FINAL CPTHN GUIDANCE DOCUMENT, September 2021

RIVAROXABAN USE IN PEDIATRIC PATIENTS

***** All children <18 years of age requiring rivaroxaban should be managed in consultation with a Pediatric Hematologist *****

Objective:

To discuss indications, dosing, monitoring, side effects, and special considerations for the use of rivaroxaban in the neonatal and pediatric populations.

Background:

Rivaroxaban is an oral Factor Xa inhibitor, approved for use in the pediatric population in Canada in January 2021. Evidence for use is based on the EINSTEIN Jr trials which were randomized, multi-centred trials assessing the pharmacokinetics, efficacy and safety of rivaroxaban in children. The EINSTEIN Jr phase III trial specifically used weight adjusted regimens for rivaroxaban dosing and showed non-inferiority to standard anticoagulants (low molecular weight heparin or vitamin K antagonist) and a similar safety profile. The study treatment period was 3 months with the exception of catheter-related VTE in children younger than 2 years, for whom it was 1 month. Children received at least 5 days of initial heparinization before starting rivaroxaban treatment. Bodyweight adjusted 20 mg equivalent dosing was based on phase 1 and 2 data. In total, 335 children were allocated to rivaroxaban, 5.7% excluded. Symptomatic recurrent VTE occurred in 2 children (0.6%) during treatment. No major bleeds occurred on treatment.

Indications and considerations for use:

Rivaroxaban is currently licensed for children < 18 years of age in Canada for the following:

- Treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence.
- Children younger than 6 months should be prescribed rivaroxaban only if they meet the following criteria:
    - Weight ≥ 2.6 kg
    - Gestational age of birth at least 37 weeks
    - Oral/nasogastric tube (NGT) feeding for at least 10 days

Dosing Regimens:

After a minimum of 5 days of anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), the following dosing regimen can be considered, as taken directly from the EINSTEIN Jr Trial.

Bodyweight, kg		Rivaroxaban dose (mg) regimens used in phase 3	
		Total Daily dose	Regimen
Min	**Max**	2.4	0.8 TID
3	<4	2.7	0.9 TID
4	<5	4.2	1.4 TID
5	<7	4.8	1.6 TID
7	<8	5.4	1.8 TID
8	<9	7.2	2.4 TID
9	<10	8.4	2.8 TID
10	<12	9.0	3.0 TID
12	<30	10.0	5.0 BID
30	<50	15.0	15.0 OD
≥ 50	120	20.0	20.0 OD

Administration:

Rivaroxaban can be administered in tablet form or via oral suspension. Tablets should be swallowed with liquid. The oral suspension, granules must be suspended with water into a homogenous solution. The concentration of the reconstituted suspension is 1 mg/ml. The bottle should be shaken after reconstitution and before each dose. Complete details on preparation and administration of the oral suspension can be found in the Instructions for Use booklet that is provided with the medicinal product. Rivaroxaban should be taken with food.

Monitoring:

- Prior to initiating rivaroxaban, baseline laboratory evaluation including coagulation (PTT/INR), complete blood count, AST, ALT, bilirubin, and creatinine are recommended. Creatinine clearance/eGFR should be maintained > 30 mL/min per 1.73 m^2.
- Rivaroxaban does not require routine monitoring. If there is a need to monitor for circumstances such as acute bleed, overdose, urgency of surgery, non-compliance, obtaining a PT using neoplastin reagent may be useful, as it is a reagent that is sensitive to rivaroxaban. Factor Xa assays calibrated to rivaroxaban levels can measure a wide range of concentrations.
- Using a neoplastin reagent, a Rivaroxaban concentration of 301 ug/l has shown to double PT in human plasma. Using an Innovin reagent, a concentration of 700 ug/l is required to double PT.
- Factor Xa can be measured using Rivaroxaban calibration curves and can generally measure a wide range of concentrations (20 – 500 ng/mL) with variability between institutions.
- If the treating clinician chooses to extend treatment beyond 3 months for ongoing risk factors, we suggest clinical assessments at least every 3 months to review compliance, bleeding risks, medication changes, health changes, and activity changes. Periodic clinical assessments may also provide an opportunity for regular re-education.

