CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Rivaroxaban Medreg
Rivaroxaban

SK/H/0279/001-004/DC

Date: 04/2025

This module reflects the scientific discussion for the approval of Rivaroxaban Medreg. The procedure was finalised on 16 March 2023 (D210). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rivaroxaban Medreg, film-coated tablets, 2.5 mg, 10 mg, 15 mg, and 20 mg, from Medreg s.r.o., Czech Republic.

The product is indicated for*:*

Rivaroxaban Medreg 2.5 mg
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.

Co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

Rivaroxaban Medreg 10 mg
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Rivaroxaban Medreg 15 mg and 20 mg
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.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

A CMDh discussion was held during the second phase of the assessment of this marketing authorisation application regarding paediatric indication of 15 mg and 20 mg strengths. For more details see section VI.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as a film-coated tablet containing 2.5 mg, 10 mg, 15 mg, or 20 mg of rivaroxaban as an active substance. Film-coated tablets are packed in PVC/PVDC/Al blisters inserted into a carton box.

Appearance of the tablets:
2.5 mg
Approximately 6 mm, yellow coloured, round, biconvex film-coated tablets marked with “2.5” on one side.

10 mg
Approximately 6 mm, peach coloured, round, biconvex film-coated tablets marked with “10” on one side.

15 mg
Approximately 6 mm, light orange coloured, round, biconvex film-coated tablets marked with “15” on one side.

20 mg
Approximately 7 mm, orange coloured, round, biconvex film-coated tablets marked with “20” on one side.

Available pack sizes are as follows:
2.5 mg: 14, 20, 28, 30, 56, 60, 98, 100, 168 or 196 film-coated tablets
10 mg: 5, 10, 14, 28, 30, 98 or 100 film-coated tablets
15 mg: 10, 14, 28, 42, 98 or 100 film-coated tablets
20 mg: 10, 14, 28, 98 or 100 film-coated tablets

The other ingredients are:

Tablet core of 2.5 mg, 10 mg, 15 mg, 20 mg tablet:
lactose monohydrate
sodium laurilsulfate
hypromellose (type 2910)
croscarmellose sodium
cellulose, microcrystalline
magnesium stearate
silica, colloidal anhydrous

Film-coating 2.5 mg:
Opadry Yellow 04F520016:
hypromellose (type 2910)
titanium dioxide (E171)
macrogol 3350 (E1521)
tartrazine aluminium lake (E102)
indigo carmine aluminium (E132)
sunset yellow FCF aluminium lake (E110)

Film-coating 10 mg:
Opadry Orange 04F530012:
hypromellose (type 2910)
titanium dioxide (E171)
macrogol 3350 (E1521)
talc (E553b)
sunset yellow FCF aluminium lake (E110)
iron oxide red (E172)

Film-coating 15 mg:
Opadry Orange 04F530006:
hypromellose (type 2910)
titanium dioxide (E171)
macrogol 3350 (E1521)
sunset yellow FCF aluminium lake (E110)
iron oxide red (E172)

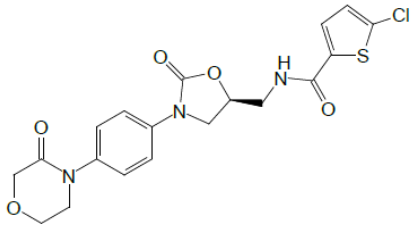
Film-coating 20 mg:
Opadry Orange 04F530010:

hypromellose (type 2910)
titanium dioxide (E171)
macrogol 3350 (E1521)
sunset yellow FCF aluminium lake (E110)
iron oxide red (E172)
iron oxide yellow (E172)
iron oxide black (E172)

II.2 Drug Substance

Rivaroxaban

Active substance structure:



Empirical formula: $C_{19}H_{18}ClN_3O_5S$

Chemical name: 5- chloro- *N*- ({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl) thiophene-2-carboxamide

Appearance: White to off-white powder.

Solubility: Rivaroxaban is insoluble in acetone, practically insoluble in methanol, very slightly soluble in tetrahydrofuran, slightly soluble in acetonitrile and glacial acetic acid and soluble in dimethylformamide and dimethyl sulfoxide.

