• Necessity to carry the Patient alert card with them at all times<br><br>• The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | dual anti-platelet therapy. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.<br><br>**4.5 Interaction with other medicinal products and other forms of interaction**<br><br>• CYP3A4 and P-gp inhibitors<br>• Anticoagulants<br>• NSAIDs/platelet aggregation inhibitors<br>• Warfarin<br><br>**4.8 Undesirable effects**<br><br>The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings (>4%) were epistaxis (5.9%) and gastrointestinal tract haemorrhage (4.2%). […]<br><br>Haemorrhage is listed in different SOCs:<br><br>• *Nervous system disorders:* cerebral and intrachaemorrhage. (uncommon)<br>• *Eye disorders:* Eye haemorrhage (common)<br>• *Gastrointestinal disorders:* Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage) (common)<br>• *Skin and subcutaneous tissue disorders:* cutaneous and subcutaneous haemorrhage (common)<br>• *Musculoskeletal and connective* | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | *tissue disorders:* Muscle haemorrahage (rare)<br>• *Renal and urinary disorders:* Urogenital tract haemorrhage (incl. haematuria and menorrhagia)[B] (common)<br>B: observed in treatment of DVT, PE and prevention of recurrence as very common in women <55 years<br>*Injury, poisoning and procedural complications:* postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage) (common)<br>Prescription only medicine | |
| **Embryo-fetal toxicity** | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>**4.3 Contraindications:**<br>Pregnancy and breast feeding (see section 4.6).<br>**4.6 Fertility, pregnancy and breast feeding**<br><u>Pregnancy</u><br>Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).<br>Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.<br><u>Fertility</u><br>No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | male and female fertility in rats no effects were seen (see section 5.3).<br><br>**5.3 Preclinical safety data**<br><br>In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and postnatal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.<br><br>Prescription only medicine | |
| **Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>**Current text in SmPC only for 10 mg (VTE-P)**<br><br>**4.1 Therapeutic indications:**<br><br>The indication is specific to "adult patients undergoing elective hip or knee replacement surgery".<br><br>**4.4 Special warnings and precautions for use:**<br><br>Hip fracture surgery<br><br>Rivaroxaban has not been studied in interventional clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety.<br><br>Prescription only medicine | None proposed |
| **Patients with severe renal impairment (CrCl < 30 Ml/lmin)** | This item is appropriately communicated through current labeling:<br><br>SPC Sections: | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | **4.2 Posology and method of administration:**<br><br>Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 mL/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 mL/min.<br><br>No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).<br><br>**4.4 Special warnings and precautions for use:**<br><br>***Renal impairment***<br><br>In patients with severe renal impairment (creatinine clearance < 30 mllmin) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15-29 mL/min. Use is not recommended in patients with creatinine clearance< 15 mL/min.<br><br>**Only for 2.5 mg (ACS) and 10 mg (VTE-P):**<br><br>Rivaroxaban is to be used with caution in patients with moderate renal impairment (creatinine clearance 30-49 mllmin) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.<br><br>**Only for 15 mg /20 mg (VTE-T, SPAF):**<br><br>Rivaroxaban is to be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | plasma concentrations.<br><br>Prescription only medicine | |
| **Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>**4.4 Special warnings and precautions for use:**<br>***Renal impairment***<br>**Only for 2.5 mg (ACS) and 10 mg (VTE-P):**<br><br>Rivaroxaban is to be used with caution in patients with moderate renal impairment (creatinine clearance 30-49 mllmin) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see below section 4.5).<br><br>**Only for 15 mg/20 mg (VTE-T, SPAF):**<br><br>Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5 below).<br><br>**Section 4.5 (Interaction with other medicinal products and other forms of interaction):**<br><br>**CYP3A4 and P-gp inhibitors**<br><br>Go-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold/1.6 fold increase in mean rivaroxaban Cmax, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp. Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in Cmax. This increase is not considered clinically relevant. Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and Cmax. This increase is not considered clinically relevant.<br><br>Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean Cmax. This increase is not considered clinically relevant. Given the limited clinical data available with dronedarone, eo-administration with rivaroxaban should be avoided.<br><br>Prescription only medicine | |
| **Remedial pro-coagulant therapy for excessive haemorrhage** | This item is appropriately communicated through current labeling:<br><br>**4.9 Overdose**<br><br><u>Management of bleeding</u><br><br>Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.<br><br>If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).<br><br>Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable. | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Prescription only medicine | |
| **Pregnant or breast-feeding women** | This item is mentioned in current labeling:<br><br>SPC Sections:<br><br>**4.3 Contraindications**<br><br>Pregnancy and breast feeding (see section 4.6).<br><br>**4.6 Fertility, pregnancy and br feeding**<br><u>Pregnancy</u><br><br>Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).<br><br>Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.<br><br><u>Breast feeding</u><br><br>Safety and efficacy of Rivaroxaban have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rivaroxaban is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.<br><br>**5.3 Preclinical safety data**<br><br>Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo- | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post¬natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.<br><br>Prescription only medicine | |
| **Patients with atrial fibrillation (AF) and a prosthetic heart valve** | **This item is mentioned only for 15mg/20mg (VTE-T, SPAF):**<br><br>SPC Sections:<br><br>**Section 4.4 Special warnings and precaution for use:**<br><br><u>Patients with prosthetic valves</u><br><br>Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients.<br><br>Prescription only medicine | None proposed |
| **Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting** | No additional activities beyond routine risk minimisation measures are proposed.<br><br>Prescription only medicine | None proposed |
| **Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>**4.2 Posology and method of administration**<br><br>*Hepatic impairment*<br><br>Rivaroxaban is contraindicated in | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).<br><br>**4.3 Contraindications**<br><br>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).<br><br>**5.2 Pharmacokinetic properties**<br><br>*Hepatic impairment*<br><br>Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.<br><br>The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.<br><br>Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).<br><br>Prescription only medicine | |
| **Patients <18 years** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>4.2 Posology and method of administration:<br><br>*Paediatric population*<br><br>The safety and efficacy of Rivaroxaban in children aged 0 to 18 years have not been established. No data are available. Therefore, Rivaroxaban is not recommended for use in children below 18 years of age.<br><br>Prescription only medicine | None proposed |

***Part VI: Summary of activities in the risk management plan by product:***

| | |
|---|---|
| Active substance | Rivaroxaban |
| Product(s) concerned<br>(brand name(s)): | Rivaroxaban 2.5 mg film-coated tablets<br>Rivaroxaban 10 mg film-coated tablets<br>Rivaroxaban 15 mg film-coated tablets<br>Rivaroxaban 20 mg film-coated tablets |
| MAH/Applicant name | [redacted] |

| | |
|---|---|
| Data lock point for this module | 20 November 2017 |
| Version number of RMP when this module was last updated | Not applicable |

## VI.1 Elements for summary tables in the EPAR

### VI.1.1 Summary table of Safety concerns

| | |
|---|---|
| **Important identified risks** | Haemorrhage |
| **Important potential risks** | Embryo-fetal toxicity |
| **Missing information** | Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery |
| | Patients with severe renal impairment (CrCl < 30 Ml/lmin) |
| | Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) |
| | Remedial pro-coagulant therapy for excessive haemorrhage |
| | Pregnant or breast-feeding women |
| | Patients with atrial fibrillation (AF) and a prosthetic heart valve |
| | Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting |
| | Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) |
| | Patients < 18 years |

### VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

### VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

### VI.1.4 Summary table of Risk Minimisation Measures

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| **Haemorrhage** | This item is appropriately communicated through current labeling:<br>SPC Sections:<br>**4.3 Contraindications:**<br>• Active clinically significant | ➢ Patient alert cards are introduced to reinforce patient counselling about key safety reminders during treatment with rivaroxaban, and as a consequence to redude the risk of bleeding. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | bleeding.<br>• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.<br>• Lesion or condition, if considered to be a significant risk for majar bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or majar intraspinal or intracerebral vascular abnormalities.<br>• Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.<br>Additional contraindication in the SmPC Section 4.3 only for 2.5 mg (ACS): | Patient alert cards must contain the following information:<br>• Signs or symptoms of bleeding and when to seek attention from a health care provider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient Alert Card that is included in each pack, with them at all times<br>• The need to inform Health Care Professionals that they are taking Rivaroxaban if they need to have any surgery or invasive procedure.<br>A patient alert card will be part of the package insert and by this be included in every package of rivaroxaban. (see Part VII Annex 10)<br>➢ A prescriber guide for each indication will be prepared prior to launch of the medicinal product. The prescriber guide should contain the following key safety messages:<br>• Details of populations potentially at higher risk of bleeding<br>• Recommendations for dose reduction in at risk populations |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | • Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke ora transient ischaemic attack (TIA).<br><br>**4.4 Special warnings and precautions for use:**<br><br><u>Haemorrhagic risk</u><br><br>Several sub-groups of patients, as detailed below, are at increased risk of bleeding.<br><br>**Further text only for 2.5 mg (ACS):** Therefore, the use of Rivaroxaban in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment.<br><br>**Further text only for 10 mg (VTE-P):** These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4. 8). This m ay be done by regular physical examination ofthe patients, clase observation of the surgical wound drainage and periodic measurements of haemoglobin.<br><br>**Further text only for 15 mgl20 mg(VTET,SPAF):**<br><br>These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation oftreatment (see section 4.8).<br><br>Any unexplained fall in haemoglobin | • Guidance regarding switching from or to rivaroxaban treatment<br>➢ The need for intake of the 15 mg and 20 mg tablets with food<br>➢ Management of overdose situations<br>➢ The use of coagulation tests and their interpretation<br>➢ That all patients should be provided with a Patient alert card and be counselled about:<br>• Signs or symptoms of bleeding and when to seek attention from a health careprovider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient alert card with them at all times<br>• The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | or blood pressure should lead toa search for a bleeding site.<br><br>Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.<br><br>**Additional warning text in the SmPC Section 4.4 only for 2.5 mg (ACS) and 15 mgl20 mg (VTE-T, SPAF):**<br><br>As with other anticoagulants, patients taking Rivaroxaban should be carefully observed for signs of bleeding. lt is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban administration should be discontinued if severe haemorrhage occurs.<br><br>In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genitourinary) and anaemia were seen more frequently during long-term rivaroxaban treatment on top of single or dual anti-platelet therapy. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.<br><br>**4.5 Interaction with other medicinal products and other forms of interaction**<br><br>• CYP3A4 and P-gp inhibitors<br>• Anticoagulants<br>• NSAIDs/platelet aggregation | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | inhibitors<br>• Warfarin<br>**4.8 Undesirable effects**<br>The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings (>4%) were epistaxis (5.9%) and gastrointestinal tract haemorrhage (4.2%). […]<br>Haemorrhage is listed in different SOCs:<br>• *Nervous system disorders:* cerebral and intrachaemorrhage. (uncommon)<br>• *Eye disorders:* Eye haemorrhage (common)<br>• *Gastrointestinal disorders:* Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage) (common)<br>• *Skin and subcutaneous tissue disorders:* cutaneous and subcutaneous haemorrhage (common)<br>• *Musculoskeletal and connective tissue disorders:* Muscle haemorrahage (rare)<br>• *Renal and urinary disorders:* Urogenital tract haemorrhage (incl. haematuria and menorrhagia)[B] (common)<br>B: observed in treatment of DVT, PE and prevention of recurrence as very common in | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | women <55 years<br><br>*Injury, poisoning and procedural complications:* postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage) (common)<br><br>Prescription only medicine | |
| **Embryo-fetal toxicity** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>**4.3 Contraindications:**<br><br>Pregnancy and breast feeding (see section 4.6).<br><br>**4.6 Fertility, pregnancy and breast feeding**<br><br><u>Pregnancy</u><br><br>Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).<br><br>Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.<br><br><u>Fertility</u><br><br>No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).<br><br>**5.3 Preclinical safety data**<br><br>In rats, no effects on male or female fertility were seen. Animal studies | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.<br><br>Prescription only medicine | |
| **Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>**Current text in SmPC only for 10 mg (VTE-P)**<br><br>**4.1 Therapeutic indications:**<br><br>The indication is specific to "adult patients undergoing elective hip or knee replacement surgery".<br><br>**4.4 Special warnings and precautions for use:**<br><br>Hip fracture surgery<br><br>Rivaroxaban has not been studied in interventional clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety.<br><br>Prescription only medicine | None proposed |
| **Patients with severe renal impairment (CrCl < 30 Ml/lmin)** | This item is appropriately communicated through current labeling:<br><br>SPC Sections: | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | **4.2 Posology and method of administration:**<br><br>Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 mL/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 mL/min.<br><br>No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).<br><br>**4.4 Special warnings and precautions for use:**<br><br>***Renal impairment***<br><br>In patients with severe renal impairment (creatinine clearance < 30 mllmin) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15-29 mL/min. Use is not recommended in patients with creatinine clearance< 15 mL/min.<br><br>**Only for 2.5 mg (ACS) and 10 mg (VTE-P):**<br><br>Rivaroxaban is to be used with caution in patients with moderate renal impairment (creatinine clearance 30-49 mllmin) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.<br><br>**Only for 15 mg /20 mg (VTE-T, SPAF):** | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Rivaroxaban is to be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.<br><br>Prescription only medicine | |
| **Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>**4.4 Special warnings and precautions for use:**<br>***Renal impairment***<br>**Only for 2.5 mg (ACS) and 10 mg (VTE-P):**<br><br>Rivaroxaban is to be used with caution in patients with moderate renal impairment (creatinine clearance 30-49 Ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see below section 4.5).<br><br>**Only for 15 mg/20 mg (VTE-T, SPAF):**<br><br>Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5 below).<br><br>**Section 4.5 (Interaction with other medicinal products and other forms of interaction):**<br><br>**CYP3A4 and P-gp inhibitors**<br><br>Go-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | and a 1.7 fold/1.6 fold increase in mean rivaroxaban Cmax, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp. Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in Cmax. This increase is not considered clinically relevant. Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and Cmax. This increase is not considered clinically relevant.<br><br>Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean Cmax. This increase is not considered clinically relevant. Given the limited clinical data available with dronedarone, eo-administration with rivaroxaban should be avoided.<br><br>Prescription only medicine | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| **Remedial pro-coagulant therapy for excessive haemorrhage** | This item is appropriately communicated through current labeling:<br>**4.9 Overdose**<br>Management of bleeding<br>Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.<br>If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).<br><br>Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.<br><br>Prescription only medicine | |
| **Pregnant or breast-feeding women** | This item is mentioned in current labeling:<br><br>SPC Sections:<br><br>**4.3 Contraindications**<br><br>Pregnancy and breast feeding (see section 4.6).<br><br>**4.6 Fertility, pregnancy and br feeding**<br><u>Pregnancy</u><br><br>Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).<br><br>Women of child-bearing potential should avoid becoming pregnant | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | during treatment with rivaroxaban.<br><br>Breast feeding<br><br>Safety and efficacy of Rivaroxaban have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rivaroxaban is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.<br><br>**5.3 Preclinical safety data**<br><br>Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post¬natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.<br><br>Prescription only medicine | |
| **Patients with atrial fibrillation (AF) and a prosthetic heart valve** | **This item is mentioned only for 15mg/20mg (VTE-T, SPAF):**<br><br>SPC Sections:<br><br>**Section 4.4 Special warnings and precaution for use:**<br><br>Patients with prosthetic valves<br><br>Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | support that Rivaroxaban 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients.<br><br>Prescription only medicine | |
| **Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting** | No additional activities beyond routine risk minimisation measures are proposed.<br><br>Prescription only medicine | None proposed |
| **Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>**4.2 Posology and method of administration**<br><br>*Hepatic impairment*<br><br>Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).<br><br>**4.3 Contraindications**<br><br>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).<br><br>**5.2 Pharmacokinetic properties**<br><br>*Hepatic impairment*<br><br>Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.<br><br>The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.<br><br>Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).<br><br>Prescription only medicine | |
| **Patients <18 years** | This item is appropriately communicated through current labeling:<br><br>SPC Sections:<br><br>4.2 Posology and method of administration:<br><br>*Paediatric population*<br><br>The safety and efficacy of Rivaroxaban in children aged 0 to 18 years have not been established. No data are available. Therefore, | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Rivaroxaban is not recommended for use in children below 18 years of age.<br><br>Prescription only medicine | |

