1. NAME OF THE MEDICINAL PRODUCT

Xarelto 1 mg/mL granules for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The granules contain 19.7 mg rivaroxaban per gram.
Each bottle contains 51.7 mg rivaroxaban or 103.4 mg rivaroxaban.
Following reconstitution the oral suspension contains 1 mg rivaroxaban per mL.

Excipient with known effect
Each mL of the reconstituted oral suspension contains 1.8 mg sodium benzoate (E 211), see section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral suspension
White granules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

4.2 Posology and method of administration

Posology
The dose and frequency of administration are determined based on body weight (see Table 1).

Table 1: Recommended dose for Xarelto in paediatric patients from full-term neonates (following at least 10 days of oral feeding and weighing at least 2.6 kg) to children less than 18 years of age

Bodyweight [kg]		**Regimen Dose rivaroxaban**			**Total daily dose**	**Suitable blue syringe**
		(1 mg rivaroxaban corresponds to 1 mL of the suspension)				
Min	**Max**	**once a day**	**2 times a day**	**3 times a day**		
2.6	< 3			0.8 mg	2.4 mg	1 mL
3	< 4			0.9 mg	2.7 mg	1 mL
4	< 5			1.4 mg	4.2 mg	5 mL
5	< 7			1.6 mg	4.8 mg	5 mL
7	< 8			1.8 mg	5.4 mg	5 mL
8	< 9			2.4 mg	7.2 mg	5 mL
9	< 10			2.8 mg	8.4 mg	5 mL
10	< 12			3.0 mg	9.0 mg	5 mL
12	< 30		5 mg		10 mg	5 mL or 10 mL
30	< 50	15 mg			15 mg	10 mL
≥ 50		20 mg			20 mg	10 mL

The weight of the child should be monitored and the dose reviewed regularly, especially for children below 12 kg. This is to ensure that a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.

Frequency of dosing:

- *For a once a day regimen*
  The doses should be taken approximately 24 hours apart.
- *For a two times a day regimen*
  The doses should be taken approximately 12 hours apart.
- *For a three times a day regimen*
  The doses should be taken approximately 8 hours apart.

For patients with body weight of at least 2.6 kg to less than 30 kg only the oral suspension should be used. Do not split Xarelto tablets or use Xarelto tablets of lower strength in an attempt to provide doses for children with body weight below 30 kg.
For patients with body weight of at least 30 kg, Xarelto oral suspension or tablets of 15 mg or 20 mg strength can be administered once a day.

Xarelto oral suspension is provided with either 1 mL or 5 mL and 10 mL blue syringes (oral dosing syringe) with their adapter. To ensure accurate dosing it is recommended to use the blue syringes as follows (see Table 1):

- 1 mL blue syringe (with 0.1 mL graduations) for patients weighing less than 4 kg
- 5 mL blue syringe (with 0.2 mL graduations) for patients weighing 4 kg up to less than 30 kg
- 10 mL blue syringe (with 0.5 mL graduations) for patients weighing 12 kg or more

For patients weighing 12 kg up to less than 30 kg, either 5 mL or 10 mL blue syringes can be used.
It is recommended that the healthcare professional advises the patient or caregiver which blue syringe to use to ensure that the correct volume is administered.
Instructions for Use booklet is provided with the medicinal product.

Initiation of treatment

- *Paediatric patients from term neonates to less than 6 months*
  Treatment for paediatric patients from term neonates to less than 6 months of age, who at birth had at least 37 weeks of gestation, weigh at least 2.6 kg, and have had at least 10 days of oral feeding should be initiated following at least 5 days of initial parenteral anticoagulation

treatment (see sections 4.4 and 5.1). Xarelto is dosed based on body weight using the oral suspension formulation (see Table 1).

- *Paediatric patients from 6 months of age to less than 18 years*
  Treatment for paediatric patients from 6 months to less than 18 years of age should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section 5.1). Xarelto is dosed based on body weight (see Table 1).

