

**הנדון: עדכון העלון לרופא והעלון לצרכן של התכשירים:**

**VOTRIENT 200 mg**  
**VOTRIENT 400 mg**

**התכשירים שבנדון רשומים בישראל להתוויות הבאות:**

Renal cell carcinoma (RCC)

Votrient is indicated in adults for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.

Soft tissue sarcoma (STS)

Votrient is indicated for the treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

**המרכיב הפעיל: PAZOPANIB**

ברצוננו להודיעכם על עדכונים בעלון לרופא והעלון לצרכן של התכשירים בנדון.

העדכון הינו בפרק תופעות הלוואי ומפורט להלן:

**תופעות לוואי שאינן שכיחות (תופעות שמופיעות ב- 1-10 משתמשים מתוך 1000):**

- דלקת של מעטפת חלל הבטן (פריטוניטיס- דלקת צפק)
- נזלת
- פריחה העלולה להיות מגרדת או מודלקת (נקודות שטוחות או בולטות או שלפוחיות)
- תנועות מעיים תכופות
- רגישות מוגברת של העור לאור שמש
- ירידה בתחושה או ברגישות, בעיקר בעור
- **פצעים בעור שאינם מתרפאים (כיבים בעור)**

**תופעות לוואי נדירות (תופעות שמופיעות ב- 1-10 משתמשים מתוך 10000):**

- דלקת של הריאות (פנאומוניטיס)
- **הרחבה והחלשות של דופן כלי הדם או קרע בדופן כלי הדם (מפרצת ובתירת העורק- דיסקציה של העורק)**

**תופעות לוואי ששכיחותן אינה ידועה (תופעות שאת שכיחותן לא ניתן לאמוד מהנתונים הזמינים):**

- הרחבה והחלשות של דופן כלי הדם או קרע בדופן כלי הדם (מפרצת ובתירת העורק- דיסקציה של העורק)
- תסמונת פירוק הגידול כתוצאה מפירוק מהיר של תאי סרטן
- אי ספיקת כבד

Tabulated list of adverse reactions

**Table 2 Treatment-related adverse reactions reported in RCC studies (n = 1149) or during post-marketing period**

System Organ Class	Frequency (all grades)	Adverse reactions	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and Infestations	Common	Infections (with or without neutropenia) <sup>†</sup>	not known	not known	not known
	Uncommon	Gingival infection	1 (<1%)	0	0
		Infectious peritonitis	1 (<1%)	0	0

<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	Uncommon	Tumour pain	1 (<1%)	1 (<1%)	0
<b>Blood and lymphatic system disorders</b>	Common	Thrombocytopenia	80 (7%)	10 (<1%)	5 (<1%)
		Neutropenia	79 (7%)	20 (2%)	4 (<1%)
		Leukopenia	63 (5%)	5 (<1%)	0
	Uncommon	Polycythaemia	6 (0.03%)	1	0
	Rare	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)†	not known	not known	not known
<b>Endocrine disorders</b>	Common	Hypothyroidism	83 (7%)	1 (<1%)	0
<b>Metabolism and nutrition disorders</b>	Very common	Decreased appetite <sup>c</sup>	317 (28%)	14 (1%)	0
	Common	Hypophosphataemia	21 (2%)	7 (<1%)	0
		Dehydration	16 (1%)	5 (<1%)	0
	Uncommon	Hypomagnesaemia	10 (<1%)	0	0
	Not known	Tumour lysis syndrome*	not known	not known	not known
<b>Psychiatric disorders</b>	Common	Insomnia	30 (3%)	0	0
<b>Nervous system disorders</b>	Very common	Dysgeusia <sup>c</sup>	254 (22%)	1 (<1%)	0
		Headache	122 (11%)	11 (<1%)	0
	Common	Dizziness	55 (5%)	3 (<1%)	1 (<1%)
		Lethargy	30 (3%)	3 (<1%)	0
		Paraesthesia	20 (2%)	2 (<1%)	0
		Peripheral sensory neuropathy	17 (1%)	0	0
	Uncommon	Hypoaesthesia	8 (<1%)	0	0
		Transient ischaemic attack	7 (<1%)	4 (<1%)	0
		Somnolence	3 (<1%)	1 (<1%)	0
		Cerebrovascular accident	2 (<1%)	1 (<1%)	1 (<1%)
		Ischaemic stroke	2 (<1%)	0	1 (<1%)
Rare	Posterior reversible encephalopathy/ reversible posterior leukoencephalopathy syndrome†	not known	not known	not known	
<b>Eye disorders</b>	Common	Vision blurred	19 (2%)	1 (<1%)	0
	Uncommon	Retinal detachment†	1 (<1%)	1 (<1%)	0
		Retinal tear†	1 (<1%)	1 (<1%)	0
		Eyelash discolouration	4 (<1%)	0	0
<b>Cardiac disorders</b>	Uncommon	Bradycardia	6 (<1%)	0	0
		Myocardial infarction	5 (<1%)	1 (<1%)	4 (<1%)
		Cardiac dysfunction <sup>f</sup>	4 (<1%)	1 (<1%)	0
		Myocardial ischaemia	3 (<1%)	1 (<1%)	0
<b>Vascular disorders</b>	Very common	Hypertension	473 (41%)	115 (10%)	1 (<1%)
	Common	Hot flush	16 (1%)	0	0

