יוני 2023

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון:
Xarelto 15mg, Xarelto 20mg
קסרלטו 15מ"ג, קסרלטו 20מ"ג
Film coated tablets
Rivaroxaban

חברת באייר מתכבדת להודיע כי העלונים לרופא ולצרכן לתכשירים שבנדון עודכנו.

התוויות מאושרות:

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.

Xarelto 15mg:
Paediatric population
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

Xarelto 20 mg:
Paediatric population
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

בהודעה זו כלולים העידכונים המהותיים בלבד. בפירוט שלהלן מופיע, מתוך כל פרק ששונה בעלונים, רק המידע שהתעדכן. תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט מסומנת ~~בקו חוצה~~.

העדכונים בעלון לרופא:

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

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Paediatric population

15 mg:

Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

20 mg:

Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

4.2 Posology and method of administration

Posology

Prevention of stroke and systemic embolism in adults

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Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE in adults.

…

Treatment of VTE and prevention of VTE recurrence in children and adolescents

Xarelto treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section 5.1).

15 mg: The dose for children and adolescent is calculated based on body weight.

- Body weight from 30 to 50 kg: a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight of 50 kg or more: a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose. …
- For patients with body weight less 30 kg refer to the physician prescribing information of Xarelto granules for oral suspension.

20 mg: The dose for children and adolescent is calculated based on body weight.

- Body weight of 50 kg or more: a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight from 30 to 50 kg: a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- For patients with body weight less 30 kg refer to the physician prescribing information of Xarelto granules for oral suspension.

The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.

Treatment should be continued for at least 3 months in children and adolescents. 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.

If a dose is missed, the 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.

Converting from Vitamin K Antagonists (VKA) to Xarelto

- ~~For patients treated for~~ Prevention of stroke and systemic embolism: VKA treatment should be stopped and Xarelto therapy should be initiated when the International Normalised Ratio (INR) is ≤ 3.0.
- ~~For patients treated for~~ Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:

…

Paediatric patients:

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).

Converting from parenteral anticoagulants to Xarelto

For adult and paediatric …

Special populations

Renal impairment

Adults:

…

Paediatric population:

- Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m2): no dose adjustment is required, based on data in adults and limited data in paediatric patients (see section 5.2).
- Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2): Xarelto is not recommended as no clinical data is available (see section 4.4).

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 sections 4.3 and 5.2).

No clinical data is available in children with hepatic impairment.

Elderly population

No dose adjustment (see section 5.2).

Body weight

No dose adjustment for adults (see section 5.2). For paediatric patients the dose is determined based on body weight.

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. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age~~. …

…

Paediatric population

The safety and efficacy of Xarelto in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. No data are available. Therefore, it 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

Adults

Xarelto is for oral use. The tablets are to be taken with food (see section 5.2).

Crushing of tablets

...

The crushed ~~Xarelto~~ tablet may also be given through gastric tubes (see sections 5.2 and 6.6). ~~after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Xarelto15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding (see section 5.2 and 6.6).~~

There is no data regarding chewing or halving the tablets.

15 mg

Children and adolescents weighing 30 kg to 50 kg Xarelto is for oral use. The patient should be advised to swallow the tablet with liquid. It should also be taken with food (see section 5.2). The tablets should be taken approximately 24 hours apart.

20 mg

Children and adolescents weighing more than 50 kg

Xarelto is for oral use.

The patient should be advised to swallow the tablet with liquid. It should also be taken with food (see section 5.2). The tablets should be taken approximately 24 hours apart.

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.

The tablet must not be split in an attempt to provide a fraction of a tablet dose.

Crushing of tablets

For patients who are unable to swallow whole tablets, Xarelto granules for oral suspension should be used. 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 orally. The crushed tablet may be given through a nasogastric or gastric feeding tube (see sections 5.2 and 6.6).

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4.4 Special warnings and precautions for use

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Paediatric population

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

In adult patients ...

Xarelto is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data is 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 (see section 4.5).

…

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.

…

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.

…

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). ~~including 53,103 patients exposed to rivaroxaban~~

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
…			
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
…			

…

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
…		
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
…		

…

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.

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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

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Paediatric population

Treatment of VTE and prevention of VTE recurrence

The safety assessment in children and adolescents is based on the safety data from two phase II and one phase III open-label active controlled studies in paediatric patients aged birth to less than 18 years. The safety findings were generally similar between rivaroxaban and comparator in the various paediatric age groups. Overall, the safety profile in the 412 children and adolescents treated with rivaroxaban was similar to that observed in the adult population

and consistent across age subgroups, although assessment is limited by the small number of patients.
In paediatric patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical studies. The adverse drug reactions in paediatric patients were primarily mild to moderate in severity.
…

4.9 Overdose

In adults, ~~R~~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 (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available for adults, but not established in children (refer to the physician prescribing information of andexanet alfa).
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding
…in adults. The half life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter (see section 5.2…in adults and in children ~~individuals~~ receiving rivaroxaban…

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

5. PHARMACOLOGICAL PROPERTIES

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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 13 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.

