פברואר 2019

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון:
Xarelto 10 mg
קסרלטו 10 מ"ג
Film coated tablets
Rivaroxaban

אנו מבקשים להודיעכם שאושרה תוספת התוויה לתכשיר ושהעלון לרופא ולצרכן של התכשיר עודכנו.

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

ההתוויה הנוספת שאושרה:
Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE), in adults (following completion of at least 6 months therapy for DVT or PE).

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

3. PHARMACEUTICAL FORM

…
(Minor change in the black box warning):

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

…

B. SPINAL/EPIDURAL HEMATOMA

…

[see special warnings and precautions for use (4.4), and Undesirable effects (4.8)].

4.1 Therapeutic indications

…
Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE), in adults (following completion of at least 6 months therapy for DVT or PE).

4.2 Posology and method of administration

Posology
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Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

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

Prevention of recurrent DVT and PE
When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily.
The safety and efficacy of treatment duration beyond 12 months has not been established. It should be considered whether to continue treatment beyond 12 months.

	Time Period	**Dosing schedule**	**Total daily dose**
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily	10 mg

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Xarelto immediately to ensure intake of 30 mg Xarelto per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, the patient should take Xarelto immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to Xarelto
For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 2.5.
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Method of administration
…
There is no data regarding chewing or halving the tablets.

4.4 Special warnings and precautions for use

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

Haemorrhagic risk
As with other anticoagulants, patients taking 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.

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.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8). In patients receiving Xarelto for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

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Interaction with other medicinal products

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Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors 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 to be used with caution~~ is not recommended in patients with an increased bleeding risk such as:

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

Patients with prosthetic valves
Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto provides adequate anticoagulation in this patient population.
Treatment with Xarelto is not recommended for these patients.

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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.

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

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4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors
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Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C_{max}. ~~This increase is not considered clinically relevant~~ 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}. ~~This increase is not considered clinically relevant~~. 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~~R~~$_{max}$ 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~~R~~$_{max}$ when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean C_{max}. ~~This increase is not considered clinically relevant.~~ 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).

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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.

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4.8 Undesirable effects

Summary of the safety profile
The safety of rivaroxaban has been evaluated in ~~eleven~~ thirteen phase III studies including ~~32,625~~ 53,103 patients exposed to rivaroxaban (see Table 1).

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

Indication	Number of patients*	~~Maximum~~Total daily dose	Maximum treatment duration
…	…	…	…
Treatment of DVT, PE and prevention of recurrence	~~4,556~~ 6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
...	…	…	…
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months

*Patients exposed to at least one dose of rivaroxaban

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings ~~(≥4 %)~~ were epistaxis (~~5.9~~ 4.5%) and gastrointestinal tract haemorrhage (~~4.2~~ 3.8%).

~~In total about 67% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 22% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery and in hospitalised medically ill patients, bleeding events occurred in approximately 6.8% and 12.6% of patients, respectively, and anaemia occurred in approximately 5.9% and 2.1% of patients, respectively. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT or PE , or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 27.8% of patients and anaemia occurred in approximately 2.2% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years~~

~~In patients treated for prevention of atherothrombotic events after an acute coronary syndrome (ACS), bleeding of any type or severity was reported with an event rate of 22 per 100 patient years. Anaemia was reported with an event rate of 1.4 per 100 patient years.~~

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed 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
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**

* 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

Tabulated list of adverse reactions

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Table ~~2~~3: All ~~treatment-emergent~~ adverse reactions reported in patients in phase III ~~studies~~ clinical trials or through post-marketing use*

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A], Thrombocytopenia ~~Thrombocythemia~~			
Immune system disorders				
	Allergic reaction, dermatitis allergic, Angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
…	…	…	…	…
Hepatobiliary disorders				
Increase in transaminases	~~Hepatic function abnormal~~ 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)		
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	
…	…	…		
Investigations				

Common	Uncommon	Rare	Very rare	Not known
~~Increase in transaminases~~	~~Increased bilirubin, increased blood alkaline phosphatase[A],~~ Increased LDH[A], increased lipase[A], increased amylase[A] ~~increased GGT[A]~~	~~Bilirubin conjugated increased (with or without concomitant increase of ALT)~~		
…		…		

A: observed in prevention of ~~venous thromboembolism (~~VTE~~)~~ in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)
* A pre-specified selective approach to adverse event collection was applied. As incidence of adverse reactions did not increase and no new adverse reaction was identified, COMPASS study data were not included for frequency calculation in this table.

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 ~~in section 4.4).~~"). Menstrual bleeding may be intensified and/or prolonged.
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~~Post-marketing observations~~
~~The following adverse reactions have been reported post-marketing in temporal association with the use of Xarelto. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.~~
~~Immune system disorders: Angioedema and allergic oedema (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).~~
~~Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (≥ 1/10,000 to < 1/1,000)).~~

~~Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).~~

…

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

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Clinical efficacy and safety

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Treatment of DVT, PE and prevention of recurrent DVT and PE
The Xarelto clinical programme was designed to demonstrate the efficacy of Xarelto in the initial and continued treatment of acute DVT and PE and prevention of recurrence.
Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice). and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

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

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

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

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

Einstein DVT, PE and Extension used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality. In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomisation date (median : 351 days). Xarelto 20 mg once daily and Xarelto 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily.The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.

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

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

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

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

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443 - 1.042), p=0.076 (superiority)

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

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

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

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

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0026$ (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749 – 1.684)

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

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

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

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

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

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

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

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

a) Rivaroxaban 20 mg once daily

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

In the Einstein Choice study (Table 9) Xarelto 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with Xarelto 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

Table 9: Efficacy and safety results from phase III Einstein Choice

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**		
Treatment dose	**Xarelto 20 mg od N=1,107**	**Xarelto 10 mg od N=1,127**	**ASA 100 mg od N=1,131**
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)
Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0	2 (0.2%)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7%)	22 (2.0%)	20 (1.8%)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%)+	17 (1.5%)++	53 (4.7%)

*p<0.001(superiority) Xarelto 20 mg od vs ASA 100 mg od; HR=0.34 (0.20–0.59)
** p<0.001 (superiority) Xarelto 10 mg od vs ASA 100 mg od; HR=0.26 (0.14–0.47)
+ Xarelto 20 mg od vs. ASA 100 mg od; HR=0.44 (0.27–0.71), p=0.0009 (nominal)
++ Xarelto 10 mg od vs. ASA 100 mg od; HR=0.32 (0.18–0.55), p<0.0001 (nominal)

In addition to the phase III EINSTEIN programme, a prospective, non-interventional, open-label cohort study (XALIA) with central outcome adjudication including recurrent VTE, major bleeding and death has been conducted. 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy in clinical practice. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted HRs

comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40 - 1.50), 0.91 (95% CI 0.54 - 1.54) and 0.51 (95% CI 0.24 - 1.07), respectively.
These results in clinical practice are consistent with the established safety profile in this indication.

~~Paediatric population~~
~~The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).~~

העדכונים בעלון לצרכן

חומרים בלתי פעילים ואלרגנים: ראה סעיף 6 "מידע נוסף" וסעיף 2 "מידע חשוב על חלק מהמרכיבים של התרופה".

...

1) למה מיועדת התרופה?

קסרלטו 10 מ"ג מיועד ל:

...

- מניעת חזרה של קרישי דם בורידי הרגליים (פקקת ורידים עמוקים) ובכלי הדם של הריאות (תסחיף ריאתי) לאחר השלמת 6 חודשי טיפול לפקקת ורידים עמוקים או תסחיף ריאתי קודם.

2) לפני השימוש בתרופה
אין להשתמש בתרופה אם:

...

אל תיטול קסרלטו 10 מ"ג וספר לרופא שלך אם אחד מהמצבים המתוארים מעלה חל עליך.

...

נדרשת זהירות מיוחדת בשימוש בקסרלטו 10 מ"ג. לפני הטיפול בקסרלטו 10 מ"ג, ספר לרופא:

- ...
- אם יש לך מסתם לב מלאכותי
- אם קבע הרופא שלחץ הדם שלך אינו יציב או שמתוכנן בעבורך טיפול ניתוחי או אחר להסרת קריש הדם מהריאות.

...

אם אתה צריך לעבור ניתוח

- חשוב ביותר ליטול קסרלטו 10 מ"ג לפני ואחרי הניתוח בדיוק בזמנים שקבע לך הרופא

<u>אינטראקציות/תגובות בין תרופתיות</u>
אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח. במיוחד ~~יש ליידע את הרופא או הרוקח~~ אם אתה לוקח:

- תרופות מסוימות נגד זיהומים פטרייתיים (כגון: ~~קטוקונאזול~~ <u>פלוקונאזול</u>, איטראקונאזול, וריקונאזול, פוסאקונאזול) פרט לאלו שמיועדות רק למריחה על העור.
- <u>טבליות המכילות קטוקונאזול לטיפול בתסמונת קושינג – מצב בו הגוף מייצר עודף של קורטיזול.</u>
- <u>תרופות מסוימות לטיפול בזיהומים חיידקיים (כגון: קלאריתרומיצין, אריתרומיצין)</u>
- תרופות נוגדות דלקת ומשככות כאב (כגון: נפרוקסן או <u>חומצה אסטילסליצילית</u> [אספירין]).
- <u>תרופות מסוימות לטיפול בדכאון (מעכבים סלקטיבים של ספיגה חוזרת של סרוטונין (SSRIs) או מעכבים של ספיגה חוזרת של סרוטונין ונוראפינפרין SNRIs))</u>
- <u>...</u>

...

<u>מידע חשוב על חלק מהמרכיבים של התרופה</u>
התרופה מכילה לקטוז <u>ונתרן.</u>
אם נאמר לך על-ידי הרופא שהנך סובל מאי סבילות לסוכרים מסוימים, פנה לרופא לפני שאתה מתחיל ליטול קסרלטו 10 מ"ג.
<u>התרופה מכילה פחות מ- 1 מילימול נתרן (23 מ"ג) בכל טבליה ועל כן נחשבת במהותה "נטולת נתרן".</u>

3) כיצד תשתמש בתרופה?

...

- המינון ואופן הטיפול יקבעו על-ידי הרופא בלבד.

<u>למניעת היווצרות קרישי דם בורידים לאחר ניתוח להחלפת ירך או ברך,</u> המינון המקובל בדרך-כלל הוא: טבליה אחת (10 מ"ג) פעם ביום.
יש ליטול את הטבליה הראשונה 6-10 שעות לאחר הניתוח. לאחר מכן יש ליטול טבליה אחת כל יום עד שהרופא המטפל יורה לך להפסיק.

<u>למניעת חזרה של קרישי דם בורידי הרגליים (פקקת ורידים עמוקים) ובכלי הדם של הריאות (תסחיף ריאתי) לאחר השלמת 6 חודשי טיפול לפקקת ורידים עמוקים או תסחיף ריאתי קודם, המינון המקובל בדרך כלל הוא: טבליה אחת (10 מ"ג) ביום.</u>

...

- <u>משך הטיפול</u>
  - בניתוח החלפת מפרק הירך, משך הטיפול בדרך-כלל הינו 5 שבועות.
  - בניתוח החלפת מפרק הברך, משך הטיפול בדרך-כלל הינו שבועיים.
  - <u>למניעת חזרה של קרשי דם בורידי הרגליים (פקקת ורידים עמוקים) ובכלי הדם של הריאות (תסחיף ריאתי) לאחר השלמת 6 חודשי טיפול לפקקת ורידים עמוקים או תסחיף ריאתי קודם, משך הטיפול יקבע על ידי הרופא.</u>

...

<u>אין מידע לגבי חציה/לעיסה.</u>

...

4) תופעות לוואי

...

<u>תופעות לוואי אפשריות אשר יכולות להוות סימן לתגובה עורית חמורה:</u>
<u>יש לפנות מיד לרופא אם</u> <u>הנך סובל מתגובות עוריות כגון:</u>

- פריחה אינטנסיבית מתפשטת על העור, שלפוחיות או פצעים ברקמה ריריתת, למשל בפה או בעיניים (Toxic Epidermal Necrolysis/Stevens-Johnson syndrome). התדירות של תופעת לוואי זו הינה נדירה מאוד (עד משתמש 1 מתוך 10,000)
- תגובה לתרופה הגורמת לפריחה, חום, דלקת של איברים פנימיים, חריגות המטולוגיות (של הדם) וחולי מערכתי (תסמונת DRESS). התדירות של תופעת לוואי זו הינה נדירה מאוד (עד משתמש 1 מתוך 10,000).

תופעות לוואי אפשריות אשר יכולות להוות סימן לתגובה אלרגית חמורה:
יש לפנות מיד לרופא אם אתה חווה כל אחת מתופעות הלוואי הבאות:
- התנפחות הפנים, השפתיים, הפה, הלשון או הגרון; קשיי בליעה; סרפדת וקשיי נשימה; צניחה פתאומית של לחץ הדם. התדירויות של תופעות לוואי אלה הינן נדירות מאוד (תגובות אנאפילקטיות, כולל שוק אנאפילקטי; עלולות להשפיע על עד משתמש 1 מתוך 10,000) ואינן שכיחות (אנגיואדמה ובצקת אלרגית; עלולות להשפיע על עד משתמש 1 מתוך 100).

תופעות לוואי נוספות
...
תופעות לוואי שאינן שכיחות (Uncommon) (תופעות שעלולות להשפיע ~~לכל היותר~~ על עד משתמש אחד מתוך 100):
- ...
- טרומבוציטופניה (מספר נמוך של טסיות דם, שהן תאים שמסייעים לקרישת הדם)

תופעות לוואי נדירות (Rare) (תופעות שעלולות להשפיע ~~לכל היותר~~ על עד משתמש אחד מתוך 1,000):
- ...
- כולסטאזיס (זרימה מופחתת של מרה), דלקת הכבד (הפאטיטיס) כולל פגיעה בתאי הכבד (כבד דלקתי כולל פגיעה כבדית)

~~תופעות הלוואי המופיעות להלן דווחו מאז אושר התכשיר לשיווק:~~
- ~~אנגיואדמה ובצקת אלרגית (התנפחות של הפנים, השפתיים, הפה, הלשון או הלוע).~~
- ~~כולסטזיס (זרימה מופחתת של מרה), צהבת הכוללת פגיעה בתאי הכבד (כבד דלקתי כולל פגיעה כבדית)~~
- ~~טרומבוציטופניה (מספר נמוך של טסיות דם שהן תאים שמסייעים בקרישת דם)~~

5) מידע נוסף
- נוסף על החומר הפעיל התרופה מכילה גם:

Cellulose microcrystalline, lactose monohydrate, croscarmellose sodium, hypromellose 5 cP, hypromellose 15 cP, magnesium stearate ,sodium laurylsulfate, macrogol 3350, titanium dioxide, ferric oxide red

העלון לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp
ניתן לקבלם מודפסים ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700.

בברכה,

באייר ישראל