Duration of treatment

- *All children, except those aged less than 2 years with catheter-related thrombosis*
  Therapy should be continued for at least 3 months. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

- *Children aged less than 2 years with catheter-related thrombosis*
  Therapy should be continued for at least 1 month. Treatment can be extended up to 3 months when clinically necessary. The benefit-risk of continued therapy after 1 month should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

Missed doses

- *Once a day regimen*
  If taken once a day, a missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

- *Two times a day regimen*
  If taken twice a day, a missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken during the same evening, the patient should not take two doses the next morning.

- *Three times a day regimen*
  If taken three times a day, the three times daily administration schedule with approximately 8-hour intervals should simply be resumed at the next scheduled dose without compensating for the missed dose.

On the following day, the child should continue with the regular once, twice or three times daily regimen.

Converting from parenteral anticoagulants to Xarelto
For patients currently receiving a parenteral anticoagulant, start Xarelto 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

Converting from Xarelto to parenteral anticoagulants
Discontinue Xarelto and give the first dose of parenteral anticoagulant at the time that the next Xarelto dose would be taken.

Converting from Vitamin K antagonists (VKA) to Xarelto

VKA treatment should be stopped and Xarelto therapy should be initiated once the International Normalised Ratio (INR) is ≤ 2.5.
When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

Converting from Xarelto to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.
Children who convert from Xarelto to VKA need to continue Xarelto for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Xarelto. Co-administration of Xarelto and VKA is advised to continue until the INR is ≥ 2.0. Once Xarelto is discontinued INR testing may be done reliably 24 hours after the last dose (see above and section 4.5).

Special populations
Renal impairment

- Children 1 year or older with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m^2): no dose adjustment is required, based on data in adults and limited data in paediatric patients (see section 5.2).
- Children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2): Xarelto is not recommended as no clinical data is available (see section 4.4).
- Children below 1 year: the renal function should only be determined using serum creatinine. Xarelto is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile (see Table 2), as no data are available (see section 4.4).

Table 2: Reference values of serum creatinine in children younger than 1 year of age (Boer et al, 2010)

Age	**97.5th percentile of creatinine (µmol/L)**	**97.5th percentile of creatinine (mg/dL)**
Day 1	81	0.92
Day 2	69	0.78
Day 3	62	0.70
Day 4	58	0.66
Day 5	55	0.62
Day 6	53	0.60
Day 7	51	0.58
Week 2	46	0.52
Week 3	41	0.46
Week 4	37	0.42
Month 2	33	0.37
Month 3	30	0.34
Month 4–6	30	0.34
Month 7–9	30	0.34
Month 10–12	32	0.36

Hepatic impairment
No clinical data is available in children with hepatic impairment.

Xarelto 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 and 5.2).

Body weight
For children the dose is determined based on body weight (see Posology above).

Gender
No dose adjustment (see section 5.2)

Paediatric population
The safety and efficacy of Xarelto in children aged 0 to < 18 years have not been established in indications other than treatment of venous thromboembolism (VTE) and prevention of VTE recurrence. No or insufficient data are available for other indications (see also section 5.1). Therefore, Xarelto is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

Method of administration
Xarelto is for oral use.
The oral suspension should be taken with feeding or with food (see section 5.2).

For details on preparation and administration of the oral suspension see section 6.6.
The oral suspension may be given through a nasogastric or gastric feeding tube (see sections 5.2 and 6.6).

Each dose should be immediately followed by the intake of one typical serving of liquid. This typical serving may include liquid volume used for feeding.
In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered and the next dose should be taken as scheduled.

If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering it orally (see sections 5.2 and 6.6).

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.

Dosing of rivaroxaban cannot be reliably determined in the following patient populations and was not studied. It is therefore not recommended in children less than 6 months of age who:

- at birth had less than 37 weeks of gestation, or
- have a body weight of less than 2.6 kg, or
- had less than 10 days of oral feeding.

Haemorrhagic risk

As with other anticoagulants, patients taking Xarelto are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xarelto administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequent 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 and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at an 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).