Chirality: Rivaroxaban contains one stereogenic centre. The enantiomer produced by the manufacturer is the (S)-configuration. The (R)-enantiomer corresponds to impurity A. Impurity A is controlled in the drug substance specification.

Manufacturing: Even though the active substance, rivaroxaban, is described in Ph.Eur.
Active substance master file (ASMF) procedure was followed and approved for this drug substance.

Specifications: The specification of the active pharmaceutical ingredient (API) includes test methods in accordance with the Ph.Eur. monograph for rivaroxaban and, additionally, tests for residual solvents and particle size distribution.

Stability: The API is packed in a double polyethylene bag contained in polyethylene drums. The proposed re-test period of 5 years was considered acceptable.

II.3 Medicinal Product

Pharmaceutical development

As rivaroxaban has poor aqueous solubility, the excipients that were selected shall help in improving the solubility of the API. Initial development trials were executed to evaluate process feasibility, to check the dissolutions and to evaluate the stability. Development was initiated with wet granulation

process. Test products manufactured had similar *in-vitro* performance including dissolution profiles in comparison the reference medicinal product. Development by wet granulation was discontinued to overcome the patent claims of reference medicinal product in presenting the drug in hydrophilized form in the finished drug product.

Development was then performed by two approaches: direct compression (using placebo granules) and dry granulation. These approaches were selected to prevent the hydrophilization of the API during unit operations of wet granulation. Finally, dry granulation was selected.

Manufacturing

The finished product is manufactured by dry granulation (roller compaction) and a detailed description of the process has been provided in the dossier. In brief, it involves air jet milling of the API with excipients, manufacturing of blend for roller compaction, granulation and manufacturing of compression mixture, tabletting and film-coating.

Specification

The finished product release and shelf-life specifications include appropriate tests and limits for description (visual), uniformity of dosage units (Ph.Eur), identification (HPLC, UV), water by Karl-Fischer (Ph.Eur), dissolution (Ph.Eur), related substances (HPLC), assay (HPLC), and microbiological quality (Ph.Eur). The proposed specification for the finished product is in line with ICH Q6A.

Stability

Stability data were provided for three batches of each strength, under long-term and accelerated conditions which were packed in PVC/PVdC-Alu blister as proposed for marketing. The proposed shelf life of 3 years (36 months) was considered acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Quality part of the dossier was adequately presented. Discussion about an azo dye in film-coating of 15 mg and 20 mg tablet led to carving out of paediatric indication for those strengths (see part VI).

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of rivaroxaban are well known. As rivaroxaban is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies were not required. Overview based on literature review was, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The consumption data of rivaroxaban in kg/year over the period of 4 years (2017-2020) in RMS (SK) and two CMS countries (CZ and RO) were provided. Data showed visibly increasing trend during those 4 years in all observed countries.

The marketing authorisation of Rivaroxaban Medreg was considered to contribute to further increase of overall amount of consumed drug substance per year in any member state involved (RMS and CMSs). Therefore, applicant was asked to submit ERA in line with the Guideline on the

environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

The applicant submitted a written commitment that the ERA will be performed in the post-authorisation phase.

III.3 Discussion on the non-clinical aspects

Sufficient references to published non-clinical data were provided for this generic application, which was considered adequate. Applicant committed to finalise ERA assessment in the post-authorisation phase, which was endorsed by the RMS.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview based on the clinical pharmacology, efficacy and safety was adequate.

The applicant conducted three bioequivalence studies (under fasting conditions with 2.5 mg and 10 mg strengths and under fed conditions with 20 mg strength) as recommended in product specific bioequivalence guidance (PSBGL) for rivaroxaban (EMA/CHMP/PKWP/151340/2015), and proposed an extrapolation to the strength 15 mg which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

The following three studies were submitted to support the bioequivalence assessment of Rivaroxaban Medreg:

1. **Study (CLCD-098-15):** A randomized, balanced, open label, two treatments, four period, two sequence, single oral dose, crossover, fully replicate, pivotal, bioequivalence study of rivaroxaban film-coated tablets 10 mg and Xarelto 10 mg film-coated tablets of Bayer Pharma AG, Germany in healthy, adult, human, male subjects under fasting condition.