## VI.2 Elements for a Public Summary

### VI.2.1 Overview of diseases epidemiology

The indications described in this Risk Management Plan (RMP) comprise the following approved indications:

- Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.
- Prevention of venous thromboembolic events (VTE) in adult patients undergoing elective hip or knee replacement knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; congestive heart failure diabetes mellitus; hypertension.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The 2010 prevalence of total hip and total knee replacement in the total U.S. population was 0.83% and 1.52%, respectively. Prevalence was higher among women than among men and increased with age, reaching 5.26% for total hip replacement (THR) and 10.38% for total knee replacement (TKR) at eighty years. These estimates corresponded to 2.5 million individuals (1.4 million women and 1.1 million men) with THR and 4.7 million individuals (3.0 million women and 1.7 million men) with TKR in 2010.[1]

The rate of THR and THK has increased over the past ten years in many European countries, due in part to population ageing but also the growing use of these interventions to improve functioning among elderly people. In Denmark, the THR rate increased by 40% between 2000 and 2010, while the TKR rate more than tripled. Similarly, in Spain, the THR rate increased by 25% and the TKR replacement rate more than doubled during the past decade. The growth rate for both interventions was somewhat slower in France, but still THR rate increased by nearly 10% while TKR rate rose by 60% between 2000 and 2010.[2]

After surgery with preventative treatment, VTE develops in about 10 of 1000 people after total or partial knee replacement, and in about 5 of 1000 after total or partial hip replacement.[3] About 300,000–600,000 Americans develop VTE each year, with about 60,000–100,000 deaths attributable to PE. [4]

The prevalence of atrial fibrillation (AF) varies with age and sex. AF is present in 0.12%–0.16% of those younger than 49 years, in 3.7%–4.2% of those aged 60–70 years, and in 10%–17% of those

aged 80 years or older. In addition, it occurs more frequently in males. AF is frequently associated with cardiac disease and comorbidities. The most common concomitant diseases are coronary artery disease, valvular heart disease, and cardiomyopathy. The most common comorbidities are hypertension, diabetes, heart failure, chronic obstructive pulmonary disease, renal failure, stroke, and cognitive disturbance. It is estimated that the number of patients with AF in 2030 in Europe will be 14–17 million and the number of new cases of AF per year at 120,000–215,000. [5]

Venous thrombosis, including deep vein thrombosis and pulmonary embolism, occurs at an annual incidence of about 1 per 1000 adults. Rates increase sharply after around age 45 years, and are slightly higher in men than women in older age. Major risk factors for thrombosis, other than age, include exogenous factors such as surgery, hospitalization, immobility, trauma, pregnancy and the puerperium and hormone use, and endogenous factors such as cancer, obesity, and inherited and acquired disorders of hypercoagulation. This review focuses on epidemiology of venous thrombosis and the general implications of this in patient management.[6]

Blood clots in the vessels supplying the heart muscle can cause unstable angina pectoris or a heart attack (myocardial infarction [MI]); both are types of acute coronary syndrome (ACS). Accumulated fatty deposits (plaques) in the walls of the arteries may rupture and lead to thrombosis (known as atherothrombosis), which can cause ACS. In the USA, 3.1% of adults aged over 20 years have a history of MI Mortality in the first year after MI in patients aged over 45 years is 19% in men and 26% in women [7]

## VI.2.2 Summary of treatment benefits

### 2.2.1 Prevention of VTE in patients undergoing elective hip or knee replacement surgery

The four phase Ill RECORD studies compared rivaroxaban (10 mg once daily) with enoxaparin (the standard therapy at the time of the studies) in patients undergoing total hip or knee replacement. A pooled analysis of the four studies, including 12,729 patients, showed that rivaroxaban reduced the occurrence of VTE, compared with enoxaparin.

### 2.2.2 Treatment of VTE and prevention of recurrent VTE

The phase Ill EINSTEIN-DVT and EINSTEIN-PE studies compared the use of rivaroxaban the reference product, (15 mg twice daily for 3 weeks followed by 20 mg once daily) with the use of standard therapy (enoxaparin in combination with vitamin K antagonists [VKA]) in 8281 patients with venous thromboembolism (VTE) over 3, 6 or 12 months. Rivaroxaban was at least as effective as enoxaparinNKA in treatment of VTE and preventing the recurrence of VTE.

In the phase Ill EINSTEIN Extension study, 1197 patients who had completed 6-12 months of treatment for VTE were administered rivaroxaban (20 mg once daily) or placebo for an additional 6 or 12 months; rivaroxaban reduced VTE recurrence compared with placebo.

### 2.2.3 Prevention of stroke and embolism elsewhere in the body in patients with AF

The phase Ill ROCKET-AF study compared rivaroxaban (20 or 15 mg once daily) with standard therapy (warfarin) in 14,264 patients with non-valvular AF (treatment duration: up to 41 months). Rivaroxaban was at least as effective as warfarin at preventing stroke and embolism elsewhere in the body.

### 2.2.4 Prevention of blood clots restricting blood flow to the heart after ACS

The ATLAS ACS 2-TIMI 51 study compared rivaroxaban, the reference product, (2.5 or 5 mg twice daily) with placebo in 15,526 patients with a recent ACS (treatment duration: up to 31 months). All patients also received standard antiplatelet therapy (ASA alone or ASA plus Thienopyridine). Compared with placebo, rivaroxaban reduced the occurrence of cardiovascular-related deaths, stroke and MI.

## VI.2.3 Unknowns relating to treatment benefits

Efficacy and safety of rivaroxaban in pregnancy and lactation, in patients with elevated severe renal impairment, in paediatric patients have not been widely studied. Therefore, treatment with rivaroxaban is currently not recommended.

## VI.2.4 Summary of safety concerns

**Important identified risks and important identified interactions**

| Risk | What is known | Preventability |
|---|---|---|
| Bleeding (Haemorrhage) | Bleeding can occur at any site during therapy with rivaroxaban. An unexplained fall in haemoglobin ( a protein in the red blood cells of all vertebrates) and/or haematocrit (volume percentage (%) of red blood cells in blood) or blood pressure should lead to a search for a bleeding site.<br><br>In clinical studies, mucosal bleedings (bleeding from the nose, gums, gastrointestinal or genitourinary systems) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA (e.g. warfarin) treatment. | Rivaroxaban should be prescribed and used in accordance with the product information and the package leaflet.<br><br>If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your doctor immediately. Your doctor may decide to keep you under closer observation or change your medicine.<br><br>Patient alert cards may improve patient risk awareness. |

## Important potential risks and important potential interactions

| Risk | What is known |
|---|---|
| Potential defects in the unborn child (embryo-fetal toxicity) | Animal studies have suggested that rivaroxaban can cross the placenta and cause birth defects in offspring. The drug was also found to increase the rate of miscarriage in animal studies. The use of rivaroxaban is contraindicated during pregnancy. |

## Missing information

| Risk | What is known |
|---|---|
| Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery | Clinical trials of rivaroxaban did not include patients undergoing hip fracture surgery. Therefore the use of rivaroxaban is not recommended. |
| Patients with severe renal impairment (creatinine clearance less than 30 Ml/min) | Patients with severe renal impairment may be at risk of both haemorrhage and thrombosis. Limited data suggest that levels of rivaroxaban in the bloodstream are increased in patients with severe renal impairment. Therefore, rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance less than 15 Ml/min. |
| Concomitantly use with systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) | The use of rivaroxaban with strong inhibitors of CYP3A4 and P- gp (such as ketoconazole [for fungal infections] or ritonavir [for HIV treatment]) results in increased levels of rivaroxaban in the bloodstream and is therefore not recommended. |
| Remedial procoagulant therapy for excessive haemorrhage | The use of drugs to promote clotting of the blood (procoagulants) may be required in the event of excessive bleeding. However, there is limited information on the use of procoagulants in patients receiving rivaroxaban. |
| Pregnant or breast feeding women | Due to lack of human data, rivaroxaban should not be used during pregnancy and should not be used during breast-feeding. |
| Patients with atrial fibrillation (AF) and a prosthetic heart valve | Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves. Therefore, treatment with rivaroxaban is not recommended for these patients. |
| Long-term therapy for treatment of DVT, PE, SPAF | Clinical trial data are available in these patient groups, but the long-term use of rivaroxaban in a 'real-life' setting needs to be |

| Risk | What is known |
|---|---|
| and ACS in real-life setting | studied to quantify the risk of bleeding and unexpected adverse events, particularly in patients who have comorbidities or who are taking other medications. |
| Patients with significant liver disease (severe hepatic impairmen/Child Pugh C) | The risks of rivaroxaban use in patients with severe liver impairment are unknown, as these patients were excluded from clinical trials. Therefore, the use of rivaroxaban is contraindicated in these patients. |
| Patients < 18 years | No data are available regarding the safety and efficacy of rivaroxaban in paediatric group. Therefore, it is not recommended for use in patients below 18 years of age. |

## VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material are included in Annex II of the product information which may be found on the eMC website; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

| Safety concern (important identified risk) | Haemorrhage |
|---|---|
| Risk minimisation measure(s) | ➢ Patient alert cards are introduced to reinforce patient counselling about key safety reminders during treatment with rivaroxaban, and as a consequence to redude the risk of bleeding. Patient alert cards must contain the following information:<br>• Signs or symptoms of bleeding and when to seek attention from a health care provider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient Alert Card that is included in each pack, with them at all times<br>• The need to inform Health Care |

| Safety concern (important identified risk) | Haemorrhage |
|---|---|
| | Professionals that they are taking Rivaroxaban if they need to have any surgery or invasive procedure.<br><br>A patient alert card will be part of the package insert and by this be included in every package of rivaroxaban. (see Part VII Annex 10)<br><br>➢ A prescriber guide for each indication will be prepared prior to launch of the medicinal product. The prescriber guide should contain the following key safety messages:<br><br>• Details of populations potentially at higher risk of bleeding<br>• Recommendations for dose reduction in at risk populations<br>• Guidance regarding switching from or to rivaroxaban treatment<br>➢ The need for intake of the 15 mg and 20 mg tablets with food<br>➢ Management of overdose situations<br>➢ The use of coagulation tests and their interpretation<br>➢ That all patients should be provided with a Patient alert card and be counselled about:<br>• Signs or symptoms of bleeding and when to seek attention from a health careprovider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient alert card with them at all times<br>• The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure. |
| Objective and rational | These measures were implemented to alert patients to the risk of haemorrhage when taking rivaroxaban and to prevent the use of rivaroxaban in patients with |

| Safety concern (important identified risk) | Haemorrhage |
|---|---|
| | increased haemorrhage risks. |
| Main additional risk minimisation measures | None |

### VI.2.6 Planned post authorisation development plan

Not applicable.

### VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.

## *Part VII: Annexes*

### *Annex 1 – EudraVigilance Interface*

Not applicable.

***Annex 2 - SmPC & Package Leaflet***

## 1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban 2.5 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg rivaroxaban.
Excipient with known effect:
Each film-coated tablet contains 35.75 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Yellow, round, biconvex, film coated tablets, aprox. 6 mm diameter, debossed with "E21" on one site and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see sections 4.3, 4.4 and 5.1).

### 4.2 Posology and method of administration

Posology
The recommended dose is 2.5 mg twice daily.
Patients should also take a daily dose of 75 - 100 mg ASA or a daily dose of 75 - 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine.
Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited (see section 5.1).
Treatment with Rivaroxaban should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.
If a dose is missed the patient should continue with the regular dose as recommended at the next scheduled time. The dose should not be doubled to make up for a missed dose.

*Converting from Vitamin K Antagonists (VKA) to Rivaroxaban*
When converting patients from VKAs to Rivaroxaban , International Normalized Ratio (INR) values will be falsely elevated after the intake of Rivaroxaban. The INR is not valid to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used (see section 4.5).

*Converting from Rivaroxaban to Vitamin K antagonists (VKA)*
There is a potential for inadequate anticoagulation during the transition from Rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Rivaroxaban can contribute to an elevated INR. In patients converting from Rivaroxaban to VKA, VKA should be given concurrently until the INR is > 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both Rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban . Once Rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

*Converting from parenteral anticoagulants to Rivaroxaban*
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

*Converting from Rivaroxaban to parenteral anticoagulants*
Give the first dose of parenteral anticoagulant at the time the next Rivaroxaban dose would be taken.

*Special populations*
*Renal impairment*
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).
No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (see section 5.2).

*Hepatic impairment*
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

*Elderly population*
No dose adjustment (see sections 4.4 and 5.2).

*Body weight*
No dose adjustment (see sections 4.4 and 5.2).

*Gender*
No dose adjustment (see section 5.2).

*Paediatric population*
The safety and efficacy of Rivaroxaban in children aged 0 to 18 years have not been established. No data are available. Therefore, Rivaroxaban is not recommended for use in children below 18 years of age.

Method of administration
For oral use.
Rivaroxaban can be taken with or without food (see sections 4.5 and 5.2).
For patients who are unable to swallow whole tablets, Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally.

The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water (see section 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Active clinically significant bleeding.
Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (see section 4.4).
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

## 4.4 Special warnings and precautions for use

Efficacy and safety of rivaroxaban has been investigated in combination with the antiplatelet agents aspirin and clopidogrel/ticlopidine. Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.
Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Haemorrhagic risk
As with other anticoagulants, patients taking Rivaroxaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban administration should be discontinued if severe haemorrhage occurs.
In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment on top of single or dual anti-platelet therapy. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. Therefore, the use of Rivaroxaban in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition, these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.
Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see sections 5.1 and 5.2).

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Rivaroxaban is to be used with caution (see section 4.5).

Interaction with other medicinal products

The use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

After an acute coronary syndrome patients on treatment with Rivaroxaban and ASA or Rivaroxaban and ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk.

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

It should be used with caution in ACS patients:

- > 75 years of age if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine
- with low body weight (< 60 kg) if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine

Patients with prior stroke or TIA

Rivaroxaban 2.5 mg is contraindicated for the treatment of ACS in patients with a prior stroke or TIA (see section 4.3). Few ACS patients with a prior stroke or TIA have been studied but the limited efficacy data available indicate that these patients do not benefit from treatment.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 2.5 mg with ASA alone or with ASA plus clopidogrel or ticlopidine in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2). However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

Dosing recommendations before and after invasive procedures and surgical intervention
If an invasive procedure or surgical intervention is required, Rivaroxaban 2.5 mg should be stopped at least 12 hours before the intervention, if possible and based on the clinical judgement of the physician. If a patient is to undergo elective surgery and anti-platelet effect is not desired, platelet aggregation inhibitors should be discontinued as directed by the manufacturer's prescribing information.
If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

Elderly population
Increasing age may increase haemorrhagic risk (see section 5.2).