There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection (see section 5.1). The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

Renal impairment

Xarelto is not recommended in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data is available.
Xarelto is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

Interaction with other medicinal products

No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp.
Xarelto 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 or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). 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 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 cancer
Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy.
In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see section 4.3).

Patients with prosthetic valves
Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that this medicinal product provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

Patients with antiphospholipid syndrome
Direct acting oral anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

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

Spinal/epidural anaesthesia or lumbar 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 rivaroxaban in these situations.
To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or lumbar 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 and should be weighed against the urgency of a diagnostic procedure.
No data is available on the timing of the placement or removal of neuraxial catheter in children while on Xarelto. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

Dosing recommendations before and after invasive procedures and surgical intervention
If an invasive procedure or surgical intervention is required, Xarelto 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.
Xarelto 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).

Dermatological reactions
Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Information about excipients
Xarelto granules for oral suspension contains 1.8 mg sodium benzoate (E 211) in each mL oral suspension. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn infants (up to 4 weeks old). Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

This medicinal product contains less than 1 mmol sodium (23 mg) per millilitre, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

The extent of interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

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 Xarelto 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}. The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (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}. The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients.
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}. The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (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).

SSRIs/SNRIs
As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

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, anti-factor 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 C_{trough} 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 lactation

Pregnancy
Safety and efficacy of Xarelto 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, Xarelto is contraindicated during pregnancy (see section 4.3).
Female adolescents of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding
Safety and efficacy of Xarelto have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto 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

Xarelto 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 thirteen pivotal phase III studies (see Table 1).

Overall, 69,608 adult patients in nineteen phase III studies and 488 paediatric patients in two phase II and two phase III studies were exposed to rivaroxaban.

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

Indication	**Number of patients***	**Total 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 VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis	6,790	Day 1 - 21: 30 mg	21 months

Indication	Number of patients*	Total daily dose	Maximum treatment duration
(DVT), pulmonary embolism (PE) and prevention of recurrence		Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 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
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

* Patients exposed to at least one dose of rivaroxaban

** From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years #	0.74 per 100 patient years*** #

* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.

** In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied

*** A selective approach to adverse event collection was applied

\# From the VOYAGER PAD study

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto in adult and paediatric patients are summarised in Table 3 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 3: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use* and in two phase II and two phase III studies in paediatric patients

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A], thrombocytopenia			
Immune system disorders				
	Allergic reaction, dermatitis allergic, angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
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			Eosinophilic pneumonia	
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				
Increase in transaminases	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]	Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)		

Common	Uncommon	Rare	Very rare	Not known
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome	
Musculoskeletal and connective tissue disorders				
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
Renal and urinary disorders				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion, Anticoagulant-related nephropathy
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				
	Increased LDH[A], increased lipase[A], increased amylase[A]			
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]		Vascular pseudoaneurysm[C]		

A: observed in prevention of 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)

* A pre-specified selective approach to adverse event collection was applied in selected phase III studies.. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

Description of selected adverse reactions
Due to the pharmacological mode of action, the use of Xarelto 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 including abnormal vaginal or increased menstrual bleeding) 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 and quantify the clinical relevance of overt 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 section 4.4 “Haemorrhagic risk”). 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, or anticoagulant-related nephropathy have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

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 the Yellow Card Scheme, Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In adults, rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section “Management of bleeding”). There is limited data available in children. 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 in adults, however no data is available at supratherapeutic doses in children.
A specific reversal agent antagonising the pharmacodynamic effect of rivaroxaban is not established in children.
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

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 in adults. The half-life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter (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 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 medicinal products in adults and in children receiving rivaroxaban (see section 5.1).

