אפריל 2020

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון:
Xarelto 2.5 mg
קסרלטו 2.5 מ"ג
Film coated tablets
Rivaroxaban

אנו מבקשים להודיעכם שהעלון לרופא והעלון לצרכן של התכשיר עודכנו.

ההתוויות המאושרות לתכשיר:

Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

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

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

4.4 Special warnings and precautions for use

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- CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with rivaroxaban (see section 5.1).

Patients with prosthetic valves
Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). 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.

Patients with antiphospholipid syndrome
Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be

associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

CAD with heart failure

The **COMMANDER HF** study included 5,022 patients with heart failure and significant coronary artery disease (CAD) following a hospitalization of decompensated heart failure (HF) which were randomly assigned into one of the two treatment groups: rivaroxaban 2.5 mg twice daily (N=2,507) or matching placebo (N=2,515), respectively. The overall median study treatment duration was 504 days.

Patients must have had symptomatic HF for at least 3 months and left ventricular ejection fraction (LVEF) of ≤40% within one year of enrollment. At baseline, the median ejection fraction was 34% (IQR: 28%-38%) and 53% of subjects were NYHA Class III or IV.

The primary efficacy analysis (i.e. composite of all-cause mortality, MI, or stroke) showed no statistically significant difference between the rivaroxaban 2.5 mg bid group and the placebo group with a HR=0.94 (95% CI 0.84 - 1.05), p=0.270. For all-cause mortality, there was no difference between rivaroxaban and placebo in the number of events (event rate per 100 patient-years; 11.41 vs. 11.63, HR: 0.98; 95% CI: 0.87 to 1.10; p=0.743). The event rates for MI per 100 patient-years (rivaroxaban vs placebo) were 2.08 vs 2.52 (HR 0.83; 95% CI: 0.63 to 1.08; p=0.165) and for stroke the event rates per 100 patient-years were 1.08 vs 1.62 (HR: 0.66; 95% CI: 0.47 to 0.95; p=0.023). The principal safety outcome (i.e. composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability), occurred in 18 (0.7%) patients in the rivaroxaban 2.5 mg twice daily treatment group and in 23 (0.9%) patients in the placebo group, respectively (HR=0.80; 95% CI 0.43 - 1.49; p=0.484). There was a statistically significant increase in ISTH major bleeding in the rivaroxaban group compared with placebo (event rate per 100 patient-years: 2.04 vs 1.21, HR 1.68; 95% CI: 1.18 to 2.39; p=0.003).

In patients with mild and moderate heart failure the treatment effects for the COMPASS study subgroup were similar to those of the entire study population (see section CAD/PAD).

Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomized open-label multicenter study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The trial was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomized to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) <50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomized to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No

events were reported in patients randomized to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

4.8 Undesirable effects

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Common	Uncommon	Rare	Very rare	Not known
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Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)[A]				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

העדכונים בעלון לצרכן

2) לפני השימוש בתרופה

☒ **נדרשת זהירות מיוחדת בשימוש בקסרלטו 2.5 מ"ג**

- אם אתה נמצא בסיכון גבוה לדימום כפי שיכול להיות באחד מהמצבים הבאים:

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  - אם יש לך מחלת עורקים כלילית עם כשל לבבי סימפטומטי חמור.
- אם יש לך מסתם לב מלאכותי.
- אם ידוע לך כי הנך סובל ממחלה בשם תסמונת אנטי-פוספוליפידית (הפרעה במערכת החיסון אשר גורמת לסיכון מוגבר לקרישי דם), ספר לרופא שלך והוא יחליט האם יש לשנות את הטיפול.

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