Information about excipients
Rivaroxaban contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors
Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban $C_{max}$, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).
Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in $C_{max}$. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).
Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and $C_{max}$. This increase is not considered clinically relevant.
In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $C_{max}$ when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $C_{max}$ when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean $C_{max}$. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).
Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid. Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive. If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, antifactor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the Ctrough of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point. No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort *(Hypericum perforatum))* may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

No clinically relevant interaction with food was observed (see section 4.2).

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

## 4.6 Fertility, pregnancy and breast feeding

Pregnancy
Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast feeding
Safety and efficacy of Rivaroxaban have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rivaroxaban is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Fertility
No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Rivaroxaban has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The safety of rivaroxaban has been evaluated in eleven phase III studies including 32,625 patients exposed to rivaroxaban (see Table 1).

**Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies**

| **Indication** | **Number of patients*** | **Maximum daily dose** | **Maximum treatment duration** |
|---|---|---|---|
| Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery | 6,097 | 10 mg | 39 days |
| Prevention of venous thromboembolism in medically ill patients | 3,997 | 10 mg | 39 days |
| Treatment of DVT, PE and prevention of recurrence | 4,556 | Day 1 - 21: 30 mg<br>Day 22 and onwards: 2 | 21 months |
| Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation | 7,750 | 20 mg | 41 months |
| Prevention of atherothrombotic events in patients after an ACS | 10,225 | 5 mg or 10 mg respectively, co-administered with eith ASA or ASA plus clopidogrel or ticlopid | 31 months |

| | | | |
|---|---|---|---|
| | | | |

*Patients exposed to at least one dose of rivaroxaban

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings (>4%) were epistaxis (5.9%) and gastrointestinal tract haemorrhage (4.2%). In total about 67% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 22% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg rivaroxaban undergoing hip or knee replacement surgery and in hospitalised medically ill patients, bleeding events occurred in approximately 6.8% and 12.6% of patients, respectively, and anaemia occurred in approximately 5.9% and 2.1% of patients, respectively. In patients treated with either 15 mg twice daily rivaroxaban followed by 20 mg once daily for treatment of DVT or PE, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 27.8% of patients and anaemia occurred in approximately 2.2% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years. In patients treated for prevention of atherothrombotic events after an acute coronary syndrome (ACS), bleeding of any type or severity was reported with an event rate of 22 per 100 patient years. Anaemia was reported with an event rate of 1.4 per 100 patient years.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:
very common (> 1/10)
common (> 1/100 to < 1/10) uncommon (> 1/1,000 to < 1/100) rare (> 1/10,000 to < 1/1,000)
very rare ( < 1/10,000)
not known (cannot be estimated from the available data)

**Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies**

| Common | Uncommon | Rare | Not known |
|---|---|---|---|
| **Blood and lymphatic system disorders** | | | |
| Anaemia (incl. respective laborator parameters) | Thrombocythemia ( platelet count increased)[A] | | |
| **Immune system disorders** | | | |
| | Allergic reaction, dermatitis allergic | | |
| **Nervous system disorders** | | | |
| Dizziness, headach | Cerebral and intrac haemorrhage, syncc | | |
| **Eye disorders** | | | |
| Eye haemorrhage (i conjunctival haemorrhage) | | | |
| **Cardiac disorders** | | | |
| | Tachycardia | | |
| **Vascular disorders** | | | |
| Hypotension, haematoma | | | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Epistaxis, haemopty | | | |
| **Gastrointestinal disorders** | | | |
| Gingival bleeding, gastrointestinal trac haemorrhage (incl. haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarr vomiting[A] | Dry mouth | | |
| **Hepatobiliary disorders** | | | |
| | Hepatic function abnormal | Jaundice | |
| **Skin and subcutaneous tissue disorders** | | | |
| Pruritus (incl. uncommon cases of generalised pruritus rash, ecchymosis, cutaneous and subcutaneous haemorrhage | Urticaria | | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Pain in extremity[A] | Haenarthrosis | Muscle haemorrahage | Compartment syndrome secondary to a bleeding |

| Common | Uncommon | Rare | Not known |
|---|---|---|---|
| **Renal and urinary disorders** | | | |
| Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), rena impairment (incl. bl creatinine increased blood urea increase | | | Renal failure/acute rena failure secondary to a bleeding sufficient to ca hypoperfusion |
| **General disorders and administration site conditions** | | | |
| Fever[A], peripheral oedema, decreased general strength an energy (incl. fatigu asthenia) | Feeling unwell (inc malaise) | Localised oedema[A] | |
| **Investigations** | | | |
| Increase in transaminases | Increased bilirubin, increased blood alk phosphatase[A], incre LDH[A], increased lipase[A], increased amylase[A], increased GGT[A] | Bilirubin conjugated increa (with or without concomit increase of ALT) | |
| **Inyury, poisoning and procedural complications** | | | |
| Postprocedural haemorrhage (incl. postoperative anae and wound haemorrhage), contusion, wound secretion[A] | | Vascular pseudoaneurysm | |

A: observed in prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in wo <55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an AC (following percutaneous coronary intervention)

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for rivaroxaban. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Post-marketing observations
The following adverse reactions have been reported post-marketing in temporal association with the use of rivaroxaban. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.
Immune system disorders: Angioedema and allergic oedema (In the pooled phase III trials, these events were uncommon (> 1/1,000 to < 1/100)).
Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (> 1/10,000 to < 1/1,000)).
Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (> 1/1,000 to < 1/100)).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard

## 4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.
A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).
Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects
Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).
The activated partial thomboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated, rivaroxaban levels can be measured by calibrated quantitative antifactor-Xa tests (see section 5.2).

Clinical efficacy and safety
The rivaroxaban clinical program was designed to demonstrate the efficacy of rivaroxaban for the prevention of cardiovascular (CV) death, MI or stroke in subjects with a recent ACS (ST-elevation myocardial infarction [STEMI], non- ST-elevation myocardial infarction [NSTEMI] or unstable angina [UA]). In the pivotal double-blind ATLAS ACS 2 TIMI 51 trial, 15,526 patients were randomly assigned in a 1:1:1 fashion to one of three treatment groups: rivaroxaban 2.5 mg orally twice daily, 5 mg orally twice daily or to placebo twice daily co-administered with ASA alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine). Patients with an ACS under the age of 55 had to have either diabetes mellitus or a previous MI. The median time on treatment was 13 months and overall treatment duration was up to almost 3 years. 93.2 % of patients received ASA concomitantly plus thienopyridine treatment and 6.8 % ASA only. Among patients receiving dual anti-platelets therapy 98.8% received clopidogrel, 0.9 % received ticlopidine and 0.3 % received prasugrel. Patients received the first dose of rivaroxaban at a minimum of 24 hours and up to 7 days (mean 4.7 days) after admission to the hospital, but as soon as possible after stabilisation of the ACS event, including revascularisation procedures and when parenteral anticoagulation therapy would normally be discontinued.
Both the 2.5 mg twice daily and the 5 mg twice daily regimens of rivaroxaban were effective in further reducing the incidence of CV events on a background of standard antiplatelet care. The 2.5 mg twice daily regimen reduced mortality, and there is evidence that the lower dose had lower bleeding risks, therefore rivaroxaban 2.5 mg twice daily co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine is recommended for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers.
Relative to placebo, rivaroxaban significantly reduced the primary composite endpoint of CV death, MI or stroke. The benefit was driven by a reduction in CV death and MI and appeared early with a constant treatment effect over the entire treatment period (see Table 3 and Figure 1). Also the first secondary endpoint (all cause death, MI or stroke) was reduced significantly. An additional retrospective analysis

showed a nominally significant reduction in the incidence rates of stent thrombosis compared with placebo (see Table 3). The incidence rates for the principal safety outcome (non-CABG TIMI major bleeding events) were higher in patients treated with rivaroxaban than in patients who received placebo (see Table 5). However the incidence rates were balanced between rivaroxaban and placebo for the components of fatal bleeding events, hypotension requiring treatment with intravenous inotropic agents and surgical intervention for ongoing bleeding.

In Table 4 the efficacy results of patients undergoing percutaneous coronary intervention (PCI) are presented. The safety results in this subgroup of patients undergoing PCI were comparable to the overall safety results.
Patients with elevated biomarkers (troponin or CK-MB) and without a prior stroke/TIA constituted 80% of the study population. The results of this patient population were also consistent with the overall efficacy and safety results.

**Table 3: Efficacy results from phase III ATLAS ACS 2 TIMI 51**

| **Study Population** | **Patients with a recent acute coronary syndrome** [a)] | |
|---|---|---|
| Treatment Dosage | Rivaroxaban 2.5 mg, twice daily, N=5,114 n (%)<br>Hazard Ratio (95 % CI) p-value [b)] | Placebo N=5,113 n (%) |
| Cardiovascular death, MI or stroke | 313 (6.1 %)<br>0.84 (0.72, 0.97) p = 0.020* | 376 (7.4 %) |
| All-cause death, MI or stroke | 320 (6.3 %)<br>0.83 (0.72, 0.97) p = 0.016* | 386 (7.5 %) |
| Cardiovascular death | 94 (1.8 %)<br>0.66 (0.51, 0.86) p = 0.002** | 143 (2.8 %) |
| All-cause death | 103 (2.0 %)<br>0.68 (0.53, 0.87) p = 0.002** | 153 (3.0 %) |
| MI | 205 (4.0 %)<br>0.90 (0.75, 1.09) p = 0.270 | 229 (4.5 %) |
| Stroke | 46 (0.9 %)<br>1.13 (0.74, 1.73) p = 0.562 | 41 (0.8 %) |
| Stent thrombosis | 61 (1.2 %)<br>0.70 (0.51, 0.97) p = 0.033** | 87 (1.7 %) |

a) modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)
b) vs. placebo; Log-Rank p-value
*statistically superior
** nominally significant

**Table 4: Efficacy results from phase III ATLAS ACS 2 TIMI 51 in patients undergoing PCI**

| **Study Population** | **Patients with recent acute coronary syndrome undergoing PCI** | |
|---|---|---|
| Treatment Dosage | Rivaroxaban 2.5 mg, twice daily, N=3114 n (<br>Hazard Ratio (95 % CI) p-value [b)] | Placebo N=3096 n (%) |
| Cardiovascular death, MI or stroke | 153 (4.9 %)<br>0.94 (0.75, 1.17) p = 0.572 | 165 (5.3 %) |
| Cardiovascular death | 24 (0.8 %) | 45 (1.5 %) |

| | | |
|---|---|---|
| | 0.54 (0.33, 0.89) p = 0.013** | |
| All-cause death | 31 (1.0 %)<br>0.64 (0.41, 1.01) p = 0.053 | 49 (1.6 %) |
| MI | 115 (3.7 %)<br>1.03 (0.79, 1.33) p = 0.829 | 113 (3.6 %) |
| Stroke | 27 (0.9 %)<br>1.30 (0.74, 2.31) p = 0.360 | 21 (0.7 %) |
| Stent thrombosis | 47 (1.5 %)<br>0.66 (0.46, 0.95) p = 0.026** | 71 (2.3 %) |

a) modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)
b) vs. placebo; Log-Rank p-value
** nominally significant

**Table 5: Safety results from phase III ATLAS ACS 2 TIMI 51**

| **Study Population** | **Patients with recent acute coronary syndrome** [a)] | |
|---|---|---|
| Treatment Dosage | Rivaroxaban 2.5 mg, twice daily, N=<br>n (%)<br>Hazard Ratio (95 % CI) p-value | Placebo N=5,<br>n(%) |
| Non-CABG TIMI major bleeding eve | 65 (1.3 %) 3.46 (2.08, 5.77) p =<br>0.001* | 19 (0.4 %) |
| Fatal bleeding event | 6 (0.1 %) 0.67 (0.24, 1.89) p = ( | 9 (0.2 %) |
| Symptomatic intracranial haemorrhag | 14 (0.3 %) 2.83 (1.02, 7.86) p<br>0.037 | 5 (0.1 %) |
| Hypotension requiring treatment with intravenous inotropic agents | 3 (0.1 %) | 3 (0.1 %) |
| Surgical intervention for ongoing ble | 7 (0.1 %) | 9 (0.2 %) |
| Transfusion of 4 or more units of bloo over a 48 hour period | 19 (0.4 %) | 6 (0.1 %) |

a) safety population, on treatment
b) vs. Placebo; Log-Rank p-value
* statistically significant

## 5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ($C_{max}$) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or $C_{max}$ at the 2.5 mg and 10 mg dose. Rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food.

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and $C_{max}$ compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and $C_{max}$) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Distribution

Plasma protein binding in humans is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with Vss being approximately 50 litres.

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations

*Gender*

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

*Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

*Different weight categories*

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

*Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

*Hepatic impairment*

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

*Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients

In patients receiving rivaroxaban 2.5 mg twice daily for the prevention of atherothrombotic events in patients with ACS the geometric mean concentration (90 % prediction interval) 2 - 4 h and about 12 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 47 (13 - 123) and 9.2 (4.4 - 18) µg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor-Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor-Xa activity was best described by an $E_{max}$ model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.
Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.
In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and postnatal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Sodium lauryl. sulphate
Magnesium stearate
Hydroxypropyl methyl cellulose

Film-coat:
Macrogol 3350
Hypromellose
Titanium dioxide (E-171)
Iron oxide yellow (E-172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Rivaroxaban 2.5 mg film-coated tablets is available in PVC-PVdC / Aluminium blisters:
10, 14, 28, 30, 42, 56, 60, 90, 98, 168 or 196 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 or in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

Distriquimica, SA, Avda. Mare de Déu de Montserrat, 221, 08041 Barcelona, Spain.

## 8. MARKETING AUTHORISATION NUMBER(S)

PL: 21562/0031

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{MM/YYYY}

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

## 1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban 10 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg rivaroxaban.
Excipient with known effect:
Each film-coated tablet contains 27.50 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Pink, round, biconvex, film coated tablets, aprox. 6 mm diameter, debossed with "E2" on one side and plain on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

### 4.2 Posology and method of administration

Posology
The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established.
The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

If a dose is missed the patient should take Rivaroxaban immediately and then continue the following day with once daily intake as before.

*Converting from Vitamin K Antagonists (VKA) to Rivaroxaban*
When converting patients from VKAs to Rivaroxaban, International Normalized Ratio (INR) values will be falsely elevated after the intake of Rivaroxaban. The INR is not valid to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used (see section 4.5).

*Converting from Rivaroxaban to Vitamin K antagonists (VKA)*
There is a potential for inadequate anticoagulation during the transition from Rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Rivaroxaban can contribute to an elevated INR.
In patients converting from Rivaroxaban to VKA, VKA should be given concurrently until the INR is > 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both Rivaroxaban and VKA the

INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban. Once Rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

*Converting from parenteral anticoagulants to Rivaroxaban*
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

*Converting from Rivaroxaban to parenteral anticoagulants*
Give the first dose of parenteral anticoagulant at the time the next Rivaroxaban dose would be taken.

Special populations
*Renal impairment*
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).
No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 -80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (see section 5.2).

*Hepatic impairment*
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

*Elderly population*
No dose adjustment (see section 5.2).

*Body weight*
No dose adjustment (see section 5.2).

*Gender*
No dose adjustment (see section 5.2).

*Paediatric population*
The safety and efficacy of Rivaroxaban in children aged 0 to 18 years have not been established. No data are available. Therefore, Rivaroxaban is not recommended for use in children below 18 years of age.

Method of administration
For oral use.
Rivaroxaban can be taken with or without food (see sections 4.5 and 5.2).
For patients who are unable to swallow whole tablets, Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally.
The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water (see section 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Active clinically significant bleeding.

Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).
Pregnancy and breast feeding (see section 4.6).

## 4.4 Special warnings and precautions for use

Haemorrhagic risk
Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8). This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.
Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see sections 5.1 and 5.2).

