פברואר 2019

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

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

אנו מבקשים להודיעכם שהעלונים לרופא והעלון לצרכן של התכשירים עודכנו.

ההתוויות המאושרות לתכשירים:
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.

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 של התכשיר Xarelto 15 mg

3. PHARMACEUTICAL FORM
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Prescriber guide
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Patient safety information card
~~This product is marketed with patient safety information card (patient card).~~
The marketing of Xarelto 15 mg is subject to a risk management plan (RMP) including a 'patient safety information card' (Patient card). Please provide a patient card to each patient who is prescribed with Xarelto 15 mg. The 'patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment and the implications of this treatment including the need for compliance. Please also explain the signs of important adverse events and instruct the patient when to seek medical care.

(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)].

…

4.2 Posology and method of administration

Posology

…

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE

The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, ~~as indicated in the table below~~.

	~~Dosing schedule~~	~~Maximum daily dose~~
~~Day 1 - 21~~	~~15 mg twice daily~~	~~30 mg~~
~~Day 22 and onwards~~	~~20 mg once daily~~	~~20 mg~~

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma).
and longer durations should be based on permanent risk factors or idiopathic DVT or 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.

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). ~~Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.~~

	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

...

Special populations
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Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement
There is limited experience of a reduced dose of 15 mg Xarelto once daily in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement (see sections 4.4 and 5.1).

Method of administration
…

There is no data regarding chewing or halving the tablets.

4.4 Special warnings and precautions for use
…

Patients with non-valvular atrial fibrillation who undergo PCI with stent placement

Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/transient ischaemic attack (TIA).

…

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.
…

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors

…

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_{max} when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in C_{max} when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean C_{max}. ~~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).

…

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in ~~twelve~~ thirteen phase III studies including ~~34,859~~ 53,103 patients exposed to rivaroxaban (see Table 1).

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

Indication	Number of patients*	Total daily dose	Maximum treatment duration
…	…	…	…
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 (4.5% ~~5.8%~~) and gastrointestinal tract haemorrhage (~~4.1%~~ 3.8%).
~~In total about 65% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 21% of the patients experienced adverse events considered related to treatment as assessed by investigators.~~

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

Indication	Any bleeding	Anaemia
…	…	…
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

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Table 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			
Immune system disorders				
	Allergic reaction, dermatitis allergic, Angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
...	...	…	…	…
Hepatobiliary disorders				
Increase in transaminases	Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]	Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)		
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.

…

~~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)).~~
~~Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (In the pooled phase III trials, these events were estimated as very rare (<1/10,000)).~~

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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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Patients with non-valvular atrial fibrillation who undergo PCI with stent placement

A randomized, open-label, multicentre study (PIONEER AF-PCI) was conducted in 2,124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12-month-therapy. Patients with a history of stroke or TIA were excluded.
Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30 - 49 ml/min) plus P2Y12 inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus DAPT (dual antiplatelet therapy i.e. clopidogrel 75 mg [or alternate P2Y12 inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with creatinine clearance 30 - 49 ml/min) once daily plus low-dose ASA. Group 3 received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose-adjusted VKA plus low-dose ASA.
The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7%), 117 (16.6%), and 167 (24.0%) subjects in group 1, group 2 and group 3, respectively (HR 0.59; 95% CI 0.47-0.76; p<0.001, and HR 0.63; 95% CI 0.50-0.80; p<0.001, respectively).
The secondary endpoint (composite of cardiovascular events CV death, MI, or stroke) occurred in 41 (5.9%), 36 (5.1%), and 36 (5.2%) subjects in the group 1, group 2 and group 3, respectively. Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement.
The primary objective of PIONEER AF-PCI was to assess safety. Data on efficacy (including thromboembolic events) in this population are limited.

Treatment of DVT, PE and prevention of recurrent DVT and PE
The Xarelto clinical ~~program~~ 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 ~~9,400~~ 12,800 patients were studied in ~~three~~ four randomised controlled phase III clinical studies (Einstein DVT , Einstein PE, ~~and~~ 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 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 Choice study (see Table 10) 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 10: 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 (0.0%)	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)

3. PHARMACEUTICAL FORM

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Prescriber guide

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Patient safety information card

~~This product is marketed with patient safety information card(patient card).~~
The marketing of Xarelto 20 mg is subject to a risk management plan (RMP) including a 'patient safety information card' (Patient card). Please provide a patient card to each patient who is prescribed with Xarelto 20 mg. The 'patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment and the implications of this treatment including the need for compliance. Please also explain the signs of important adverse events and instruct the patient when to seek medical care.

…

(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)].

…

4.2 Posology and method of administration

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Posology

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Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE
The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE~~, as indicated in the table below.~~

	~~Dosing schedule~~	~~Maximum daily dose~~
~~Day 1 - 21~~	~~15 mg twice daily~~	~~30 mg~~
~~Day 22 and onwards~~	~~20 mg once daily~~	~~20 mg~~

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma).

and longer durations should be based on permanent risk factors or idiopathic DVT or 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.

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). ~~Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.~~

	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

…

Method of administration
…

There is no data regarding chewing or halving the tablets.

4.4 Special warnings and precautions for use

…
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.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors
…

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 CRmax 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 CRmax 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).

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in ~~twelve~~ thirteen phase III studies including ~~34,859~~ 53,103 patients exposed to rivaroxaban (see Table 1).

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

Indication	Number of patients*	Total daily dose	Maximum treatment duration
…	…	…	…
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 (~~5.8~~ 4.5%) and gastrointestinal tract haemorrhage (~~4.1~~ 3.8%).
~~In total about 65% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 21% of the patients experienced adverse events considered related to treatment as assessed by investigators.~~

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

Indication	Any bleeding	Anaemia
…	…	…
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

…

Table 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			
Immune system disorders				
	Allergic reaction, dermatitis allergic, Angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
…	…	…	…	…
Hepatobiliary disorders				
Increase in transaminases	Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]	Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)		
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				
~~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.

…

~~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)).~~
~~Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (In the pooled phase III trials, these events were estimated as very rare (<1/10,000)).~~

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01
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Clinical efficacy and safety
…

Patients with non-valvular atrial fibrillation who undergo PCI with stent placement

A randomised, open-label, multicentre study (PIONEER AF-PCI) was conducted in 2,124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12-month-therapy. Patients with a history of stroke or TIA were excluded.
Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30 - 49 ml/min) plus P2Y12 inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus DAPT (dual antiplatelet therapy i.e. clopidogrel 75 mg [or alternate P2Y12 inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with creatinine clearance 30 - 49 ml/min) once daily plus low-dose

ASA. Group 3 received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose-adjusted VKA plus low-dose ASA.
The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7%), 117 (16.6%), and 167 (24.0%) subjects in group 1, group 2 and group 3, respectively (HR 0.59; 95% CI 0.47-0.76; p<0.001, and HR 0.63; 95% CI 0.50-0.80; p<0.001, respectively).
The secondary endpoint (composite of cardiovascular events CV death, MI, or stroke) occurred in 41 (5.9%), 36 (5.1%), and 36 (5.2%) subjects in the group 1, group 2 and group 3, respectively. Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement.
The primary objective of PIONEER AF-PCI was to assess safety. Data on efficacy (including thromboembolic events) in this population are limited.

Treatment of DVT, PE and prevention of recurrent DVT and PE
The Xarelto clinical ~~program~~ 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 ~~9,400~~ 12,800 patients were studied in ~~three~~ four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, ~~and~~ 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 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 Choice study (see Table 10) 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 10: 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 (0.0%)	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)

העדכונים בעלון לצרכן המשותף לתכשירים Xarelto 15 mg + Xarelto 20 mg

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

...

~~כרטיס מידע בטיחותי למטופל~~

בנוסף לעלון, לתכשיר קסרלטו קיים כרטיס מידע בטיחותי למטופל. כרטיס זה מכיל מידע חשוב שעליך לדעת לפני ~~נטילת התכשיר~~ התחלת הטיפול ובמהלך הטיפול בקסרלטו ולפעול על פיו.
יש לעיין בכרטיס ~~ה~~מידע בטיחותי למטופל ובעלון לצרכן בטרם ~~נטילת הטבליה~~ תחילת השימוש בתכשיר.
יש לשמור את הכרטיס והעלון לעיון נוסף במידת הצורך.

...

2) לפני השימוש בתרופה

אין להשתמש בתרופה אם:
...

אל תיטול קסרלטו וספר לרופא שלך אם אחד מהמצבים המתוארים מעלה חל עליך.

...

אינטראקציות/תגובות בין תרופתיות
אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.
במיוחד אם אתה לוקח:

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

תרופות אלו עלולות לגרום להגברת פעילות קסרלטו. הרופא שלך יחליט האם לטפל בך עם קסרלטו והאם יש צורך בהשגחה רפואית צמודה.

...

- **מידע חשוב על חלק מהמרכיבים של התרופה**

התרופה מכילה לקטוז ונתרן.
אם נאמר לך על-ידי הרופא שהנך סובל מאי סבילות לסוכרים מסויימים, פנה לרופא לפני שאתה מתחיל ליטול קסרלטו.

התרופה מכילה פחות מ- 1 מילימול נתרן (23 מ"ג) בכל טבליה ועל כן נחשבת במהותה "נטולת נתרן".

3) כיצד תשתמש בתרופה?

...

המינון ואופן הטיפול יקבעו על-ידי הרופא בלבד.

- למניעת קרישי דם במוח (שבץ) ובכלי דם אחרים בגוף המינון המקובל בדרך כלל הוא טבליה אחת של 20 מ"ג פעם ביום.

במידה והנך סובל מליקוי בתפקוד הכליות, ייתכן והמינון יופחת לטבליה אחת של 15 מ"ג פעם ביום.

אם אתה צריך לעבור הליך לטיפול בחסימה בכלי הדם בלב (הליך בשם: התערבות כלילית מלעורית – PCI עם החדרת תומכן), קיים מידע מוגבל על הפחתת המינון לטבליה אחת של קסרלטו 15 מ"ג פעם אחת ביום בנוסף לתרופה מעכבת טסיות, כגון: קלופידוגרל.

- לטיפול בקרישי דם בורידי הרגליים ובכלי הדם של הריאות ולמניעת הופעה חוזרת של קרישי דם המינון המקובל בדרך כלל הוא טבליה אחת של 15 מ"ג פעמיים ביום למשך 3 השבועות הראשונים, ובהמשך טבליה אחת של 20 מ"ג פעם ביום. לאחר השלמת לפחות 6 חודשים של טיפול, ייתכן והרופא יחליט להמשיך את הטיפול בקסרלטו 10 מ"ג טבליה אחת ביום.

במידה והנך סובל מליקוי בתפקוד הכליות ונוטל קסרלטו 20 מ"ג פעם אחת ביום ייתכן שהרופא יחליט להפחית את המינון לאחר 3 שבועות, לטבליה אחת של 15 מ"ג פעם ביום, זאת במידה שהסיכון לדימום גדול יותר מהסיכון להיווצרות עוד קריש דם.

- צורת הנטילה

...

אין מידע לגבי חציה/ לעיסה.

...

4) תופעות לוואי

...

תופעות לוואי אפשריות אשר יכולות להוות סימן לתגובה עורית חמורה:

יש לפנות מיד לרופא אם אתה חווה ~~תגובה עורית~~ תגובות עוריות כגון:

- פריחה אינטנסיבית מתפשטת על העור, שלפוחיות או פצעים ברקמה רירית, למשל בפה או בעיניים (Toxic Epidermal Necrolysis/ Stevens-Johnson syndrome). התדירות של תופעת לוואי זו הינה נדירה מאוד (~~פחות ממשתמש אחד~~ 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~~ 1 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~~ 1 מתוך 1000):

- ...
- 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), דלקת כבד (צהבת) הכוללת פגיעה בתאי הכבד (כבד דלקתי כולל פגיעה כבדית)~~

~~– טרומבוציטופניה (מספר נמוך של טסיות דם, שהן תאים שמסייעים בקרישת דם)~~

...

העלונים לרופא והעלון לצרכן 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