…

Paediatric population

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 11 and 12 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 165 patients 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 11: 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 12: 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.

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5.2 Pharmacokinetic properties

Absorption
The following information is based on the data obtained in adults.
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Paediatric population
Children received 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 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 are available so that 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 20 mg tablets should be taken with feeding or with food (see section 4.2).

Distribution
Plasma protein binding in adults ~~humans~~ 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
No data on rivaroxaban plasma protein binding specific to children is available. 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, ~~O~~of …

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

Gender

In adults, ~~T~~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.

Elderly population

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

Different weight categories

In adults, ~~E~~extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.
In children, rivaroxaban is dosed based on body weight. An exploratory analysis did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure in children.

Inter-ethnic differences

In adults, ~~N~~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.

Hepatic impairment

Cirrhotic adult …
No clinical data is available in children with hepatic impairment.

Renal impairment

In adults, ~~T~~there…
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).
…
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 13.

Table 13: 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 1/2 LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

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Paediatric population

Safety and efficacy have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation for children and adolescents up to 18 years.

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6.3 Shelf life

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Crushed tablets

Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

6.6 Special precautions for disposal

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Crushing of tablets

Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. 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 of a crushed rivaroxaban 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding.

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העדכונים בעלון לצרכן:

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1) למה מיועדת התרופה?

קסרלטו מיועד ~~לטיפול~~ למבוגרים במצבים הבאים:

- למניעת קרישי דם במוח (שבץ) ובכלי דם אחרים בגוף, בחולים ~~מבוגרים~~ הסובלים מקצב לב לא סדיר הנקרא פרפור פרוזדורים שלא על רקע מסתמי, ומגורם סיכון אחד או יותר מהבאים: אי ספיקת לב, יתר לחץ דם, גיל (75 או מעל), סוכרת, שבץ או התקף איסכמי חולף בעבר.
- לטיפול קרישי דם בורידי הרגליים (פקקת ורידים עמוקים) ובכלי הדם של הריאות (תסחיף ריאתי) ולמניעת הופעה חוזרת של קרישי דם בכלי הדם ברגליים ו/או בריאות.

קסרלטו מיועד לילדים ומתבגרים מתחת לגיל 18 השוקלים 30 ק"ג או יותר:

- לטיפול בקרישי דם ולמניעת הופעה חוזרת של קרישי דם בווריד או בכלי הדם של הריאות, לאחר טיפול התחלתי של לפחות 5 ימים עם תרופות להזרקה המשמשות לטיפול בקרישי דם.

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2) לפני השימוש בתרופה

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נדרשת זהירות מיוחדת בשימוש בקסרלטו. לפני הטיפול בקסרלטו, ספר לרופא:

- אם אתה בסיכון גבוה לדימום כפי שיכול להיות באחד מהמצבים הבאים:
  - מחלת כליות חמורה במבוגרים ובינונית עד חמורה בילדים ומתבגרים מאחר ותפקוד הכליות עלול להשפיע על כמות התרופה הפועלת בגופך (ראה סעיף 3 "כיצד תשתמש בתרופה?" לגבי המינון המומלץ במקרה של מחלת כליות).
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ילדים ומתבגרים

טבליות קסרלטו **אינן מומלצות לילדים השוקלים פחות מ 30 ק"ג.** ~~**התרופה אינה מיועדת לילדים ומתבגרים מתחת לגיל 18 שנים.**~~ אין מספיק מידע על השימוש בילדים ובמתבגרים בהתוויות המיועדות למבוגרים.

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3) כיצד תשתמש בתרופה?

יש להשתמש בתכשיר תמיד בהתאם להוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן הטיפול בתכשיר.

- המינון ואופן הטיפול יקבעו על-ידי הרופא בלבד.
- **מבוגרים**

...

- **ילדים ומתבגרים**

המינון של קסרלטו תלוי במשקל הגוף, ויחושב ע"י הרופא.

- המינון המומלץ עבור ילדים ומתבגרים **השוקלים בין 30 ק"ג ופחות מ 50 ק"ג** הוא **טבליה** אחת של **קסרלטו 15** מ"ג פעם ביום.
- המינון המומלץ עבור ילדים ומתבגרים **השוקלים 50 ק"ג או יותר** הוא **טבליה** אחת **של קסרלטו 20** מ"ג פעם ביום.

יש ליטול מנת קסרלטו עם משקה (לדוגמא מים או מיץ) במהלך ארוחה. יש ליטול את הטבליות כל יום בשעה קבועה. אנא שקול שימוש בשעון מעורר כדי להזכיר לך. להורים או מטפלים: אנא התבוננו בילד במהלך הנטילה כדי לוודא שהמינון המלא נלקח.