Renal impairment
In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6-fold on average) which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Rivaroxaban is to be used with caution (see section 4.5).

Interaction with other medicinal products
The use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).
Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Other haemorrhagic risk factors
As with other antithrombotics, rivaroxaban is to be used with caution in patients with an increased bleeding risk such as:
- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension

- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

Hip fracture surgery
Rivaroxaban has not been studied in interventional clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety.

Spinal/epidural anaesthesia or puncture
When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2). At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Dosing recommendations before and after invasive procedures and surgical intervention other than elective hip or knee replacement surgery
If an invasive procedure or surgical intervention is required, Rivaroxaban 10 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

Elderly population
Increasing age may increase haemorrhagic risk (see section 5.2).

Information about excipients
Rivaroxaban contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors
Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban $C_{max}$, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole

and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).
Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in $C_{max}$. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).
Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and $C_{max}$. This increase is not considered clinically relevant.
In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $C_{max}$ when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $CR_{max}$ when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).
Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean $C_{max}$. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).
Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Anticoagulants
After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors
No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid. Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

Warfarin
Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive. If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, antifactor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.
If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the Ctrough of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point. No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort *(Hypericum perforatum))* may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4. No clinically relevant interaction with food was observed (see section 4.2).

Laboratory parameters
Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

## 4.6 Fertility, pregnancy and breast feeding

Pregnancy
Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).
Women of child bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast feeding
Safety and efficacy of Rivaroxaban have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rivaroxaban is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Fertility
No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Rivaroxaban has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The safety of rivaroxaban has been evaluated in eleven phase III studies including 32,625 patients exposed to rivaroxaban (see Table 1).

**Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies**

| Indication | Number of patients* | Maximum daily dose | Maximum treatment duration |
|---|---|---|---|
| Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery | 6,097 | 10 mg | 39 days |
| Prevention of venous thromboembolism in medically ill patients | 3,997 | 10 mg | 39 days |
| Treatment of DVT, PE and prevention of recurrence | 4,556 | Day 1 - 21: 30 mg<br>Day 22 and onwards: 2 | 21 months |
| Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation | 7,750 | 20 mg | 41 months |
| Prevention of atherothrombotic events in patients after an ACS | 10,225 | 5 mg or 10 mg respectively, co-administered with eith ASA or ASA plus clopidogrel or ticlopid | 31 months |

*Patients exposed to at least one dose of rivaroxaban

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings (>4%) were epistaxis (5.9%) and gastrointestinal tract haemorrhage (4.2%). In total about 67% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 22% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg rivaroxaban undergoing hip or knee replacement surgery and in hospitalised medically ill patients, bleeding events occurred in approximately 6.8% and 12.6% of patients, respectively, and anaemia occurred in approximately 5.9% and 2.1% of patients, respectively. In patients treated with either 15 mg twice daily rivaroxaban followed by 20 mg once daily for treatment of DVT or PE, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 27.8% of patients and anaemia occurred in approximately 2.2% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years. In patients treated for prevention of atherothrombotic events after an acute coronary syndrome (ACS), bleeding of any type or severity was reported with an event rate of 22 per 100 patient years. Anaemia was reported with an event rate of 1.4 per 100 patient years.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:
very common (> 1/10)
common (> 1/100 to < 1/10)
uncommon (> 1/1,000 to < 1/100)
rare (> 1/10,000 to < 1/1,000)
very rare ( < 1/10,000)
not known (cannot be estimated from the available data)

**Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies**

| Common | Uncommon | Rare | Not known |
|---|---|---|---|
| **Blood and lymphatic system disorders** | | | |
| Anaemia (incl. respective laborator parameters) | Thrombocythemia ( platelet count increased)[A] | | |
| **Immune system disorders** | | | |
| | Allergic reaction, dermatitis allergic | | |
| **Nervous system disorders** | | | |
| Dizziness, headach | Cerebral and intrac haemorrhage, syncc | | |
| **Eye disorders** | | | |
| Eye haemorrhage (i conjunctival haemorrhage) | | | |
| **Cardiac disorders** | | | |
| | Tachycardia | | |
| **Vascular disorders** | | | |
| Hypotension, haematoma | | | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Epistaxis, haemopty | | | |
| **Gastrointestinal disorders** | | | |
| Gingival bleeding, gastrointestinal trac haemorrhage (incl. haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarr vomiting[A] | Dry mouth | | |
| **Hepatobiliary disorders** | | | |
| | Hepatic function abnormal | Jaundice | |
| **Skin and subcutaneous tissue disorders** | | | |
| Pruritus (incl. uncommon cases of generalised pruritus rash, ecchymosis, cutaneous and subcutaneous haemorrhage | Urticaria | | |

| Common | Uncommon | Rare | Not known |
|---|---|---|---|
| **Musculoskeletal and connective tissue disorders** | | | |
| Pain in extremity[A] | Haenarthrosis | Muscle haemorrahage | Compartment syndrome secondary to a bleeding |
| **Renal and urinary disorders** | | | |
| Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), rena impairment (incl. b creatinine increased blood urea increase | | | Renal failure/acute renal fa secondary to a bleeding sufficient to cause hypoperfusion |
| **General disorders and administration site conditions** | | | |
| Fever[A], peripheral oedema, decreased general strength an energy (incl. fatigu asthenia) | Feeling unwell (incl. malaise) | Localised oedema[A] | |
| **Investigations** | | | |
| Increase in transaminases | Increased bilirubin, increased blood alk phosphatase[A], incre LDH[A], increased lipase[A], increased amylase[A], increased GGT[A] | Bilirubin conjugated incre (with or without concomit increase of ALT) | |
| **Inyury, poisoning and procedural complications** | | | |
| Postprocedural haemorrhage (incl. postoperative anae and wound haemorrhage), contusion, wound secretion[A] | | Vascular pseudoaneurysm | |

A: observed in prevention of venous thromboembolism (VTE) in adult patients under elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in wome years

C: observed as uncommon in prevention of atherothrombotic events in patients after an (following percutaneous coronary intervention)

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain

patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.
Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for rivaroxaban. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Post-marketing observations
The following adverse reactions have been reported post-marketing in temporal association with the use of rivaroxaban. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.
Immune system disorders: Angioedema and allergic oedema (In the pooled phase III trials, these events were uncommon (> 1/1,000 to < 1/100)).
Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (> 1/10,000 to < 1/1,000)).
Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (> 1/1,000 to < 1/100)).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard

## 4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.
A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).
Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## 5. PHARMACOLOGICAL PROPERTIES 5.1 Pharmacodynamic properties

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 s (baseline values before surgery 12 to 15s).

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).

The activated partial thomboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative antifactor Xa tests (see section 5.2).

Clinical efficacy and safety

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of VTE, i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050 in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind phase III clinical studies, the RECORD-programme. Rivaroxaban 10 mg once daily (od) started no sooner than 6 hours post-operatively was compared with enoxaparin 40 mg once daily started 12 hours pre-operatively.

In all three phase III studies (see table 3), rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non-fatal PE and death) and major VTE (proximal DVT, non-fatal PE and VTE-related death), the pre-specified primary and major secondary efficacy endpoints. Furthermore, in all three studies the rate of symptomatic VTE (symptomatic DVT, non-fatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin.

The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

**Table 3: Efficacy and safety results from phase III clinical studies**

| | RECORD 1 | | | RECORD 2 | | | RECORD 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| Study Population | 4,541 patients undergoing total replacement surgery | | | 2,509 patients undergoing total replacement surgery | | | 2,531 patients undergoing total k replacement surgery | | |
| Treatment and duratic after surge | Rivaroxaban 10 mg od 35 ± 4 days | Enoxaparin 40 mg od 35 ± 4 days | p | Rivaroxaban 10 mg od 35 ± 4 days | Enoxaparin 40 mg od 12 ± 2 days | p | Rivaroxaban 10 mg od 12 ± 2 days | Enoxaparin 40 mg od 12 ± 2 days | p |
| Total VTE | 18 (1.1 %) | 58 (3.7 %) | < 0. | 17 (2.0 %) | 81 (9.3 %) | < 0 | 79 (9.6 %) | 166 (18.9 %) | < 0 |
| Major VTE | 4 (0.2 %) | 33 (2.0 %) | < 0.0 | 6 (0.6 %) | 49 (5.1 %) | < 0. | 9 (1.0 %) | 24 (2.6 %) | 0.0 |
| Sympto-m VTE | 6 (0.4 %) | 11 (0.7 %) | | 3 (0.4 %) | 15 (1.7 %) | | 8 (1.0 %) | 24 (2.7 %) | |
| Major blee | 6 (0.3 %) | 2 (0.1 %) | | 1 (0.1 %) | 1 (0.1 %) | | 7 (0.6 %) | 6 (0.5 %) | |

The analysis of the pooled results of the phase III trials corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE with rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily.

In addition to the phase III RECORD program, a post-authorization, non-interventional, open-label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopaedic surgery of the hip or knee, to compare rivaroxaban with other pharmacological thromboprophylaxis (standard-of-care) under real-life setting. Symptomatic VTE occurred in 57 (0.6%) patients in the rivaroxaban group (n=8,778) and 88 (1.0%) of patients in the standard-of-care group (n=8,635; HR 0.63; 95% CI 0.43-0.91); safety population). Major bleeding occurred in 35 (0.4%) and 29 (0.3%) of patients in the rivaroxaban and standard-of-care groups (HR 1.10; 95% CI 0.67-1.80). Thus, the results were consistent with the results of the pivotal randomised studies.

## 5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (Cmax) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or $C_{max}$ at the 2.5 mg and 10 mg dose. Rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30% to 40%, apart from on the day of surgery and the following day when variability in exposure is high (70%).

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and $C_{max}$ compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and $C_{max}$) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Distribution
Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with Vss being approximately 50 litres.

Biotransformation and elimination
Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.
Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).
Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations
*Gender*
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

*Elderly population*
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

*Different weight categories*
Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.

*Inter-ethnic differences*
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

*Hepatic impairment*
Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.
The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

*Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.
Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.
Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients
In patients receiving rivaroxaban for prevention of VTE 10 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 101 (7 - 273) and 14 (4 -51) |µg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an $E_{max}$ model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects. In patients, baseline factor Xa and PT were influenced by the surgery resulting in a difference in the concentration-PT slope between the day post-surgery and steady state.

Paediatric population
Safety and efficacy have not been established for children and adolescents up to 18 years.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.
Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.
In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and postnatal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Sodium lauryl sulphate
Magnesium stearate
Hydroxypropyl methyl cellulose

Film-coat:
Macrogol 3350
Hypromellose
Titanium dioxide (E-171)
Iron oxide red (E172)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

2 years

## 6.4 Special precautions for storage

This medicine does not require any special storage conditions.

## 6.5 Nature and contents of container

Rivaroxaban 10 mg film-coated tablets is available in:
PVC-PVdC / Aluminium blisters:
5, 10, 14, 28, 30, 42, 56, 60, 90, 98, 168, 196 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 or in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets.
Bottles:
30, 50, 60, 90, 100, 500, 1000 film-coated tablets.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements for disposal.

# 7. MARKETING AUTHORISATION HOLDER

Distriquimica, SA, Avda. Mare de Déu de Montserrat, 221, 08041 Barcelona, Spain.

## 8. MARKETING AUTHORISATION NUMBER(S)

PL: 21562/0032

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{MM/YYYY}

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

## 1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban 15 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 15 mg rivaroxaban.
Excipient with known effect:
Each film-coated tablet contains 16.50 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Red, round biconvex, film coated tablets, aprox. 6 mm diameter, debossed with "E3" on one side and plain on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age > 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

### 4.2 Posology and method of administration

Posology
*Prevention of stroke and systemic embolism*
The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Rivaroxaban should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).
If a dose is missed the patient should take Rivaroxaban immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

*Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE*
The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, as indicated in the table below.

| | Dosing schedule | Maximum daily dose |
|---|---|---|
| Day 1 - 21 | 15 mg twice daily | 30 mg |

| | | |
|---|---|---|
| Day 22 and onwards | 20 mg once daily | 20 mg |

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.
If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Rivaroxaban immediately to ensure intake of 30 mg Rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Rivaroxaban immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

*Converting from Vitamin K Antagonists (VKA) to Rivaroxaban*
For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Rivaroxaban therapy should be initiated when the International Normalized Ratio (INR) is < 3.0.
For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rivaroxaban therapy should be initiated once the INR is < 2.5.
When converting patients from VKAs to Rivaroxaban, INR values will be falsely elevated after the intake of Rivaroxaban. The INR is not valid to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used (see section 4.5).

*Converting from Rivaroxaban to Vitamin K antagonists (VKA)*
There is a potential for inadequate anticoagulation during the transition from Rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Rivaroxaban can contribute to an elevated INR. In patients converting from Rivaroxaban to VKA, VKA should be given concurrently until the INR is > 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both Rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban. Once Rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

*Converting from parenteral anticoagulants to Rivaroxaban*
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

*Converting from Rivaroxaban to parenteral anticoagulants*
Give the first dose of parenteral anticoagulant at the time the next Rivaroxaban dose would be taken.

Special populations
*Renal impairment*
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance
< 15 ml/min (see sections 4.4 and 5.2).
In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks.
  Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 – 80 ml/min) (see section 5.2).

*Hepatic impairment*
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

*Elderly population*
No dose adjustment (see section 5.2).

*Body weight*
No dose adjustment (see section 5.2).

*Gender*
No dose adjustment (see section 5.2).

*Paediatric population*
The safety and efficacy of Rivaroxaban in children aged 0 to 18 years have not been established. No data are available. Therefore, Rivaroxaban is not recommended for use in children below 18 years of age.

*Patients undergoing cardioversion*
Rivaroxaban can be initiated or continued in patients who may require cardioversion. For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rivaroxaban treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation (see sections 5.1 and 5.2). **For all patients,** confirmation should be sought prior to cardioversion that the patient has taken Rivaroxaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Method of administration
For oral use.
The tablets are to be taken with food (see section 5.2).
For patients who are unable to swallow whole tablets, Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding (see section 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active clinically significant bleeding.
Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

## 4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Haemorrhagic risk
As with other anticoagulants, patients taking Rivaroxaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban administration should be discontinued if severe haemorrhage occurs.
In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.
Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.
Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see sections 5.1 and 5.2).

Renal impairment
In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Interaction with other medicinal products
The use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both

CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5). Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Other haemorrhagic risk factors
As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:
- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

Patients with prosthetic valves
Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
Rivaroxaban 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 Rivaroxaban have not been established in these clinical situations.

Spinal/epidural anaesthesia or puncture
When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15 mg rivaroxaban in these situations.
To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Dosing recommendations before and after invasive procedures and surgical intervention
If an invasive procedure or surgical intervention is required, Rivaroxaban 15 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

Elderly population
Increasing age may increase haemorrhagic risk (see section 5.2).

Information about excipients
Rivaroxaban contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors
Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban $C_{max}$, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).
Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in $C_{max}$. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).
Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and $C_{max}$. This increase is not considered clinically relevant. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $CR_{max}$ when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $CR_{max}$ when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean $C_{max}$. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).
Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Anticoagulants
After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors
No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

Warfarin
Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.
If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, antifactor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.
If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the Ctrough of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.
No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers
Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort *(Hypericum perforatum))* may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Laboratory parameters
Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

## 4.6 Fertility, pregnancy and breast feeding

Pregnancy
Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast feeding
Safety and efficacy of Rivaroxaban have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rivaroxaban is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Fertility
No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Rivaroxaban has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The safety of rivaroxaban has been evaluated in eleven phase III studies including 32,625 patients exposed to rivaroxaban (see Table 1).

**Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies**

| **Indication** | **Number Of patients** | **Maximum daily dose** | **Maximum treatment duration** |
|---|---|---|---|
| Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery | 6,097 | 10 mg | 39 days |
| Prevention of venous thromboembolism in medically ill patients | 3,997 | 10 mg | 39 days |
| Treatment of DVT, PE and prevention of recurrence | 4,556 | Day 1 - 21: 30 mg<br>Day 22 and onwards: 20 mg | 21 months |
| Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation | 7,750 | 20 mg | 41 months |
| Prevention of atherothrombotic events in patients after an ACS | 10,225 | 5 mg or 10 mg<br><br>respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine | 31 months |

*Patients exposed to at least one dose of rivaroxaban

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings (>4%) were epistaxis (5.9%) and gastrointestinal tract haemorrhage (4.2%). In total about 67% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 22% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg rivaroxaban undergoing hip or knee replacement surgery and in hospitalised medically ill patients, bleeding events occurred in approximately 6.8% and 12.6% of patients, respectively, and anaemia occurred in approximately 5.9% and 2.1% of patients, respectively. In patients treated with either 15 mg twice daily rivaroxaban followed by 20 mg once daily for treatment of DVT or PE, or with 20 mg once daily

for prevention of recurrent DVT and PE, bleeding events occurred in approximately 27.8% of patients and anaemia occurred in approximately 2.2% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years. In patients treated for prevention of cardiovascular death and myocardial infarction after an acute coronary syndrome (ACS), bleeding of any type or severity was reported with an event rate of 22 per 100 patient years. Anaemia was reported with an event rate of 1.4 per 100 patient years.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:
very common (> 1/10)
common (> 1/100 to < 1/10)
uncommon (> 1/1,000 to < 1/100)
rare (> 1/10,000 to < 1/1,000)
very rare ( < 1/10,000)
not known (cannot be estimated from the available data)

**Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies**

| Common | Uncommon | Rare | Not known |
|---|---|---|---|
| **Blood and lymphatic system disorders** | | | |
| Anaemia (incl. respective laboratory parameters) | Thrombocythemia (incl. platelet count increased)[A] | | |
| **Immune system disorders** | | | |
| | Allergic reaction, dermatitis allergic | | |
| **Nervous system disorders** | | | |
| Dizziness, headache | Cerebral and intracranial haemorrhage, syncope | | |
| **Eye disorders** | | | |
| Eye haemorrhage (incl. conjunctival haemorrhage) | | | |
| **Cardiac disorders** | | | |
| | Tachycardia | | |
| **Vascular disorders** | | | |
| Hypotension, haematoma | | | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Epistaxis, haemoptysis | | | |
| **Gastrointestinal disorders** | | | |
| Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A] | Dry mouth | | |
| **Hepatobiliary disorders** | | | |
| | Hepatic function abnormal | Jaundice | |
| **Skin and subcutaneous tissue disorders** | | | |
| Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage | Urticaria | | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Pain in extremity[A] | Haenarthrosis | Muscle haemorrahage | Compartment syndrome secondary to a bleeding |

| Common | Uncommon | Rare | Not known |
|---|---|---|---|
| **Renal and urinary disorders** | | | |
| Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)[A] | | | Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion |
| **General disorders and administration site conditions** | | | |
| Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia) | Feeling unwell (incl. malaise) | Localised oedema[A] | |
| **Investigations** | | | |
| Increase in transaminases | Increased bilirubin, increased blood alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A] | Bilirubin conjugated increased (with or without concomitant increase of ALT) | |
| **Inyury, poisoning and procedural complications** | | | |
| Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A] | | Vascular pseudoaneurysm[C] | |

A: observed in prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women <55 years

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a

consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.
Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for rivaroxaban. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Post-marketing observations
The following adverse reactions have been reported post-marketing in temporal association with the use of rivaroxaban. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.
Immune system disorders: Angioedema and allergic oedema (In the pooled phase III trials, these events were uncommon (> 1/1,000 to < 1/100)).
Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (> 1/10,000 to < 1/1,000)).
Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (> 1/1,000 to < 1/100)).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard

## 4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.
A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).
Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects
Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.
In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.
In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).
The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative antifactor Xa tests (see section 5.2).

Clinical efficacy and safety
*Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation*
The rivaroxaban clinical program was designed to demonstrate the efficacy of rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to rivaroxaban 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to

warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.
34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.
Rivaroxaban was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 - 0.96; P<0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74-1.03; P<0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 3.
Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).
The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 4).

**Table 3: Efficacy results from phase III ROCKET AF**

| **Study population** | **ITT analyses of efficacy in patients with non-valvular atrial fibrillation** | | |
|---|---|---|---|
| Treatment dosage | Rivaroxaban 20 mg od (15 mg od in patients with moderate renal impairment)<br><br>Event rate (100 pt-yr) | Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)<br><br>Event rate (100 pt-yr) | Hazard ratio (95% CI)<br>p-value, test for superiority |
| Stroke and non-CNS systemic embolism | 269<br>(2.12) | 306<br>(2.42) | 0.88<br>(0.74 - 1.03)<br>0.117 |
| Stroke, non-CNS systemic embolism and vascular death | 572<br>(4.51) | 609<br>(4.81) | 0.94<br>(0.84 - 1.05)<br>0.265 |
| Stroke, non-CNS systemic embolism, vascular death and myocardial infarction | 659<br>(5.24) | 709<br>(5.65) | 0.93<br>(0.83 - 1.03)<br>0.158 |
| Stroke | 253<br>(1.99) | 281<br>(2.22) | 0.90<br>(0.76 - 1.07)<br>0.221 |
| Non-CNS systemic embolism | 20<br>(0.16) | 27<br>(0.21) | 0.74<br>(0.42 - 1.32)<br>0.308 |
| Myocardial infarction | 130<br>(1.02) | 142<br>(1.11) | 0.91<br>(0.72 - 1.16)<br>0.464 |

**Table 4: Safety results from phase III ROCKET AF**

| **Study population** | **Patients with non-valvular atrial fibrillation[a)]** | | |
|---|---|---|---|
| Treatment dosage | Rivaroxaban 20 mg once a day (15 mg once a day in patients with moderate renal impairment)<br><br>Event rate (100 pt-yr) | Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)<br><br>Event rate (100 pt-yr) | Hazard ratio (95% CI) p-value |
| Major and non-major clinically relevant bleeding events | 1,475 (14.91) | 1,449 (14.52) | 1.03 (0.96 - 1.11) 0.442 |
| Major bleeding events | 395 (3.60) | 386 (3.45) | 1.04 (0.90 - 1.20) 0.576 |
| Death due to bleeding* | 27 (0.24) | 55 (0.48) | 0.50 (0.31 - 0.79) 0.003 |
| Critical organ bleeding* | 91 (0.82) | 133 (1.18) | 0.69 (0.53 - 0.91) 0.007 |
| Intracranial haemorrhage* | 55 (0.49) | 84 (0.74) | 0.67 (0.47 - 0.93) 0.019 |
| Haemoglobin drop* | 305 (2.77) | 254 (2.26) | 1.22 (1.03 - 1.44) 0.019 |
| Transfusion of 2 or more units of packed red blood cells or whole blood* | 183 (1.65) | 149 (1.32) | 1.25 (1.01 - 1.55) 0.044 |
| Non-major clinically relevant bleeding events | 1,185 (11.80) | 1,151 (11.37) | 1.04 (0.96 - 1.13) 0.345 |
| All cause mortality | 208 (1.87) | 250 (2.21) | 0.85 (0.70 - 1.02) 0.073 |

a) Safety population, on treatment
* Nominally significant

Patients undergoing cardioversion

A prospective, randomized, open-label, multicenter, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomized 2:1), for the prevention of cardiovascular events. TEE- guided (1 - 5 days of pre-treatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischemic attack, non-CNS systemic embolism, MI and cardiovascular death) occurred in 5 (0.5%) patients in the rivaroxaban group (n = 978) and 5 (1.0%) patients in the VKA group (n = 492; RR 0.50; 95% CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6%) and 4 (0.8%) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95 % CI 0.212.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

*Treatment of DVT, PE and prevention of recurrent DVT and PE*

The rivaroxaban clinical program was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.

Over 9,400 patients were studied in three randomised controlled phase III clinical studies (Einstein DVT, Einstein PE and Einstein Extension) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.
In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.
In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range (> 2.0). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.
In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Rivaroxaban 20 mg once daily was compared with placebo.

All phase III studies used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality.In the Einstein DVT study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ($p < 0.0001$ (test for non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.67 ((95% CI: 0.47 - 0.95), nominal p value p=0.027) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

**Table 5: Efficacy and safety results from phase III Einstein DVT**

| **Study population** | **3,449 patients with symptomatic acute deep vein thrombosis** | |
|---|---|---|
| Treatment dosage and duration | Rivaroxaban[a)]<br>3, 6 or 12 months<br>N=1,731 | Enoxaparin/VKA[b)]<br>3, 6 or 12 months<br>N=1,718 |
| Symptomatic recurrent VTE* | 36<br>(2.1%) | 51<br>(3.0%) |
| Symptomatic recurrent PE | 20<br>(1.2%) | 18<br>(1.0%) |
| Symptomatic recurrent DVT | 14<br>(0.8%) | 28<br>(1.6%) |
| Symptomatic PE and DVT | 1<br>(0.1%) | 0 |

| | | |
|---|---|---|
| Fatal PE/Death where PE cannot be ruled out | 4 (0.2%) | 6 (0.3%) |
| Major or clinically relevant non-major bleeding | 139 (8.1%) | 138 (8.1%) |
| Major bleeding events | 14 (0.8%) | 20 (1.2%) |

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

* $p < 0.0001$ (non-inferiority to a prespecified hazard ratio of 2.0); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (superiority)

In the Einstein PE study (see Table 6) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); hazard ratio: 1.123 (0.749 - 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.849 ((95% CI: 0.633 - 1.139), nominal p value p= 0.275). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (p=0.082 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).
The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) were slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a hazard ratio 0.493 (95% CI: 0.308 - 0.789).

**Table 6: Efficacy and safety results from phase III Einstein PE**

| **Study population** | **4,832 patients with an acute symptomatic PE** | |
|---|---|---|
| Treatment dosage and duration | Rivaroxaban[a)] 3, 6 or 12 months N=2,419 | Enoxaparin/VKA[b)] 3, 6 or 12 months N=2,413 |
| Symptomatic recurrent VTE* | 50 (2.1%) | 44 (1.8%) |
| Symptomatic recurrent PE | 23 (1.0%) | 20 (0.8%) |
| Symptomatic recurrent DVT | 18 (0.7%) | 17 (0.7%) |
| Symptomatic PE and DVT | 0 | 2 (<0.1%) |
| Fatal PE/Death where PE cannot be ruled out | 11 (0.5%) | 7 (0.3%) |
| Major or clinically relevant non-major bleeding | 249 (10.3%) | 274 (11.4%) |
| Major bleeding events | 26 (1.1%) | 52 (2.2%) |

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

* $p < 0.0026$ (non-inferiority to a prespecified hazard ratio of 2.0); hazard ratio: 1.123 (0.749 – 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 7).

**Table 7: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE**

| **Study population** | **8,281 patients with an acute symptomatic DVT or PE** | |
|---|---|---|
| Treatment dosage and duration | Rivaroxaban[a)]<br>3, 6 or 12 months<br>N=4,150 | Enoxaparin/VKA[b)]<br>3, 6 or 12 months<br>N=4,131 |
| Symptomatic recurrent VTE* | 86<br>(2.1%) | 95<br>(2.3%) |
| Symptomatic recurrent PE | 43<br>(1.0%) | 38<br>(0.9%) |
| Symptomatic recurrent DVT | 32<br>(0.8%) | 45<br>(1.1%) |
| Symptomatic PE and DVT | 1<br>(<0.1%) | 2<br>(<0.1%) |
| Fatal PE/Death where PE cannot be ruled out | 15<br>(0.4%) | 13<br>(0.3%) |
| Major or clinically relevant non-major bleeding | 388<br>(9.4%) | 412<br>(10.0%) |
| Major bleeding events | 40<br>(1.0%) | 72<br>(1.7%) |

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified hazard ratio of 1.75); hazard ratio: 0.886 (0.661 - 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a hazard ratio of 0.771 ((95% CI: 0.614 - 0.967), nominal p value p= 0.0244).

In the Einstein Extension study (see Table 8) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

**Table 8: Efficacy and safety results from phase III Einstein Extension**

| **Study population** | **1,197 patients continued treatment and prevention of recurrent venous thromboembolism** | |
|---|---|---|
| Treatment dosage and duration | Rivaroxaban[a)]<br>6 or 12 months<br>N=602 | Placebo<br>6 or 12 months<br>N=594 |
| Symptomatic recurrent VTE* | 8<br>(1.3%) | 42<br>(7.1%) |
| Symptomatic recurrent PE | 2<br>(0.3%) | 13<br>(2.2%) |
| Symptomatic recurrent DVT | 5<br>(0.8%) | 31<br>(5.2%) |
| Fatal PE/Death where PE cannot be ruled out | 1<br>(0.2%) | 1<br>(0.2%) |
| Major bleeding events | 4<br>(0.7%) | 0<br>(0.0%) |
| Clinically relevant non-major bleeding | 32<br>(5.4%) | 7<br>(1.2%) |

a) Rivaroxaban 20 mg once daily

* p < 0.0001 (superiority), hazard ratio: 0.185 (0.087 - 0.393)

## 5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ($C_{max}$) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or $C_{max}$ at the 2.5 mg and 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. rivaroxaban 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and $C_{max}$ compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and $C_{max}$) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with Vss being approximately 50 litres.

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations

*Gender*

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

*Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

*Different weight categories*

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.

*Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

*Hepatic impairment*

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

*Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing

maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) |µg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an $E_{max}$ model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

Paediatric population
Safety and efficacy have not been established for children and adolescents up to 18 years.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.
Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.
In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and postnatal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Sodium lauryl sulphate
Magnesium stearate
Hydroxypropyl methyl cellulose

Film-coat:
Macrogol 3350
Polyvinyl alcohol-partially hydrolyzed
Titanium dioxide (E-171)
Iron oxide red (E-172)
Talc

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life
2 years

### 6.4 Special precautions for storage

This medicine does not require any special storage conditions.

### 6.5 Nature and contents of container

**Rivaroxaban 15 mg film-coated tablets and is available in:**
**PVC-PVdC / Aluminium blisters:**
10, 14, 28, 30, 42, 56, 60, 90, 98, 168, 196 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 or in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets.
Bottles:
30, 50, 60, 90, 100, 500, 1000 film-coated tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

Distriquimica, SA, Avda. Mare de Déu de Montserrat, 221, 08041 Barcelona, Spain.

## 8. MARKETING AUTHORISATION NUMBER(S)

PL: 21562/0033

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{MM/YYYY}

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

## 1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban 20 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg rivaroxaban.
Excipient with known effect:
Each film-coated tablet contains 22.00 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Red, round biconvex, film coated tablets, aprox. 6 mm diameter, debossed with "E4" on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age > 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

### 4.2 Posology and method of administration

Posology
*Prevention of stroke and systemic embolism*
The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Rivaroxaban should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).
If a dose is missed the patient should take Rivaroxaban immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

*Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE*
The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, as indicated in the table below.

| | Dosing schedule | Maximum daily dose |
|---|---|---|
| Day 1 - 21 | 15 mg twice daily | 30 mg |
| Day 22 and onwards | 20 mg once daily | 20 mg |

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (at least 3 months) should

be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.
If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Rivaroxaban immediately to ensure intake of 30 mg Rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Rivaroxaban immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

*Converting from Vitamin K Antagonists (VKA) to Rivaroxaban*
For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Rivaroxaban therapy should be initiated when the International Normalized Ratio (INR) is < 3.0.
For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rivaroxaban therapy should be initiated once the INR is < 2.5.
When converting patients from VKAs to Rivaroxaban, INR values will be falsely elevated after the intake of Rivaroxaban. The INR is not valid to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used (see section 4.5).