Adverse Effects:

The major adverse effect of rivaroxaban is bleeding. EINSTEIN Jr Phase III trial showed no major bleeding events. Clinically relevant non-major bleeding occurred in 3.2% and trivial bleeding was observed in 35.1%.

Bleeding management: Consult a pediatric hematologist. Current management of bleeds in patients on rivaroxaban are supportive and include resuscitation, local control of bleeding, holding further doses of rivaroxaban, and blood product support based on the clinical scenario. Blood products such as packed red blood cells, platelets, plasma, cryoprecipitate/fibrinogen can be used to correct detected abnormalities, as required. Consider platelet transfusion if <50 or <100 if there is critical organ bleeding. Limited evidence is available for the use of pro-hemostatic agents. However, it can be considered in significant bleeding. Andexanet alfa is the FDA approved reversal agent for rivaroxaban, however it has not been trialed in pediatrics and is not approved in Canada. For further details, refer to Thrombosis Canada's Clinical Guide: "NOACs/DOACs: Management of Bleeding".

Overdose management: Consult a pediatric hematologist and inform poison control. There is a lack of evidence to guide management of overdose.

Procedures:

Rivaroxaban should be held for 24 hours prior to procedures with mild or moderate bleeding risk and 48 hours prior to procedures with high bleeding risk. Rivaroxaban can be restarted once adequate hemostasis has been achieved and in consultation with the surgical team. For lumbar punctures (LP) in children, we suggest holding Rivaroxaban for 24 hours prior to procedure and resuming after a minimum 6 to 12 hours (in the absence of a traumatic LP). The management may need to be case specific in patients with other bleeding risks (e.g., thrombocytopenia). For further details refer to Thrombosis Canada's Clinical Guide: "NOACs/DOACs: Peri-operative management".

TABLE 1. BLEEDING RISK ASSOCIATED WITH INVASIVE/SURGICAL PROCEDURES

MILD/MODERATE RISK	HIGH RISK
- Dental extractions - Dermatologic procedures (e.g., biopsy) - Endoscopy or colonoscopy (+/- biopsies) - Bone marrow biopsy - Lumbar puncture - Other abdominal surgery (e.g., laparoscopic cholecystectomy, hernia repair) - Other orthopedic surgery - Ophthalmologic surgery	- Neurosurgery (intracranial or intraspinal) - Neuraxial anesthesia (spinal or epidural) - Cardiac surgery - Major abdominal surgery (e.g., intestinal anastomosis) - Major orthopedic surgery (e.g., joint replacement) - Lung resection - Extensive tumour resection - Kidney/liver biopsy

Special Considerations:

Drug interactions: Prior to starting rivaroxaban therapy, review of concomitant medications is recommended. Use of rivaroxaban is contraindicated in patients receiving concomitant systemic treatments with strong inhibitors or inducers of both CYP 3A4 and P-gp. Patients taking strong inhibitors of P-gp and CYP3A4 (e.g., azole antifungals) are at increased risk of bleeding. Patients taking strong inducers of CYP3A4 (e.g., phenytoin, phenobarbital, carbamazepine, rifampin, St. John's Wort) can have reduced rivaroxaban levels and decreased rivaroxaban effect. Please refer to product monograph for further information.

Obesity: Limited information is available regarding the efficacy and safety of rivaroxaban in pediatric obese patients, and we recommend avoiding its use in patients with a BMI > 40 kg/m2 or weighing >

120kg. Informed discussion with the patient is recommended regarding the limited information within this subgroup as well as the risk of under-dosing. Consider alternate anticoagulation in patients with obesity.