Protamine sulphate 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 adults receiving rivaroxaban. There is no experience on the use of these agents in children receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, 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 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 routine clinical practice. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

Paediatric population
PT (neoplastin reagent), aPTT, and anti-Xa assay (with a calibrated quantitative test) display a close correlation to plasma concentrations in children. The correlation between anti-Xa to plasma concentrations is linear with a slope close to 1. Individual discrepancies with higher or lower anti-Xa

values as compared to the corresponding plasma concentrations may occur. There is no need for routine monitoring of coagulation parameters during clinical treatment with rivaroxaban. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests in mcg/L (see Table 8 in section 5.2 for ranges of observed rivaroxaban plasma concentrations in children). The lower limit of quantifications must be considered when the anti-Xa test is used to quantify plasma concentrations of rivaroxaban in children. No threshold for efficacy or safety events has been established.

Clinical efficacy and safety

Treatment of VTE and prevention of VTE recurrence in paediatric patients

A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in 6 open-label, multicentre paediatric studies. Body weight-adjusted dosing in patients from birth to less than 18 years resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily as confirmed in the phase III study (see section 5.2).

The EINSTEIN Junior phase III study was a randomised, active-controlled, open-label multicentre clinical study in 500 paediatric patients (aged from birth to < 18 years) with confirmed acute VTE. There were 276 children aged 12 to < 18 years, 101 children aged 6 to < 12 years, 69 children aged 2 to < 6 years, and 54 children aged < 2 years.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE; 90/335 patients in the rivaroxaban group, 37/165 patients in the comparator group), cerebral vein and sinus thrombosis (CVST; 74/335 patients in the rivaroxaban group, 43/165 patients in the comparator group), and all others including DVT and PE (non-CVC-VTE; 171/335 patients in the rivaroxaban group, 85/165 patients in the comparator group). The most common presentation of index thrombosis in children aged 12 to < 18 years was non-CVC-VTE in 211 (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST in 48 (47.5%) and 35 (50.7%), respectively; and in children aged < 2 years was CVC-VTE in 37 (68.5%). There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a CNS infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

VTE was provoked by persistent, transient, or both persistent and transient risk factors in 438 (87.6%) children.

Patients received initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for at least 5 days, and were randomised 2:1 to receive either body weight-adjusted doses of rivaroxaban or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). At the end of the main study treatment period, the diagnostic imaging test, which was obtained at baseline, was repeated, if clinically feasible. The study treatment could be stopped at this point, or at the discretion of the Investigator continued for up to 12 months (for children < 2 years with CVC-VTE up to 3 months) in total.

The primary efficacy outcome was symptomatic recurrent VTE. The primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding (CRNMB). All efficacy and safety outcomes were centrally adjudicated by an independent committee blinded for treatment allocation. The efficacy and safety results are shown in Tables 6 and 7 below.

Recurrent VTEs occurred in the rivaroxaban group in 4 of 335 patients and in the comparator group in 5 of 165 patients. The composite of major bleeding and CRNMB was reported in 10 of 329 patients (3%) treated with rivaroxaban and in 3 of 162 patients (1.9%) treated with comparator. Net clinical benefit (symptomatic recurrent VTE plus major bleeding events) was reported in the rivaroxaban group in 4 of 335 patients and in the comparator group in 7 of 165 patients. Normalisation of the thrombus burden on repeat imaging occurred in 128 of 335 patients with rivaroxaban treatment and in 43 of 165patients in the comparator group. These findings were generally similar among age groups.

There were 119 (36.2%) children with any treatment-emergent bleeding in the rivaroxaban group and 45 (27.8%) children in the comparator group.

Table 6: Efficacy results at the end of the main treatment period

Event	**Rivaroxaban N=335***	**Comparator N=165***
Recurrent VTE (primary efficacy outcome)	4 (1.2%, 95% CI 0.4% – 3.0%)	5 (3.0%, 95% CI 1.2% - 6.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%, 95% CI 0.6% – 3.4%)	6 (3.6%, 95% CI 1.6% – 7.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%, 95% CI 4.0% – 9.2%)	19 (11.5%, 95% CI 7.3% – 17.4%)
Normalisation on repeat imaging	128 (38.2%, 95% CI 33.0% - 43.5%)	43 (26.1%, 95% CI 19.8% - 33.0%)
Composite: Symptomatic recurrent VTE + major bleeding (net clinical benefit)	4 (1.2%, 95% CI 0.4% - 3.0%)	7 (4.2%, 95% CI 2.0% - 8.4%)
Fatal or non-fatal pulmonary embolism	1 (0.3%, 95% CI 0.0% – 1.6%)	1 (0.6%, 95% CI 0.0% – 3.1%)