Results of study (CLCD-098-15)

Pharmacokinetic parameters for rivaroxaban in study (CLCD-098-15)

Pharmacokinetic Parameter (Units)	Arithmetic Means (± SD) (n=46)	
	Test Product - T	Reference Product - R
*T_{max} (hr)	2.50 (1.00, 5.00)	2.33 (0.66, 5.00)
C_{max} (ng/mL)	251.59 ± 59.741	214.63 ± 56.830
AUC_{0-t} (ng*hr/mL)	1784.61 ± 391.450	1611.05 ± 349.194
AUC_{0-inf} (ng*hr/mL)	1892.96 ± 415.113	1754.00 ± 377.073

* Median, Min and Max values reported for T_{max}

The 90% confidence intervals rivaroxaban mean treatment T/R ratios in bioequivalence evaluation of rivaroxaban 10 mg in study (CLCD-098-15)

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	110.54	106.63-114.58	14.58
C_{max}	117.64	112.00-123.55	19.98

[1] Estimated from the Residual Mean Squares

Additional pharmacokinetic data for rivaroxaban 10 mg in study (CLCD-098-15)

Plasma concentration curves where	Related Information
$AUC_{(0-t)}$ / $AUC_{(0-\infty)}$ <0.8	No
C_{max} is the first point	None
Pre-dose sample >5% C_{max}	None

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

C_{max} Maximum plasma concentration

t_{max} Time until Cmax is reached

Conclusion on study (CLCD-098-15)

Based on the submitted bioequivalence study rivaroxaban film-coated tablets 10 mg is considered bioequivalent with Xarelto 10 mg.

2. **Study (CLCD-099-15):** A randomized, balanced, open label, two treatments, two period, two sequence, single oral dose, crossover, pivotal, bioequivalence study of rivaroxaban film-coated tablets 20 mg and Xarelto 20 mg film-coated tablets of Bayer Pharma AG, Germany in healthy, adult, human, male subjects under fed condition.

Results of study (CLCD-099-15)

Pharmacokinetic parameters for rivaroxaban 20 mg in study (CLCD-099-15)

Pharmacokinetic Parameter (Units)	Arithmetic Means (± SD) (n=18)	
	Test Product - T	Reference Product - R
*T_{max} (hr)	4.17 (1.33, 5.52)	2.50 (1.33, 5.50)
C_{max} (ng/mL)	437.70 ± 52.646	414.98 ± 72.424
AUC_{0-t} (ng*hr/mL)	3575.68 ± 561.403	3617.38 ± 628.955
AUC_{0-inf} (ng*hr/mL)	3638.70 ± 589.843	3693.11 ± 644.554

* Median, Min and Max values reported for T_{max}

The 90% confidence intervals rivaroxaban mean treatment T/R ratios in bioequivalence evaluation of rivaroxaban 20 mg in study (CLCD-099-15)

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	99.07	93.95 - 104.48	9.15
C_{max}	106.34	100.37 - 112.66	9.96

[1]Estimated from the Residual Mean Squares.

Additional pharmacokinetic data for rivaroxaban 20 mg in study CLCD-099-15

Plasma concentration curves where	Related Information
$AUC_{(0-t)}/AUC_{(0-\infty)}$ <0.8	No
C_{max} is the first point	None
Pre-dose sample > 5% C_{max}	None

Conclusion on study (CLCD-099-15)

Based on the submitted bioequivalence study rivaroxaban film-coated tablets 20 mg is considered bioequivalent with Xarelto 20 mg when studied in healthy, adult, male human subjects under fed condition.

3. **Study (18-VIN-0451):** An open label, balanced, randomized, single-dose, two-treatments, two-sequence, two-period, two-way crossover, oral bioequivalence study of rivaroxaban 2.5 mg film-coated tablets and Xarelto 2.5 mg film-coated tablets of Bayer AG, Germany in healthy, adult, human, male subjects under fasting condition.