*Converting from Rivaroxaban to Vitamin K antagonists (VKA)*
There is a potential for inadequate anticoagulation during the transition from Rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Rivaroxaban can contribute to an elevated INR.
In patients converting from Rivaroxaban to VKA, VKA should be given concurrently until the INR is > 2.0.
For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both Rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban Distriquimica. Once Rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

*Converting from parenteral anticoagulants to Rivaroxaban*
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

*Converting from Rivaroxaban to parenteral anticoagulants*
Give the first dose of parenteral anticoagulant at the time the next Rivaroxaban dose would be taken.

Special populations
*Renal impairment*
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban Distriquimica is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).
In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 – 29 ml/min) renal impairment the following dosage recommendations apply:
- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks.

Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 – 80 ml/min) (see section 5.2).

*Hepatic impairment*
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

*Elderly population*
No dose adjustment (see section 5.2).

*Body weight*
No dose adjustment (see section 5.2).

*Gender*
No dose adjustment (see section 5.2).

*Paediatric population*
The safety and efficacy of Rivaroxaban in children aged 0 to 18 years have not been established. No data are available. Therefore, Rivaroxaban is not recommended for use in children below 18 years of age.

*Patients undergoing cardioversion*
Rivaroxaban can be initiated or continued in patients who may require cardioversion. For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rivaroxaban treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation (see sections 5.1 and 5.2). **For all patients,** confirmation should be sought prior to cardioversion that the patient has taken Rivaroxaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Method of administration
For oral use.
The tablets are to be taken with food (see section 5.2).
For patients who are unable to swallow whole tablets, Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Rivaroxaban Distriquimica15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding (see section 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active clinically significant bleeding.
Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

## 4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Haemorrhagic risk
As with other anticoagulants, patients taking Rivaroxaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban administration should be discontinued if severe haemorrhage occurs.
In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.
Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.
Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see sections 5.1 and 5.2).

Renal impairment
In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Interaction with other medicinal products

The use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).
Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Other haemorrhagic risk factors
As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:
- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

Patients with prosthetic valves
Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
Rivaroxaban 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 Rivaroxaban have not been established in these clinical situations.

Spinal/epidural anaesthesia or puncture
When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 20 mg rivaroxaban in these situations.
To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the

last administration of rivaroxaban (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Dosing recommendations before and after invasive procedures and surgical intervention
If an invasive procedure or surgical intervention is required, Rivaroxaban 20 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

Elderly population
Increasing age may increase haemorrhagic risk (see section 5.2).

Information about excipients
Rivaroxaban contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors
Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban $C_{max}$, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).
Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in $C_{max}$. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).
Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and $C_{max}$. This increase is not considered clinically relevant. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $C_{max}$ when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $CR_{max}$ when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean $C_{max}$. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).
Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors
No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid. Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

Warfarin
Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.
If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, antifactor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.
If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the Ctrough of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.
No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers
Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort *(Hypericum perforatum))* may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Laboratory parameters
Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

## 4.6 Fertility, pregnancy and breast feeding

Pregnancy
Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy (see section 4.3).
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast feeding
Safety and efficacy of Rivaroxaban have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rivaroxaban is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Fertility
No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Rivaroxaban has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The safety of rivaroxaban has been evaluated in eleven phase III studies including 32,625 patients exposed to rivaroxaban (see Table 1).

**Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies**

| **Indication** | **Number of patients*** | **Maximum daily dose** | **Maximum treatment duration** |
|---|---|---|---|
| Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery | 6,097 | 10 mg | 39 days |
| Prevention of venous thromboembolism in medically ill patients | 3,997 | 10 mg | 39 days |
| Treatment of DVT, PE and prevention of recurrence | 4,556 | Day 1 - 21: 30 mg<br>Day 22 and onwards: 20 mg | 21 months |
| Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation | 7,750 | 20 mg | 41 months |
| Prevention of atherothrombotic events in patients after an ACS | 10,225 | 5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine | 31 months |

*Patients exposed to at least one dose of rivaroxaban

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings (>4%) were epistaxis (5.9%) and gastrointestinal tract haemorrhage (4.2%).
In total about 67% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 22% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg rivaroxaban undergoing hip or knee replacement surgery and in hospitalised medically ill patients, bleeding events occurred in approximately 6.8% and 12.6% of patients, respectively, and anaemia occurred in approximately 5.9% and 2.1% of patients, respectively. In patients treated with either 15 mg twice daily rivaroxaban followed by 20 mg once daily for treatment of DVT or PE, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 27.8% of patients and anaemia occurred in approximately 2.2% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years. In patients treated for prevention of cardiovascular death and myocardial infarction after an acute coronary syndrome (ACS), bleeding of any type or severity was reported with an event rate of 22 per 100 patient years. Anaemia was reported with an event rate of 1.4 per 100 patient years.

Tabulated list of adverse reactions
The frequencies of adverse reactions reported with rivaroxaban are summarised in table 2 below by system organ class (in MedDRA) and by frequency.
Frequencies are defined as:
very common (> 1/10)
common (> 1/100 to < 1/10)
uncommon (> 1/1,000 to < 1/100)
rare (> 1/10,000 to < 1/1,000)
very rare ( < 1/10,000)
not known (cannot be estimated from the available data)

**Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies**

| Common | Uncommon | Rare | Not known |
|---|---|---|---|
| **Blood and lymphatic system disorders** | | | |
| Anaemia (incl. respective laboratory parameters) | Thrombocythemia (incl. platelet count increased)[A] | | |
| **Immune system disorders** | | | |
| | Allergic reaction, dermatitis allergic | | |
| **Nervous system disorders** | | | |
| Dizziness, headache | Cerebral and intracranial haemorrhage, syncope | | |
| **Eye disorders** | | | |
| Eye haemorrhage (incl. conjunctival haemorrhage) | | | |
| **Cardiac disorders** | | | |
| | Tachycardia | | |
| **Vascular disorders** | | | |
| Hypotension, haematoma | | | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Epistaxis, haemoptysis | | | |
| **Gastrointestinal disorders** | | | |
| Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A] | Dry mouth | | |
| **Hepatobiliary disorders** | | | |
| | Hepatic function abnormal | Jaundice | |
| **Skin and subcutaneous tissue disorders** | | | |
| Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage | Urticaria | | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Pain in extremity[A] | Haenarthrosis | Muscle haemorrahage | Compartment syndrome |

| | | | |
|---|---|---|---|
| | | | secondary to a bleeding |

| Common | Uncommon | Rare | Not known |
|---|---|---|---|
| **Renal and urinary disorders** | | | |
| Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)[A] | | | Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion |
| **General disorders and administration site conditions** | | | |
| Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia) | Feeling unwell (incl. malaise) | Localised oedema[A] | |
| **Investigations** | | | |
| Increase in transaminases | Increased bilirubin, increased blood alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A] | Bilirubin conjugated increased (with or without concomitant increase of ALT) | |
| **Inyury, poisoning and procedural complications** | | | |
| Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A] | | Vascular pseudoaneurysm[C] | |

A: observed in prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women <55 years

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness,

dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.
Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for rivaroxaban. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Post-marketing observations
The following adverse reactions have been reported post-marketing in temporal association with the use of rivaroxaban. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.
Immune system disorders: Angioedema and allergic oedema (In the pooled phase III trials, these events were uncommon (> 1/1,000 to < 1/100)).
Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (> 1/10,000 to < 1/1,000)).
Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (> 1/1,000 to < 1/100)).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard

## 4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.
A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).
Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor

experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects
Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.
In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.
In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.
In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).
The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative antifactor Xa tests (see section 5.2).

Clinical efficacy and safety
*Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation*
The rivaroxaban clinical program was designed to demonstrate the efficacy of rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to rivaroxaban 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.
Rivaroxaban was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism

occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 - 0.96; P<0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 - 1.03; P<0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 3.
Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).
The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 4).

**Table 3: Efficacy results from phase III ROCKET AF**

| **Study population** | **ITT analyses of efficacy in patients with non-valvular atrial fibrillation** | | |
|---|---|---|---|
| Treatment dosage | Rivaroxaban 20 mg od (15 mg od in patients with moderate renal impairment)<br><br>Event rate (100 pt-yr) | Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)<br><br>Event rate (100 pt-yr) | Hazard ratio (95% CI)<br>p-value, test for superiority |
| Stroke and non-CNS systemic embolism | 269<br>(2.12) | 306<br>(2.42) | 0.88<br>(0.74 - 1.03)<br>0.117 |
| Stroke, non-CNS systemic embolism and vascular death | 572<br>(4.51) | 609<br>(4.81) | 0.94<br>(0.84 - 1.05)<br>0.265 |
| Stroke, non-CNS systemic embolism, vascular death and myocardial infarction | 659<br>(5.24) | 709<br>(5.65) | 0.93<br>(0.83 - 1.03)<br>0.158 |
| Stroke | 253<br>(1.99) | 281<br>(2.22) | 0.90<br>(0.76 - 1.07)<br>0.221 |
| Non-CNS systemic embolism | 20<br>(0.16) | 27<br>(0.21) | 0.74<br>(0.42 - 1.32)<br>0.308 |
| Myocardial infarction | 130<br>(1.02) | 142<br>(1.11) | 0.91<br>(0.72 - 1.16)<br>0.464 |

**Table 4: Safety results from phase III ROCKET AF**

| **Study population** | **Patients with non-valvular atrial fibrillation[a)]** | | |
|---|---|---|---|
| Treatment dosage | Rivaroxaban 20 mg once a day (15 mg once a day in patients with moderate renal impairment)<br><br>Event rate (100 pt-yr) | Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)<br><br>Event rate (100 pt-yr) | Hazard ratio (95% CI) p-value |
| Major and non-major clinically relevant bleeding events | 1,475 (14.91) | 1,449 (14.52) | 1.03 (0.96 - 1.11) 0.442 |
| Major bleeding events | 395 (3.60) | 386 (3.45) | 1.04 (0.90 - 1.20) 0.576 |
| Death due to bleeding* | 27 (0.24) | 55 (0.48) | 0.50 (0.31 - 0.79) 0.003 |
| Critical organ bleeding* | 91 (0.82) | 133 (1.18) | 0.69 (0.53 - 0.91) 0.007 |
| Intracranial haemorrhage* | 55 (0.49) | 84 (0.74) | 0.67 (0.47 - 0.93) 0.019 |
| Haemoglobin drop* | 305 (2.77) | 254 (2.26) | 1.22 (1.03 - 1.44) 0.019 |
| Transfusion of 2 or more units of packed red blood cells or whole blood* | 183 (1.65) | 149 (1.32) | 1.25 (1.01 - 1.55) 0.044 |
| Non-major clinically relevant bleeding events | 1,185 (11.80) | 1,151 (11.37) | 1.04 (0.96 - 1.13) 0.345 |
| All cause mortality | 208 (1.87) | 250 (2.21) | 0.85 (0.70 - 1.02) 0.073 |

a) Safety population, on treatment
* Nominally significant

Patients undergoing cardioversion

A prospective, randomized, open-label, multicenter, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomized 2:1), for the prevention of cardiovascular events. TEE- guided (1 - 5 days of pre-treatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischemic attack, non-CNS systemic embolism, MI and cardiovascular death) occurred in 5 (0.5%) patients in the rivaroxaban group (n = 978) and 5 (1.0%) patients in the VKA group (n = 492; RR 0.50; 95 % CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6%) and 4 (0.8%) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95 % CI 0.212.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

*Treatment of DVT, PE and prevention of recurrent DVT and PE*

The rivaroxaban clinical program was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.

Over 9,400 patients were studied in three randomised controlled phase III clinical studies (Einstein DVT, Einstein PE and Einstein Extension) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range (> 2.0). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. rivaroxaban 20 mg once daily was compared with placebo.

All phase III studies used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality.

In the Einstein DVT study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ($p < 0.0001$ (test for non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.67 ((95% CI: 0.47 - 0.95), nominal p value p=0.027) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

**Table 5: Efficacy and safety results from phase III Einstein DVT**

| **Study population** | **3,449 patients with symptomatic acute deep vein thrombosis** | |
|---|---|---|
| Treatment dosage and duration | Rivaroxaban[a)]<br>3, 6 or 12 months<br>N=1,731 | Enoxaparin/VKA[b)]<br>3, 6 or 12 months<br>N=1,718 |
| Symptomatic recurrent VTE* | 36<br>(2.1%) | 51<br>(3.0%) |
| Symptomatic recurrent PE | 20<br>(1.2%) | 18<br>(1.0%) |
| Symptomatic recurrent DVT | 14<br>(0.8%) | 28<br>(1.6%) |
| Symptomatic PE and DVT | 1<br>(0.1%) | 0 |
| Fatal PE/Death where PE cannot be ruled out | 4<br>(0.2%) | 6<br>(0.3%) |
| Major or clinically relevant non-major bleeding | 139<br>(8.1%) | 138<br>(8.1%) |
| Major bleeding events | 14<br>(0.8%) | 20<br>(1.2%) |

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

* $p < 0.0001$ (non-inferiority to a prespecified hazard ratio of 2.0); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (superiority)

In the Einstein PE study (see Table 6) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); hazard ratio: 1.123 (0.749 - 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.849 ((95% CI: 0.633 - 1.139), nominal p value p= 0.275). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (p=0.082 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) were slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a hazard ratio 0.493 (95% CI: 0.308 - 0.789).

**Table 6: Efficacy and safety results from phase III Einstein PE**

| **Study population** | **4,832 patients with an acute symptomatic PE** | |
|---|---|---|
| Treatment dosage and duration | Rivaroxaban[a)] 3, 6 or 12 months N=2,419 | Enoxaparin/VKA[b)] 3, 6 or 12 months N=2,413 |
| Symptomatic recurrent VTE* | 50 (2.1%) | 44 (1.8%) |
| Symptomatic recurrent PE | 23 (1.0%) | 20 (0.8%) |
| Symptomatic recurrent DVT | 18 (0.7%) | 17 (0.7%) |
| Symptomatic PE and DVT | 0 | 2 (<0.1%) |
| Fatal PE/Death where PE cannot be ruled out | 11 (0.5%) | 7 (0.3%) |
| Major or clinically relevant non-major bleeding | 249 (10.3%) | 274 (11.4%) |
| Major bleeding events | 26 (1.1%) | 52 (2.2%) |

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

* $p < 0.0026$ (non-inferiority to a prespecified hazard ratio of 2.0); hazard ratio: 1.123 (0.749 – 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 7).