* FAS = full analysis set, all children who were randomised

Table 7: Safety results at the end of the main treatment period

	Rivaroxaban N=329*	**Comparator N=162***
Composite: Major bleeding + CRNMB (primary safety outcome)	10 (3.0%, 95% CI 1.6% - 5.5%)	3 (1.9%, 95% CI 0.5% - 5.3%)
Major bleeding	0 (0.0%, 95% CI 0.0% - 1.1%)	2 (1.2%, 95% CI 0.2% - 4.3%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)

* SAF = safety analysis set, all children who were randomised and received at least 1 dose of study medicinal product

The efficacy and safety profile of rivaroxaban was largely similar between the paediatric VTE population and the DVT/PE adult population, however, the proportion of subjects with any bleeding was higher in the paediatric VTE population as compared to the DVT/PE adult population.

Thromboprophylaxis in Paediatric Patients with Congenital Heart Disease after the Fontan Procedure

The efficacy and safety of rivaroxaban for thromboprophylaxis in 110 paediatric patients with congenital heart disease who have undergone the Fontan procedure within 4 months prior to enrolment was evaluated in a prospective, open-label, 2-part (part B active-controlled) study (UNIVERSE) where rivaroxaban was used for thromboprophylaxis for 12 months compared with acetylsalicylic acid in children 2 to 8 years of age with single ventricle physiology who had the Fontan procedure. Patients received either body weight-adjusted doses of rivaroxaban ([n=76], exposures to match that of 10 mg daily dose in adults) or acetylsalicylic acid ([n=34] approximately

5 mg/kg). The dosing studied in UNIVERSE for thromboprophylaxis was thus lower and cannot be derived from the approved paediatric dose for the treatment of VTE.
Few thromboembolic events were observed in the UNIVERSE study (rivaroxaban group (1 [1.6%]) vs acetylsalicylic acid group (3 [8.8%])) and the amount of bleeding events was similar between study arms with 5 (7.8%) clinically relevant bleedings (including 1 major) in the rivaroxaban group versus 3 (8.8%; none of which major) in the acetylsalicylic acid group.

Patients with high risk triple positive antiphospholipid syndrome
In an investigator sponsored, randomised open-label multicentre study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) < 50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

5.2 Pharmacokinetic properties

Absorption
The following information is based on the data obtained in adults.
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.
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 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.
Bioequivalence was demonstrated for the granules for oral suspension formulation compared to the marketed tablet at the 10 mg dose in fasted state as well as for the 20 mg dose 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.

Paediatric population

Children received a rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as a tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children is available so the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food.
Rivaroxaban oral suspension should be taken with feeding or with food (see section 4.2).

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

Paediatric population
In vitro data does not indicate relevant differences in rivaroxaban plasma protein binding in children across different age groups and compared to adults. No PK data following intravenous administration of rivaroxaban to children is available. V_{ss} estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 113 L for a subject with a body weight of 82.8 kg.

Biotransformation and elimination
In adults, 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.

Paediatric population
No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition half-lives ($t_{1/2}$) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2-12 years down to 1.9 and 1.6 h in children aged 0.5-< 2 years and less than 0.5 years, respectively.

Special populations
Hepatic impairment
No clinical data is available in children with hepatic impairment. In adults, 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
No clinical data is available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2) or in children younger than 1 year with serum creatinine results above 97.5th percentile (see section 4.4).
In adults, 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.

Gender
In adults, there were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients. An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children.

Different weight categories
In adults, extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). In children, rivaroxaban is dosed based on body weight. An exploratory analysis in children did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure.

Inter-ethnic differences
In adults, no clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.
An exploratory analysis did not reveal relevant inter-ethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall paediatric population.