Results of study (18-VIN-0451)

Pharmacokinetic parameters for rivaroxaban 2.5 mg in study 18-VIN-0451

Pharmacokinetic Parameter (Units)	Arithmetic Means (± SD) (n=54)	
	Test Product - T	Reference Product - R
*T_{max} (hr)	2.330 (0.75, 4.67)	2.000 (0.75, 4.00)
C_{max} (ng/mL)	81.791 ± 21.933	82.423 ± 18.6035
AUC_{0-t} (ng*hr/mL)	507.310 ± 120.1265	497.433 ± 122.3736
AUC_{0-inf} (ng*hr/mL)	523.239 ± 126.9957	509.887 ± 129.7386

* Median, Min and Max values reported for T_{max}

The 90% confidence intervals rivaroxaban 2.5 mg mean treatment T/R ratios in bioequivalence evaluation of rivaroxaban in study 18-VIN-0451

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	102.19	99.55 - 104.89	8.13
C_{max}	98.30	94.11 - 102.67	13.56

[1]Estimated from the Residual Mean Squares.

Additional pharmacokinetic data for rivaroxaban 2.5 mg in study 18-VIN-0451

Plasma concentration curves where	Related Information
$AUC_{(0-t)}/AUC_{(0-\infty)}$ <0.8	No
C_{max} is the first point	None
Pre-dose sample > 5% C_{max}	None

Conclusion on study (18-VIN-0451)

Based on the submitted bioequivalence study rivaroxaban 2.5 mg film-coated tablets is considered bioequivalent with Xarelto 2.5 mg under fasting conditions.

Biowaiver

BCS-based biowaiver approach/biowaiver for additional strength: As per Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1/Corr**), all conditions were fulfilled for rivaroxaban film-coated tablets to allow extrapolation of the results of the presented bioequivalence study on the 20 mg strength to 15 mg strength. No further bioequivalence studies were required as 15 mg strength is dose weight proportional to 20 mg formulation, shows comparative dissolution and exhibits linear pharmacokinetics when given with food.

Dissolution profiles comparing test bio-batch and reference product of 10 mg, 20 mg and 2.5 mg strength at 0.1 N HCl, pH 4.5 and 6.8 were provided by the applicant.
Dissolution profiles comparing test and reference products used in the bioequivalence studies (all three strengths) were not comparable in multiple pHs. As the bioequivalence studies showed the bioequivalence between test and reference product, this was accepted. The applicant has submitted proper justification for the identified discrepancy of dissolution profiles between test and reference products, thus resolving it sufficiently.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rivaroxaban Medreg.

- Summary table of safety concerns as approved in RMP

Important identified risks	Haemorrhage
Important potential risks	Embryo-foetal toxicity
Missing information	Remedial pro-coagulant therapy for excessive haemorrhage Patients with atrial fibrillation (AF) and a prosthetic heart valve

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Haemorrhage	Routine risk minimisation measures: *SmPC section 4.3 Contraindications*	**Routine PV activities:** AE/ADR collection, evaluation, and reporting Signal detection Periodic analysis and update on

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	SmPC section 4.4 Special Warnings and precautions for use *SmPC section 4.8 Undesirable effects* *PL section 2 What you need to know before you take Rivaroxaban Medreg* *PL section 3 How to take Rivaroxaban Medreg* *PL section 4 Possible side effects* Prescription-only medicine Limited pack sizes <u>Additional risk minimisation measures:</u> *Patient Alert Card* *Prescriber Guide*	'haemorrhage', including different subcategories (e.g. critical organ bleeding, fatal bleeding, etc.) in every PBRER/PSUR – if required **Additional PV activities:** None
Important Potential Risks		
Embryo-foetal toxicity	<u>Routine risk minimisation measures:</u> *SmPC section 4.3 Contraindications* *SmPC section 4.6 Fertility, pregnancy and lactation* *SmPC section 5.3 Preclinical safety data* Prescription-only medicine Limited pack sizes <u>Additional risk minimisation measures:</u> No risk minimisation measures	**Routine PV activities:** AE/ADR collection, evaluation, and reporting Signal detection Periodic analysis and update on 'embryo-foetal toxicity', including updates of pregnancy reports and maternal exposure and breast-feeding incl. outcome (if available) in every PBRER/PSUR – if required **Additional PV activities:** None
Missing Information		
Remedial pro-coagulant therapy for excessive haemorrhage	<u>Routine risk minimisation measures:</u> *SmPC section 4.9 Overdose* Prescription-only medicine Limited pack sizes <u>Additional risk minimisation measures:</u> No risk minimisation measures	**Routine PV activities:** AE/ADR collection, evaluation and reporting Signal detection **Additional PV activities:** None
Patients with atrial fibrillation (AF) and a prosthetic heart valve	<u>Routine risk minimisation measures:</u> *SmPC section 4.4 Special warnings and precaution for use* Prescription-only medicine Limited pack sizes <u>Additional risk minimisation measures:</u> No risk minimisation measures	**Routine PV activities:** AE/ADR collection, evaluation and reporting Signal detection **Additional PV activities:** None