כיוון שמינון קסרלטו מבוסס על משקל גוף, חשוב להקפיד על ביקורים מתוכננים אצל הרופא, כי ייתכן שיהיה צורך להתאים את המינון ככל שמשקל הגוף משתנה.
לעולם אין להתאים מינון של קסרלטו בעצמך. הרופא יתאים את המינון במידת הצורך.

אין לחצות את הטבליה בניסיון לספק חלק ממנת הטבליה. אם נדרש מינון נמוך יותר, השתמש בקסרלטו 1 מ"ג/מ"ל גרגירים להכנת תרחיף למתן פומי. לילדים ומתבגרים שאינם מסוגלים לבלוע טבליות שלמות, יש להשתמש בקסרלטו 1 מ"ג/מ"ל גרגירים להכנת תרחיף למתן פומי.
אם קסרלטו 1 מ"ג/מ"ל גרגירים להכנת תרחיף למתן פומי אינו זמין, ניתן לרסק את הטבליה ולערבב עם מים או מחית תפוחים, מיד לפני נטילתה. יש לאכול מיד לאחר נטילת התרופה המרוסקת. במידת הצורך, הרופא שלך יתן לך קסרלטו מרוסק דרך צינור הזנה לקיבה.

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אם אתה יורק את המנה או מקיא
• אם חלפו פחות מ-30 דקות לאחר נטילת קסרלטו, יש ליטול מנה חדשה.
• אם חלפו יותר מ-30 דקות לאחר נטילת קסרלטו, **אין** ליטול מנה חדשה. במקרה זה, יש ליטול את המנה הבאה של קסרלטו במועד המתוכנן הבא.

יש לפנות לרופא אם אתה יורק את המנה או מקיא לאחר נטילת קסרלטו שוב ושוב.

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אם שכחת ליטול תרופה זו בזמן הדרוש
מבוגרים, ילדים ומתבגרים:

- במינון של טבליה אחת של קסרלטו 15 מ"ג או קסרלטו 20 מ"ג **פעם** ביום, יש ליטול מנה מיד כשנזכרת אך בשום אופן אין ליטול מנה כפולה או שתי מנות באותו יום! יש ליטול את המנה הבאה למחרת היום ובהמשך פעם ביום כרגיל והיוועץ ברופא.

מבוגרים:

- במינון של טבליה אחת של 15 מ"ג **פעמיים** ביום יש ליטול מנה מיד כשנזכרת. אין ליטול יותר משתי טבליות של 15 מ"ג ביום אחד. ניתן ליטול שתי טבליות של 15 מ"ג ביחד לקבלת מינון של 30 מ"ג ליום אחד. למחרת היום יש להמשיך וליטול טבליה אחת של 15 מ"ג פעמיים ביום.

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4) תופעות לוואי

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יש לפנות מיד לרופא אם <u>אתה או הילד</u> ~~הוא~~ סובל מאחת מתופעות הלוואי הבאות:
סימנים לדימום:
...

תופעות לוואי נוספות <u>שדווחו במבוגרים, ילדים ומתבגרים</u>
...

<u>תופעות לוואי בילדים ומתבגרים</u>

<u>באופן כללי, תופעות הלוואי שנצפו בילדים ומתבגרים שטופלו בקסרלטו היו דומות לאלו שנצפו במבוגרים והיו בעיקר קלות עד בינוניות בחומרתן.</u>

<u>תופעות לוואי שנצפו לעיתים קרובות יותר בילדים ומתבגרים:</u>

<u>תופעות לוואי שכיחות מאוד</u> <u>(very common) (תופעות שעלולות להשפיע על יותר ממשתמש 1 מתוך 10):</u>
- <u>כאב ראש</u>
- <u>חום</u>
- <u>דימום מהאף</u>
- <u>הקאות</u>

<u>תופעות לוואי שכיחות</u> <u>(common) (תופעות שעלולות להשפיע על עד משתמש 1 מתוך 10):</u>
- <u>דופק מוגבר</u>
- <u>בדיקות דם יכולות להצביע על עלייה בבילירובין (פיגמנט מרה)</u>
- <u>טרומבוציטופניה (מספר נמוך של טסיות דם, שהן תאים שמסייעים לקרישת הדם)</u>
- <u>דימום וסתי כבד</u>

<u>תופעות לוואי שאינן שכיחות</u> <u>(uncommon) (תופעות שעלולות להשפיע על עד משתמש 1 מתוך 100):</u>
- <u>בדיקות דם יכולות להצביע על עלייה בתת קטגוריה של בילירובין (בילירובין ישיר, פיגמנט מרה)</u>

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5)איך לאחסן את התרופה?

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<u>טבליות מרוסקות</u>
<u>טבליות מרוסקות יציבות במים או מחית תפוחים עד 4 שעות.</u>
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העלון לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/

ניתן לקבלם מודפסים ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700.

בברכה,

באייר ישראל