<u>Pharmacokinetic data in patients</u>
In paediatric patients with acute VTE receiving body weight-adjusted rivaroxaban leading to an exposure similar to that in adult DVT patients receiving a 20 mg once daily dose, the geometric mean concentrations (90% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 8.

Table 8: Summary statistics (geometric mean (90% interval)) of rivaroxaban steady state plasma concentrations (mcg/L) by dosing regimen and age

Time intervals								
o.d.	**N**	**12 - < 18 years**	**N**	**6 -< 12 years**				
2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
b.i.d.	**N**	**6 -< 12 years**	**N**	**2 -< 6 years**	**N**	**0.5 -< 2 years**		
2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
t.i.d.	**N**	**2 -< 6 years**	**N**	**Birth - < 2 years**	**N**	**0.5 -< 2 years**	**N**	**Birth - < 0.5 years**
0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
7-8h post	5	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated
Values below lower limit of quantification (LLOQ) were substituted by ½ LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

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 mcg/L). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

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 post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

Rivaroxaban was tested in juvenile rats up to 3-month treatment duration starting at postnatal day 4 showing a non dose-related increase in periinsular haemorrhage. No evidence of target organ-specific toxicity was seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous (E 330)
Hypromellose (2910)
Mannitol (E 421)
Microcrystalline cellulose and carmellose sodium
Sodium benzoate (E 211)
Sucralose (E 955)
Xanthan gum (E 415)
Flavour sweet and creamy: flavouring substances, maltodextrin (maize), propylene glycol (E 1520) and acacia gum (E 414).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
After reconstitution the suspension is stable for 14 days.

6.4 Special precautions for storage

Do not store above 30 °C.
Do not freeze.
Store the prepared suspension upright.

6.5 Nature and contents of container

Xarelto 1 mg/mL granules for oral suspension is packed in a folding box containing:

- For children weighing **less than 4 kg**:
  - 2.625 g granules, corresponding to 51.7 mg rivaroxaban, in 1 brown glass bottle, for reconstitution in 50 mL water, closed with a child resistant screw cap
  - 2 blue syringes 1 mL with 0.1 mL marked graduations
  - 1 adapter for bottles and blue syringes
  - 1 water syringe 50 mL with 1 mL marked graduations

or

- For children weighing **4 kg and more**:
  - 5.25 g granules, corresponding to 103.4 mg rivaroxaban, in 1 brown glass bottle, for reconstitution in 100 mL water, closed with a child resistant screw cap
  - 2 blue syringes 5 mL with 0.2 mL marked graduations
  - 2 blue syringes 10 mL with 0.5 mL marked graduations
  - 1 adapter for bottles and blue syringes
  - 1 water syringe 100 mL with 2 mL marked graduations

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Suspension

Before administration the granules must be suspended into a homogenous suspension with non-carbonated water giving a final concentration of 1 mg per mL.
The amount of water to be used is:

- 50 mL for the bottle containing 2.625 g granules (51.7 mg of rivaroxaban), resulting in 51.7 mL total volume after reconstitution
- 100 mL for the bottle containing 5.25 g granules (103.4 mg of rivaroxaban), resulting in 103.4 mL total volume after reconstitution

The bottle has to be shaken after reconstitution for 60 seconds and before each dose for 10 seconds.
After reconstitution the medicinal product is a white to off-white suspension.
For dose administration after reconstitution, the blue syringes (1 mL, 5 mL or 10 mL) are provided (see section 4.2, Table 1).
Complete details on preparation and administration of the oral suspension can be found in the Instructions for Use that is provided with the medicinal product or in an educational video which can be accessed via QR code displayed on the Patient Alert Card that is also provided with the medicinal product.

The suspension may be given through a nasogastric or gastric feeding tube. Gastric placement of the tube should be confirmed before administering Xarelto. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. After the administration, the feeding tube should be flushed with water. This should then be immediately followed by nasogastric or gastric feeding.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer plc, 400 South Oak Way, Reading, RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00010/0746

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

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