IV.4 Discussion on the clinical aspects

Submitted clinical dossier was of sufficient quality. Submitted data supported the chosen legal basis "generic application".
Based on the results of submitted three bioequivalence studies it was concluded, that Rivaroxaban Medreg 2.5 mg, 10 mg and 20 mg is bioequivalent with Xarelto 2.5 mg, 10 mg and 20 mg. A BSC-based biowaiver for 15 mg strength was accepted because it is dose weight proportional to 20 mg formulation, shows comparative dissolution and exhibits linear pharmacokinetics when given with food.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results show that the package leaflet of Rivaroxaban Medreg 15 mg and 20 mg meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

A user consultation with target patient groups on the package leaflet (PL) of Rivaroxaban Medreg 2.5 mg and 10 mg has been performed based on a bridging report referring to Rivaroxaban Medreg 15 mg and 20 mg (SK/H/0279/003,004/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This was an application for a marketing authorisation (MAA) of medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended. Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS. The applicant Medreg s.r.o., Czech Republic, has submitted this MAA under procedural number SK/H/0279/001-004/DC.

Reference medicinal product was Xarelto, film-coated tablets from Bayer AG, Germany authorised in the European Union via centralised procedure (EMEA/H/C/944) since 30 September 2008.

Based on the results of submitted three bioequivalence studies it was concluded, that Rivaroxaban Medreg 2.5 mg, 10 mg and 20 mg is bioequivalent with Xarelto 2.5 mg, 10 mg and 20 mg. A BSC-based biowaiver for 15 mg strength was accepted because it is dose weight proportional to 20 mg formulation, shows comparative dissolution and exhibits linear pharmacokinetics when given with food.

Quality aspects of the dossier were adequately described; specifications of API rivaroxaban were approved in the ASMF procedure and that of finished medicinal product are in line with ICH Q6A.

There was a discussion in the CMDh. A potential serious risk to public health (PSRPH) was raised regarding the content of an azo dye (sunset yellow FCF) in two strengths 15 mg and 20 mg for which a paediatric indication was sought for. After the CMDh discussion and break-out session with the applicant, they decided to withdraw the paediatric indication.

Eventually, after withdrawal of paediatric indication in strengths 15 mg and 20 mg and based on

submitted data the member states considered that the essential similarity and safety with the reference medicinal product Xarelto film-coated tablets was adequately demonstrated and have, therefore, granted the marketing authorisation. This decentralised procedure was positively concluded on 16 March 2023 (D210).

VI.1 Proposed list of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

MAH shall submit the ERA in line with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2) in post-authorisation phase of DCP SK/H/0279/001-004/DC.

VI.2 Proposed list of conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC

Additional risk minimisation measures (including educational material)

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use this medicinal product. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with rivaroxaban and providing guidance on how to manage that risk.
The physician educational pack should contain:
• The Summary of Product Characteristics
• Prescriber Guide
• Patient Alert Cards

The MAH must agree the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory. The Prescriber Guide should contain the following key safety messages:
• Details of populations potentially at higher risk of bleeding
• Recommendations for dose reduction in at risk populations
• Guidance regarding switching from or to rivaroxaban treatment
• The need for intake of the 15 mg and 20 mg tablets with food
• Management of overdose situations
• The use of coagulation tests and their interpretation
• That all patients should be counselled about:
- Signs or symptoms of bleeding and when to seek attention from a health care provider.
- Importance of treatment compliance
- The need for intake of the 15 mg and 20 mg tablets with food
- Necessity to carry the Patient Alert Card that is included in each pack, with them at all times
- The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure.