הודעה על החמרה (מידע בטיחות)

תאריך: 24.1.2012

שם תכשיר באנגלית: Xarelto 10mg

מספר רישום: 142 57 31927 01 / 142 57 31927 00

שם בעל הרישום: באייר ישראל בע"מ

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
Posology and method of administration		Method of administration For oral use.
Special warnings and precautions for use	*Interaction with other medicinal products* The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see section 4.5). Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution. Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. (see section 4.5).	*Interaction with other medicinal products* The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see section 4.5). Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution. Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Syncope and dizziness have been reported in the post-operative setting and may affect the ability to drive and use machines, these adverse reactions have been reported to be uncommon (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

~~No studies of the effects on the ability to drive and use machines have been performed.~~
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Effects on ability to drive and use machines

Summary of the safety profile
The safety of rivaroxaban 10 mg has been evaluated in ~~three~~ four phase III studies (RECORD 1-4) including ~~4,571~~ 6,097 patients exposed to rivaroxaban undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) treated for up to 39 days.
In total, about 14 % of the treated patients experienced adverse reactions. Bleedings or anaemia occurred in approximately 3.3 % and 1 % of patients, respectively. Other common adverse reactions were nausea, increased GGT and an increase in transaminases. The adverse reactions should be interpreted within the surgical setting.
Tabulated summary of adverse reactions
~~, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia symptoms of cardiac ischaemia like chest pain or angina pectoris may occur. Furthermore, known complications secondary to bleeding, such as compartment syndrome or renal failure might occur.~~

The frequencies of adverse reactions reported with Xarelto in the phase III studies in patients undergoing elective hip or knee replacement surgery are summarized in table 1 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:
≥ 1/100 to < 1/10 Common:
≥ 1/1,000 to < 1/100 Uncommon:
≥ 1/10,000 to < 1/1,000 Rare:
~~< 1/10,000 Very rare:~~

cannot be estimated from the available data. Not known:

Treatment-emergent adverse reactions Table 1:

Common	**Uncommon**	**Rare**	**Not known***
Investigations			
Increased GGT, increase in transaminases (incl. ALT increase, AST increase)	Increased lipase, increased amylase, blood bilirubin increased, increased LDH, increased alkaline phosphatase	Bilirubin conjugated increased (with or without concomitant increase of ALT)	

Undesirable effects

Cardiac disorders			
	Tachycardia		
Blood and lymphatic system disorders			
~~Anemia (incl. respective laboratory parameter)~~	Anemia (incl. respective laboratory parameter) thrombocythaemia (incl. platelet count increased)		
Nervous system disorders			
	~~Syncope (incl. loss of consciousness),~~ Dizziness, headache	Syncope (incl. loss of consciousness)	
Gastrointestinal disorders			
Nausea	Constipation, diarrhoea, abdominal and gastrointestinal pain (incl. upper abdominal pain, stomach discomfort), dyspepsia (incl. epigastric discomfort), dry mouth, vomiting		
Renal and urinary disorders			
	Renal impairment (incl. blood creatinine increased, blood urea increased)		Renal failure/ acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
Skin and subcutaneous tissue disorders			
	Pruritus (incl. rare cases of generalised pruritus), rash, ~~urticaria (incl. rare cases of generalised urticaria),~~ contusion	urticaria (incl. rare cases of generalised urticaria),	
Musculoskeletal and connective tissue disorders			
	Pain in extremity		Compartment syndrome secondary to a bleeding
Injury, poisoning and procedural complications			
	Wound secretion		
Vascular disorders			

Post-procedural haemorrhage (incl. post-operative anaemia, and wound haemorrhage)	~~Haemorrhage,~~ Haematoma (incl. rare cases of muscle haemorrhage), gastrointestinal tract haemorrhage (incl. gingival bleeding, rectal haemorrhage, haememesis), ~~haematuria (incl. blood urine present), genital tract haemorrhage (incl. menorrhagia),~~ urogenital tract haemorrhage, hypotension (incl. blood pressure decreased, procedural hypotension), nose bleed		Bleeding into a critical organ (e.g. brain), adrenal haemorrhage, conjunctival haemorrhage, haemoptysis, pseudoaneurysm formation following percutaneous intervention **
General disorders and administration site conditions			
Fever, peripheral oedema	Localised oedema, ~~Fever, peripheral oedema, Feeling unwell (incl. malaise),~~ decreased general strength and energy (incl. fatigue, asthenia)	Feeling unwell (incl. malaise)	
Immune system disorders			
		Dermatitis allergic	Hypersensitivity
Hepatobiliary disorders			
		Hepatic function abnormal	Jaundice

*) Adverse events have been reported in other clinical studies than the three phase III studies in patients undergoing major orthopaedic surgery of the lower limbs or during postmarketing surveillance, for which a frequency could not be estimated.
**) These events occurred in clinical studies in other indications than prevention of VTE in patiens undergoing major orthopaedic surgery.

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 posthaemorrhagic anaemia. The signs, symptoms, and severity (including possibly fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. 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 with other medicinal products affecting haemostasis (see Haemorrhagic risk in section 4.4).
Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia symptoms of cardiac ischaemia like chest pain or angina pectoris may occur. Furthermore, known complications secondary to bleeding, such as compartment syndrome or renal failure might occur. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.