**Table 7: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE**

| **Study population** | **8,281 patients with an acute symptomatic DVT or PE** | |
|---|---|---|
| Treatment dosage and duration | Rivaroxaban[a)] 3, 6 or 12 months N=4,150 | Enoxaparin/VKA[b)] 3, 6 or 12 months N=4,131 |
| Symptomatic recurrent VTE* | 86 (2.1%) | 95 (2.3%) |
| Symptomatic recurrent PE | 43 (1.0%) | 38 (0.9%) |
| Symptomatic recurrent DVT | 32 (0.8%) | 45 (1.1%) |
| Symptomatic PE and DVT | 1 (<0.1%) | 2 (<0.1%) |
| Fatal PE/Death where PE cannot be ruled out | 15 (0.4%) | 13 (0.3%) |
| Major or clinically relevant non-major bleeding | 388 (9.4%) | 412 (10.0%) |
| Major bleeding events | 40 (1.0%) | 72 (1.7%) |

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

* $p < 0.0001$ (non-inferiority to a prespecified hazard ratio of 1.75); hazard ratio: 0.886 (0.661 - 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a hazard ratio of 0.771 ((95% CI: 0.614 - 0.967), nominal p value p= 0.0244).

In the Einstein Extension study (see Table 8) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

**Table 8: Efficacy and safety results from phase III Einstein Extension**

| Study population | 1,197 patients continued treatment and prevention of recurrent venous thromboembolism | |
|---|---|---|
| Treatment dosage and duration | Rivaroxaban[a)]<br>6 or 12 months<br>N=602 | Placebo<br>6 or 12 months<br>N=594 |
| Symptomatic recurrent VTE* | 8<br>(1.3%) | 42<br>(7.1%) |
| Symptomatic recurrent PE | 2<br>(0.3%) | 13<br>(2.2%) |
| Symptomatic recurrent DVT | 5<br>(0.8%) | 31<br>(5.2%) |
| Fatal PE/Death where PE cannot be ruled out | 1<br>(0.2%) | 1<br>(0.2%) |
| Major bleeding events | 4<br>(0.7%) | 0<br>(0.0%) |
| Clinically relevant non-major bleeding | 32<br>(5.4%) | 7<br>(1.2%) |

a) Rivaroxaban 20 mg once daily

* $p < 0.0001$ (superiority), hazard ratio: 0.185 (0.087 - 0.393)

## 5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ($C_{max}$) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or $C_{max}$ at the 2.5 mg and 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and $C_{max}$ compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and $C_{max}$

) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole

tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Distribution
Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with Vss being approximately 50 litres.

Biotransformation and elimination
Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.
Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).
Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations
*Gender*
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

*Elderly population*
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

*Different weight categories*
Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

*Inter-ethnic differences*
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

*Hepatic impairment*
Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.
The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

*Renal impairment*
There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.
Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.
Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients
In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an $E_{max}$ model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

Paediatric population
Safety and efficacy have not been established for children and adolescents up to 18 years.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.
Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.
In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and postnatal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Hydroxypropyl methyl cellulose
Sodium laurylsulphate
Magnesium stearate

Film-coat:
Macrogol 3350
Hypromellose
Titanium dioxide (E-171)
Iron oxide red (E-172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

**This medicine does not require any special storage conditions.**

### 6.5 Nature and contents of container

**Rivaroxaban 20 mg film-coated tablets is available in:**
PVC-PVdC / Aluminium blisters:
10, 14, 28, 30, 42, 56, 60, 90, 98, 168, 196 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 or in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets.
Bottles:
30, 50, 60, 90, 100, 500, 1000 film-coated tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

Distriquimica, SA, Avda. Mare de Déu de Montserrat, 221, 08041 Barcelona, Spain.

## 8. MARKETING AUTHORISATION NUMBER(S)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{MM/YYYY}

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

**Package leaflet: Information for the user**
**Rivaroxaban 2.5 mg film-coated tablets**
rivaroxaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. What Rivaroxaban Distriquimica is and what it is used for

You have been given Rivaroxaban because you have been diagnosed with an acute coronary syndrome (a group of conditions that includes heart attack and unstable angina, a severe type of chest pain) and have been shown to have had an increase in certain cardiac blood tests.
Rivaroxaban reduces the risk in adults of having another heart attack or reduces the risk of dying from a disease related to your heart or your blood vessels.
Rivaroxaban contains the active substance rivaroxaban and belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots.
Rivaroxaban will not be given to you on its own. Your doctor will also tell you to take either:
- acetylsalicylic acid (also known as aspirin) or
- acetylsalicylic acid plus clopidogrel or ticlopidine.

## 2. What you need to know before you take Rivaroxaban

**Do not take Rivaroxaban**
- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes)
- if you are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open
- if you have an acute coronary syndrome and previously had a bleeding or a blood clot in your brain (stroke)
- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast feeding

**Do not take Rivaroxaban and tell your doctor** if any of these apply to you.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Rivaroxaban.
Rivaroxaban should not be used in combination with certain other medicines which reduce blood clotting such as prasugrel or ticagrelor other than aspirin and clopidogrel/ticlopidine.

**Take special care with Rivaroxaban**
- if you have an increased risk of bleeding, as could be the case in situations such as:
  - severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section "Other medicines and Rivaroxaban ")
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet) e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus)
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
  - you are older than 75 years
  - you weigh 60 kg or less

**If any of the above apply to you, tell your doctor** before you take Rivaroxaban. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

**If you need to have an operation:**
- it is very important to take Rivaroxaban before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):

  - it is very important to take Rivaroxaban before and after the injection or removal of the catheter exactly at the times you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

**Children and adolescents**
Rivaroxaban is **not recommended for people under 18 years of age.** There is not enough information on its use in children and adolescents.

**Other medicines and Rivaroxaban**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

- **If you are taking:**
  - some medicines for fungal infections (e.g. ketoconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - some anti-viral medicines for HIV / AIDS (e.g. ritonavir)
  - other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol)
  - anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid)
  - dronedarone, a medicine to treat abnormal heart beat

**If any of the above apply to you, tell your doctor** before taking Rivaroxaban, because the effect of Rivaroxaban may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.
If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

- **If you are taking:**
- some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
- St John's Wort *(Hypericum perforatum)*, a herbal product used for depression
- rifampicin, an antibiotic

**If any of the above apply to you, tell your doctor** before taking Rivaroxaban, because the effect of Rivaroxaban may be reduced. Your doctor will decide, if you should be treated with Rivaroxaban and if you should be kept under closer observation.

**Pregnancy and breast feeding**
Do not take Rivaroxaban if you are pregnant or breast feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Rivaroxaban. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

**Driving and using machines**
Rivaroxaban may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, 'Possible side effects'). You should not drive or use machines if you are affected by these symptoms.

**Rivaroxaban contains lactose**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Rivaroxaban

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

**How much to take**
The recommended dose is one 2.5 mg tablet twice a day. Take Rivaroxaban around the same time every day (for example, one tablet in the morning and one in the evening). This medicine can be taken with or without food.
If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Rivaroxaban. The tablet may be crushed and mixed with water or apple puree immediately before you take it.
If necessary, your doctor may also give you the crushed Rivaroxaban tablet through a stomach tube.
Rivaroxaban will not be given to you on its own. Your doctor will also tell you to take either:
- acetylsalicylic acid (also known as aspirin) or
- acetylsalicylic acid plus clopidogrel or ticlopidine.

Your doctor will tell you how much of these to take (usually between 75 to 100 mg acetylsalicylic acid daily or a daily dose of 75 to 100 mg acetylsalicylic acid plus a daily dose of either 75 mg clopidogrel or a standard daily dose of ticlopidine).

**When to start Rivaroxaban**
Treatment with Rivaroxaban should be started as soon as possible after stabilisation of the acute coronary syndrome, at the earliest 24 hours after admission to hospital and at the time when parenteral (via

injection) anticoagulation therapy would normally be stopped. Your doctor will decide how long you must continue treatment.

**If you take more Rivaroxaban than you should**
Contact your doctor immediately if you have taken too many Rivaroxaban tablets. Taking too much Rivaroxaban increases the risk of bleeding.

**If you forget to take Rivaroxaban**
Do not take a double dose to make up for a missed dose. If you miss a dose, take your next dose at the usual time.

**If you stop taking Rivaroxaban**
Take Rivaroxaban on a regular basis and for as long as your doctor keeps prescribing it.
Do not stop taking Rivaroxaban without talking to your doctor first. If you stop taking this medicine, it may increase your risk of having another heart attack or stroke or dying from a disease related to your heart or your blood vessels.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, Rivaroxaban can cause side effects, although not everybody gets them.
Like other similar medicines (antithrombotic agents), Rivaroxaban may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

**Possible side effects which may be a sign of bleeding:**
**Tell your doctor immediately** if you experience any of the following side effects:
- long or excessive bleeding
- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris, which may be signs of bleeding.

Your doctor may decide to keep you under closer observation or change how you should be treated.

**Overall list of possible side effects:**

**Common** (may affect up to 1 in 10 people):
- bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum
- bleeding into the eye (including bleeding from the whites of the eyes)
- bleeding into tissue or a cavity of the body (haematoma, bruising)
- coughing up blood
- bleeding from the skin or under the skin
- bleeding following an operation
- oozing of blood or fluid from surgical wound
- swelling in the limbs
- pain in the limbs
- fever
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- stomach ache, indigestion, feeling or being sick, constipation, diarrhoea
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness
- rash, itchy skin
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- blood tests may show an increase in some liver enzymes

**Uncommon** (may affect up to 1 in 100 people):
- bleeding into the brain or inside the skull
- bleeding into a joint causing pain and swelling
- fainting
- feeling unwell
- dry mouth
- faster heartbeat
- allergic reactions, including allergic skin reactions
- hives
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets

**Rare** (may affect up to 1 in 1,000 people):
- bleeding into a muscle
- localised swelling
- yellowing of the skin and eye (jaundice)
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

**Not known** (frequency cannot be estimated from the available data):
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)
- kidney failure after a severe bleeding

The following side effects have been reported since authorisation:
- Angioedema and allergic oedema (swelling of the face, lips, mouth, tongue or throat)
- Cholestasis (decreased bile flow), Hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- Thrombocytopenia (low number of platelets, which are cells that help blood to clot).

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard.

By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Rivaroxaban

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Rivaroxaban contains**
- The active substance is rivaroxaban. Each tablet contains 2.5 mg of rivaroxaban.
- The other ingredients are:

Tablet core: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, sodium lauryl sulphate, magnesium stearate and hydroxypropyl methyl cellulose.
Tablet film coat: macrogol 3350, hypromellose, titanium dioxide (E-171), iron oxide yellow (E-172).

**What Rivaroxaban looks like and contents of the pack**
Rivaroxaban 2.5 mg film-coated tablets are yellow, round, biconvex, debossed with "E21" on one side and plain on the other side.

Rivaroxaban 2.5 mg film-coated tablets is available in PVC-PVdC / Aluminium blisters:
10, 14, 28, 30, 42, 56, 60, 90, 98, 168 or 196 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 or in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Distriquimica, S.A.,
Avda. Mare de Déu de Montserrat, 221,
08041, Barcelona, Spain

**Manufacturer**
Laboratorios Dr. Esteve, S.A.,
C/Sant Martí s/n, Polígono Industrial,
08107, Martorelles, Barcelona, Spain.

Pharmadox Healthcare Ltd.
KW20A Kordin Industrial Park
Paola - PLA3000 – Malta

**This leaflet was last revised in** {MM/YYYY}.

**Package leaflet: Information for the user**
**Rivaroxaban 10 mg film-coated tablets**
rivaroxaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

## 1. What Rivaroxaban is and what it is used for

Rivaroxaban contains the active substance rivaroxaban and is used in adults to prevent blood clots in the veins after a hip or knee replacement operation. Your doctor has prescribed this medicine for you because after an operation you are at an increased risk of getting blood clots.
Rivaroxaban belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots.

## 2. What you need to know before you take Rivaroxaban

**Do not take Rivaroxaban**
- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g. stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes)
- if you are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open
- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast feeding

**Do not take Rivaroxaban and tell your doctor** if any of these apply to you.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Rivaroxaban.

**Take special care with Rivaroxaban**
- if you have an increased risk of bleeding, as could be the case in situations such as:
  - moderate or severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section "Other medicines and Rivaroxaban ")
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet) e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus)
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung

**If any of the above apply to you, tell your doctor** before you take Rivaroxaban. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.
If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
- it is very important to take Rivaroxaban exactly at the times you have been told by your doctor
- tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

**Children and adolescents**
Rivaroxaban is **not recommended for people under 18 years of age.** There is not enough information on its use in children and adolescents.

**Other medicines and Rivaroxaban**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

- **If you are taking:**
  - some medicines for fungal infections (e.g. ketoconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - some anti-viral medicines for HIV / AIDS (e.g. ritonavir)
  - other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol)
  - anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid)
  - dronedarone, a medicine to treat abnormal heart beat

  **If any of the above apply to you, tell your doctor** before taking Rivaroxaban, because the effect of Rivaroxaban may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.
  If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.
- **If you are taking:**
  - some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
  - St John's Wort *(Hypericum perforatum),* a herbal product used for depression
  - rifampicin, an antibiotic

  **If any of the above apply to you, tell your doctor** before taking Rivaroxaban, because the effect of Rivaroxaban may be reduced. Your doctor will decide, if you should be treated with Rivaroxaban and if you should be kept under closer observation.

**Pregnancy and breast feeding**
Do not take Rivaroxaban if you are pregnant or breast feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Rivaroxaban. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

**Driving and using machines**
Rivaroxaban may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4 'Possible side effects'). You should not drive or use machines if you are affected by these symptoms.

**Rivaroxaban contains lactose**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Rivaroxaban

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

**How much to take**
The recommended dose is one tablet (10 mg) once a day. Swallow the tablet preferably with water. Rivaroxaban can be taken with or without food.
If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Rivaroxaban. The tablet may be crushed and mixed with water or apple puree immediately before you take it.
If necessary, your doctor may also give you the crushed Rivaroxaban tablet through a stomach tube.

**When to take Rivaroxaban**
Take the first tablet 6 - 10 hours after your operation.
Then take a tablet every day until your doctor tells you to stop.
Try to take the tablet at the same time every day to help you to remember it.
If you have had a major hip operation you will usually take the tablets for 5 weeks.
If you have had a major knee operation you will usually take the tablets for 2 weeks.

**If you take more Rivaroxaban than you should**
Contact your doctor immediately if you have taken too many Rivaroxaban tablets. Taking too much Rivaroxaban increases the risk of bleeding.

**If you forget to take Rivaroxaban**
If you have missed a dose, take it as soon as you remember. Take the next tablet on the following day and then carry on taking a tablet once a day as normal. Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Rivaroxaban**
Do not stop taking Rivaroxaban without talking to your doctor first, because Rivaroxaban prevents the development of a serious condition.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, Rivaroxaban can cause side effects, although not everybody gets them.
Like other similar medicines (antithrombotic agents), Rivaroxaban may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

**Possible side effects which may be a sign of bleeding:**
**Tell your doctor immediately,** if you experience any of the following side effects:
- long or excessive bleeding
- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris, which may be signs of bleeding.

Your doctor may decide to keep you under closer observation or change how you should be treated.

**Overall list of possible side effects:**

**Common** (may affect up to 1 in 10 people):
- bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum
- bleeding into the eye (including bleeding from the whites of the eyes)
- bleeding into tissue or a cavity of the body (haematoma, bruising)
- coughing up blood
- bleeding from the skin or under the skin
- bleeding following an operation
- oozing of blood or fluid from surgical wound
- swelling in the limbs
- pain in the limbs
- fever
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- stomach ache, indigestion, feeling or being sick, constipation, diarrhoea
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness
- rash, itchy skin
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- blood tests may show an increase in some liver enzymes

**Uncommon** (may affect up to 1 in 100 people):
- bleeding into the brain or inside the skull
- bleeding into a joint causing pain and swelling

- fainting
- feeling unwell
- dry mouth
- faster heartbeat
- allergic reactions, including allergic skin reactions
- hives
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets

**Rare** (may affect up to 1 in 1,000 people):
- bleeding into a muscle
- localised swelling
- yellowing of the skin and eye (jaundice)
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

**Not known** (frequency cannot be estimated from the available data):
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)
- kidney failure after a severe bleeding

The following side effects have been reported since authorisation:
- Angioedema and allergic oedema (swelling of the face, lips, mouth, tongue or throat)
- Cholestasis (decreased bile flow), Hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
7. - Thrombocytopenia (low number of platelets, which are cells that help blood to clot).