CSVT: The subset study of the EINSTEIN-Jr phase 3 trial evaluated the safety and efficacy of rivaroxaban in children with sinus venous thromboembolisms (CSVT). Clot resolution was similar in rivaroxaban (73 children) and standard anticoagulation (41 children) groups with complete recanalization evident in 25% vs 15%, respectively. Rivaroxaban was associated with clinically relevant bleeding in 6.8% vs 2.4% in the standard anticoagulation group, with major bleeding occurring only in the latter (1/41 children). However, this study was not well powered, hence it should be used with caution and after careful assessment of bleeding risk in the pediatric population.

Central Venous Catheters: An exploratory analysis of 126 children with CVC-VTE from the EINSTEIN-Jr trial was completed. Ninety children with CVC-VTE received Rivaroxaban. 67% of patients with CVC-VTE were children in age group birth to 1 year. Three children had clinically relevant non major bleeding in the rivaroxaban arm. Overall, Rivaroxaban showed safety and efficacy in catheter related thromboembolisms. No symptomatic recurrent DVTs occurred in any child. Preterm neonates were not included in this study. The study treatment period was 3 months with the exception of catheter-related VTE in children younger than 2 years, for whom it was 1 month as long as the CVC was removed and thrombus was completely resolved.

VTE prophylaxis: Rivaroxaban has not been studied to date for thromboprophylaxis in children.

Renal/Liver impairment: Rivaroxaban should be used with caution in patients with renal impairment (eGFR < 30 mL/min/1.73 m^2) and/or liver impairment, as plasma levels of the drug may be elevated, leading to an increased bleeding risk.

Antiphospholipid Syndrome: Rivaroxaban is contraindicated in patients (children and adults) who are triple positive for lupus anticoagulant, anti-cardiolipin, and anti-B2-glycoprotein.

Pregnancy and Breastfeeding: Rivaroxaban crosses the placenta and should not be used during pregnancy. It has been shown that rivaroxaban also appears in breastmilk and therefore should be avoided in nursing mothers.

References:

1. Canada T. Management of bleeding in patients who are receiving a new oral anticoagulant (Dabigatran, Rivaroxaban, Apixaban). 2013.
2. Connor P, van Kammen MS, Lensing AWA. Safety and efficacy of rivaroxaban in the pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). Blood Adv. 2020;4(4):6250-6258.
3. Di Nisio M, Vedovati MC, Riera-Mestre A et al. Treatment of venous thromboembolism with rivaroxaban in relation to body weight: a sub-analysis of the EINSTEIN DVT/PE studies. Thrombosis and Haemostasis. 2016; 116(4):739-736.
4. Dodd KC, Emsely HSCA, Desborough MJR et al. Periprocedural antithrombotic management for lumbar puncture: Association of British Neurologists clinical guideline. Pract Neurol. 2018;0:1-11.
5. Dubois V, Dincq AS. Douxfils J. Perioperative management of patients on direct anticoagulants. Thrombosis Journal. 2017:14.

6. Monagle P, Lensing AWA, Thelen K. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm phase 2 studies. The Lancet Hematology. 2019;6(10): e500-e509.
7. Pengo V, Denas G, Zoppellaro G et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018;132(13): 1365-1371.
8. Samama MM, Contant G, Spiro TE et al. Laboratory assessment of rivaroxaban: a review. Thrombosis journal. 2013;11.
9. Shaw JR, Kaplovitch E, Douketis J. Periprocedural management of oral anticoagulation. Medical Clinics of North America. 2020;104(4):709-726.
10. Thom K, Lensing AWA, Nurmeev I et al. Safety and efficacy of anticoagulant therapy in pediatric catheter-related venous thrombosis (EINSTEIN-Jr CVC-VTE). Blood Adv. 2020:4(19):4632-4639.
11. Young G, Lensing AWA, Monagle P, et al. Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation. *J Thromb Haemost*. 07 2020;18(7):1672-1685.
12. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 07 2018;36(20):2017-2023.
13. Bayer Inc. Xarelto product monograph. Revision date: January 6, 2021.