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard.
By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Rivaroxaban

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or blister or bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Rivaroxaban contains**
- The active substance is rivaroxaban. Each tablet contains 10 mg of rivaroxaban.
- The other ingredients are:
  Tablet core: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, sodium lauryl sulphate, magnesium stearate and hydroxypropyl methyl cellulose.
  Tablet film coat: macrogol 3350, hypromellose, titanium dioxide (E-171), iron oxide red (E-172).

**What Rivaroxaban looks like and contents of the pack**
Rivaroxaban 10 mg film-coated tablets are pink, round, biconvex, debossed with "E2" on one site and plain on other side.

Rivaroxaban 10 mg film-coated tablets is available in:
PVC-PVdC / Aluminium blisters:
5, 10, 14, 28, 30, 42, 56, 60, 90, 98, 168, 196 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 or in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets.
Bottles:
30, 50, 60, 90, 100, 500, 1000 film-coated tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Distriquimica, S.A.,
Avda. Mare de Déu de Montserrat, 221,
08041, Barcelona, Spain

**Manufacturer**
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KW20A Kordin Industrial Park
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**This leaflet was last revised in** {MM/YYYY}.

**Package leaflet: Information for the user**
**Rivaroxaban 15 mg film-coated tablets**
**Rivaroxaban 20 mg film-coated tablets**
rivaroxaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. What Rivaroxaban is and what it is used for

Rivaroxaban contains the active substance rivaroxaban and is used in adults to:
- prevent blood clots in brain (stroke) and other blood vessels in your body if you have a form of irregular heart rhythm called non-valvular atrial fibrillation.
- treat blood clots in the veins of your legs (deep vein thrombosis) and in the blood vessels of your lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of your legs and/or lungs.

Rivaroxaban belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots.

## 2. What you need to know before you take Rivaroxaban

**Do not take Rivaroxaban**
- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes)
- if you are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open.
- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast feeding

**Do not take Rivaroxaban and tell your doctor** if any of these apply to you.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Rivaroxaban.

**Take special care with Rivaroxaban**

- if you have an increased risk of bleeding, as could be the case in situations such as:
  - severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section "Other medicines and Rivaroxaban ")
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet) e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus)
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
- if you have a prosthetic heart valve
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned

**If any of the above apply to you, tell your doctor** before you take Rivaroxaban. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

**If you need to have an operation:**
- it is very important to take Rivaroxaban before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to take Rivaroxaban before and after the injection or removal of the catheter exactly at the times you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

**Children and adolescents**
Rivaroxaban is **not recommended for people under 18 years of age.** There is not enough information on its use in children and adolescents.

**Other medicines and Rivaroxaban**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.
- **If you are taking:**
  - some medicines for fungal infections (e.g. ketoconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - some anti-viral medicines for HIV / AIDS (e.g. ritonavir)
  - other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol)
  - anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid)
  - dronedarone, a medicine to treat abnormal heart beat

  **If any of the above apply to you, tell your doctor** before taking Rivaroxaban Distriquimica, because the effect of Rivaroxaban may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

  If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

- **If you are taking:**
  - some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
  - St John's Wort *(Hypericum perforatum)*, a herbal product used for depression
  - rifampicin, an antibiotic

**If any of the above apply to you, tell your doctor** before taking Rivaroxaban, because the effect of Rivaroxaban may be reduced. Your doctor will decide, if you should be treated with Rivaroxaban and if you should be kept under closer observation.

**Pregnancy and breast feeding**
Do not take Rivaroxaban if you are pregnant or breast feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Rivaroxaban. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

**Driving and using machines**
Rivaroxaban may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, 'Possible side effects'). You should not drive or use machines if you are affected by these symptoms.

**Rivaroxaban contains lactose**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Rivaroxaban

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

**How much to take**
- To prevent blood clots in brain (stroke) and other blood vessels in your body.
  The recommended dose is one 20 mg tablet once a day.
  If you have kidney problems, the dose may be reduced to one 15 mg tablet once a day.

- To treat blood clots in the veins of your legs and blood clots in the blood vessels of your lungs, and for preventing blood clots from re-occurring
  The recommended dose is one 15 mg tablet twice a day for the first 3 weeks. For treatment after 3 weeks, the recommended dose is one 20 mg tablet once a day.
  If you have kidney problems, your doctor may decide to reduce the dose for the treatment after 3 weeks to one 15 mg tablet once a day if the risk for bleeding is greater than the risk for having another blood clot.

Swallow the tablet(s) preferably with water. Take Rivaroxaban together with a meal.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Rivaroxaban. The tablet may be crushed and mixed with water or apple puree immediately before you take it. This mixture should be immediately followed by food.
If necessary, your doctor may also give you the crushed Rivaroxaban tablet through a stomach tube.

**When to take Rivaroxaban**
Take the tablet(s) every day until your doctor tells you to stop.
Try to take the tablet(s) at the same time every day to help you to remember it.
Your doctor will decide how long you must continue treatment.
To prevent blood clots in the brain (stroke) and other blood vessels in your body:
If your heart beat needs to be restored to normal by a procedure called cardioversion, take Rivaroxaban at the times your doctor tells you.

**If you take more Rivaroxaban than you should**
Contact your doctor immediately if you have taken too many Rivaroxaban tablets. Taking too much Rivaroxaban increases the risk of bleeding.

**If you forget to take Rivaroxaban**
- If you are taking one 20 mg tablet or one 15 mg tablet once a day and have missed a dose, take it as soon as you remember. Do not take more than one tablet in a single day to make up for a forgotten

dose. Take the next tablet on the following day and then carry on taking one tablet once a day.

- If you are taking one 15 mg tablet twice a day and have missed a dose, take it as soon as you remember. Do not take more than two 15 mg tablets in a single day. If you forget to take a dose you can take two 15 mg tablets at the same time to get a total of two tablets (30 mg) on one day. On the following day you should carry on taking one 15 mg tablet twice a day.

**If you stop taking Rivaroxaban**
Do not stop taking Rivaroxaban without talking to your doctor first, because Rivaroxaban treats and prevents serious conditions.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, Rivaroxaban can cause side effects, although not everybody gets them.

Like other similar medicines (antithrombotic agents), Rivaroxaban may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

**Possible side effects which may be a sign of bleeding:**
**Tell your doctor immediately** if you experience any of the following side effects:
- long or excessive bleeding
- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris, which may be signs of bleeding.

Your doctor may decide to keep you under closer observation or change how you should be treated.

**Overall list of possible side effects:**

**Common** (may affect up to 1 in 10 people):
- bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum
- bleeding into the eye (including bleeding from the whites of the eyes)
- bleeding into tissue or a cavity of the body (haematoma, bruising)
- coughing up blood
- bleeding from the skin or under the skin
- bleeding following an operation
- oozing of blood or fluid from surgical wound
- swelling in the limbs
- pain in the limbs
- fever
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- stomach ache, indigestion, feeling or being sick, constipation, diarrhoea
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness
- rash, itchy skin
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- blood tests may show an increase in some liver enzymes

**Uncommon** (may affect up to 1 in 100 people):
- bleeding into the brain or inside the skull
- bleeding into a joint causing pain and swelling
- fainting
- feeling unwell
- dry mouth
- faster heartbeat
- allergic reactions, including allergic skin reactions

- hives
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets

**Rare** (may affect up to 1 in 1,000 people):
- bleeding into a muscle
- localised swelling
- yellowing of the skin and eye (jaundice)
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

**Not known** (frequency cannot be estimated from the available data):
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)
- kidney failure after a severe bleeding

The following side effects have been reported since authorisation:
- Angioedema and allergic oedema (swelling of the face, lips, mouth, tongue or throat)
- Cholestasis (decreased bile flow), Hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- Thrombocytopenia (low number of platelets, which are cells that help blood to clot).

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard.
By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Rivaroxaban

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton or bottle or blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Rivaroxaban contains**
The active substance is rivaroxaban. Each tablet contains 15 mg or 20 mg of rivaroxaban.
The other ingredients are:
Tablet core: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, sodium lauryl sulphate, magnesium stearate and hydroxypropyl methyl cellulose.
Tablet film coat for 15 mg: macrogol 3350, polyvinyl alcohol-partially hydrolyzed, titanium dioxide (E 171), iron oxide red (E 172) and talc.
Tablet film coat for 20 mg: macrogol 3350, hypromellose, titanium dioxide (E 171), iron oxide red (E 172).

**What Rivaroxaban looks like and contents of the pack**
Rivaroxaban 15 mg film-coated tablets are red, round, biconvex, debossed with “E3” on one side and plain on other side.

Rivaroxaban 20 mg film-coated tablets are red, round, biconvex, debossed with “E4” on one side and plain on other side.

Rivaroxaban 15 mg film-coated tablets is available in:
PVC-PVdC / Aluminium blisters:
10, 14, 28, 30, 42, 56, 60, 90, 98, 168, 196 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 or in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets.
Bottles:
30, 50, 60, 90, 100, 500, 1000 film-coated tablets.

Rivaroxaban 20 mg film-coated tablets is available in:
PVC-PVdC / Aluminium blisters:
10, 14, 28, 30, 42, 56, 60, 90, 98, 168, 196 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 or in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets.
Bottles:
30, 50, 60, 90, 100, 500, 1000 film-coated tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

Distriquimica, S.A.,
Avda. Mare de Déu de Montserrat, 221,
08041, Barcelona, Spain

**Manufacturer**

Laboratorios Dr. Esteve, S.A.,
C/Sant Martí s/n, Polígono Industrial,
08107, Martorelles, Barcelona, Spain.

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Paola - PLA3000 – Malta

**This leaflet was last revised in** {MM/YYYY}.

## *Annex 3 - Worldwide marketing authorisation by country (including EEA)*

### *A3.1 Licensing status in the EEA*

Not applicable.

### *A3.2 Licensing status in the rest of the world*

Not applicable.

## *Annex 4 - Synopsis of on-going and completed clinical trial programme*

Not applicable.

## *Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme*

Not applicable.

## *Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III*

Not applicable.

### *Annex 7 - Specific adverse event follow-up forms*

Not applicable.

## *Annex 8 - Protocols for proposed and on-going studies in RMP part IV*

Not applicable.

### *Annex 9 - Newly available study reports for RMP parts III & IV*

Not applicable.

***Annex 10 - Details of proposed additional risk minimisation measures (if applicable).***

| **Safety concern (important identified risk)** | **Haemorrhage** |
|---|---|
| Risk minimisation measure(s) | ➢ Patient alert cards are introduced to reinforce patient counselling about key safety reminders during treatment with rivaroxaban, and as a consequence to redude the risk of bleeding. Patient alert cards must contain the following information:<br>• Signs or symptoms of bleeding and when to seek attention from a health care provider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient Alert Card that is included in each pack, with them at all times<br>• The need to inform Health Care Professionals that they are taking Rivaroxaban distriquimica if they need to have any surgery or invasive procedure.<br>A patient alert card will be part of the package insert and by this be included in every package of rivaroxaban. (see Part VII Annex 10)<br>➢ A prescriber guide for each indication will be prepared prior to launch of the medicinal product. The prescriber guide should contain the following key safety messages:<br>• Details of populations potentially at higher risk of bleeding<br>• Recommendations for dose reduction in at risk populations<br>• Guidance regarding switching from or to rivaroxaban treatment<br>➢ The need for intake of the 15 mg and 20 mg tablets with food<br>➢ Management of overdose situations<br>➢ The use of coagulation tests and their interpretation<br>➢ That all patients should be provided with a Patient alert card and be counselled about:<br>• Signs or symptoms of bleeding and when to seek attention from a health |

| Safety concern (important identified risk) | Haemorrhage |
|---|---|
| | careprovider.<br>• Importance of treatment compliance<br>• The need for intake of the 15 mg and 20 mg tablets with food<br>• Necessity to carry the Patient alert card with them at all times<br>• The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure. |
| Objective and rational | These measures were implemented to alert patients to the risk of haemorrhage when taking rivaroxaban and to prevent the use of rivaroxaban in patients with increased haemorrhage risks. |
| Main additional risk minimisation measures | None |

## *Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)*

**Patient Alert Card**
Company (logo)

**Rivaroxaban 2.5 mg film-coated tablets**
**Rivaroxaban 10 mg film-coated tablets**
**Rivaroxaban 15 mg film-coated tablets**
**Rivaroxaban 20 mg film-coated tablets**

- **Keep this card with you at all times**
- **Present this card to every physician or dentist prior to treatment**

**I am under anticoagulation treatment with Rivaroxaban (rivaroxaban)**
Name: Address:
Birth date: Blood
type: Weight:
Other medications / conditions:

**In case of emergency, please notify:**
Doctor's name: Doctor's
phone: Doctor's stamp:

**Please also notify:**
Name: Phone:
Relationship:

**Information for health care providers:**
- INR values should not be used as they are not a dependable measure of the anticoagulant activity of Rivaroxaban.

**What should I know about Rivaroxaban?**
- **Rivaroxaban** thins the blood, which prevents you from getting dangerous blood clots.
- Rivaroxaban must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, never skip a dose.
- You must not stop taking Rivaroxaban without first talking to your doctor as your risk of blood clots may increase.
- Tell your health care provider about any other medicines you are currently taking, took recently or intend to start taking, before you start Rivaroxaban
- Tell your health care provider that you are taking Rivaroxaban before any surgery or invasive procedure.

**When should I seek advice from my health care provider?**
When taking a blood thinner such as Rivaroxaban it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start taking Rivaroxaban if you know you are at risk of bleeding, without first discussing this with your doctor. Tell your health care provider straight away if you have any signs or symptoms of bleeding such as the following:
- pain
- swelling or discomfort
- headache, dizziness or weakness
- unusual bruising, nosebleeds, bleeding of gums, cuts that take a long time to stop bleeding
- menstrual flow or vaginal bleeding that is heavier than normal
- blood in your urine which may be pink or brown, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds

**How do I take Rivaroxaban?**

- To ensure optimal protection, Rivaroxaban
  - 2.5 mg can be taken with or without food
  - 15 mg must be taken with food
- 20 mg must be taken with food

### *Annex 12 - Other supporting data (including referenced material)*


1. Hilal Maradit Kremers, MD et al. Prevalence of total hip (THA) and total knee (TKA) arthroplasty in the United States.J Bone Joint Surg Am, 2015 Sep 02; 97 (17): 1386 - 1397.

2. OECD (2012), Hip and knee replacement, in Health at a Glance: Europe 2012, OECD Publishing.

3. Januel JM, Chen G, Ruffieux C, et al. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: A systematic review. 2012. JAMA 307 (3): 294–303.

4. Beckman MG et al. Venous thromboembolism: a public health concern. Am J Prev Med. 2010 Apr;38(4 Suppl):S495-501.

5. Massimo Zoni-Berisso et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014; 6: 213–220.

6. Mary Cushman et al. Epidemiology and Risk Factors for Venous Thrombosis, Seminars in Hematology, Volume 44, Issue 2, April 2007, Pages 62-69.

7. Roger VL et al.American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012 Jan 3;125(1):e2-e220.