		Venous thromboembolic event <sup>‡</sup>	13 (1%)	6 (<1%)	7 (<1%)
		Flushing	12 (1%)	0	0
	Uncommon	Hypertensive crisis	6 (<1%)	0	2 (<1%)
		Haemorrhage	1 (<1%)	0	0
	Rare	Aneurysms and artery dissections	not known	not known	not known
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	50 (4%)	1 (<1%)	0
		Dysphonia	48 (4%)	0	0
		Dyspnoea	42 (4%)	8 (<1%)	1 (<1%)
		Haemoptysis	15 (1%)	1 (<1%)	0
	Uncommon	Rhinorrhoea	8 (<1%)	0	0
		Pulmonary haemorrhage	2 (<1%)	0	0
		Pneumothorax	1 (<1%)	0	0
Rare	Interstitial lung disease/pneumonitis <sup>†</sup>	not known	not known	not known	
Gastrointestinal disorders	Very common	Diarrhoea	614 (53%)	65 (6%)	2 (<1%)
		Nausea	386 (34%)	14 (1%)	0
		Vomiting	225 (20%)	18 (2%)	1 (<1%)
		Abdominal pain <sup>a</sup>	139 (12%)	15 (1%)	0
	Common	Stomatitis	96 (8%)	4 (<1%)	0
		Dyspepsia	83 (7%)	2 (<1%)	0
		Flatulence	43 (4%)	0	0
		Abdominal distension	36 (3%)	2 (<1%)	0
		Mouth ulceration	28 (2%)	3 (<1%)	0
		Dry mouth	27 (2%)	0	0
		Uncommon	Pancreatitis	8 (<1%)	4 (<1%)
	Rectal haemorrhage		8 (<1%)	2 (<1%)	0
	Haematochezia		6 (<1%)	0	0
	Gastrointestinal haemorrhage		4 (<1%)	2 (<1%)	0
	Melaena		4 (<1%)	1 (<1%)	0
	Frequent bowel movements		3 (<1%)	0	0
	Anal haemorrhage		2 (<1%)	0	0
	Large intestine perforation		2 (<1%)	1 (<1%)	0
	Mouth haemorrhage		2 (<1%)	0	0
	Upper gastrointestinal haemorrhage		2 (<1%)	1 (<1%)	0
	Enterocutaneous fistula		1 (<1%)	0	0
	Haematemesis		1 (<1%)	0	0
	Haemorrhoidal haemorrhage	1 (<1%)	0	0	
Ileal perforation	1 (<1%)	0	1 (<1%)		
Oesophageal haemorrhage	1 (<1%)	0	0		
Retroperitoneal haemorrhage	1 (<1%)	0	0		
Hepatobiliary disorders	Common	Hyperbilirubinaemia	38 (3%)	2 (<1%)	1 (<1%)
		Hepatic function abnormal	29 (3%)	13 (1%)	2 (<1%)
		Hepatotoxicity	18 (2%)	11 (<1%)	2 (<1%)
	Uncommon	Jaundice	3 (<1%)	1 (<1%)	0
		Drug induced liver injury	2 (<1%)	2 (<1%)	0
		Hepatic failure <sup>†</sup>	1 (<1%)	0	1 (<1%)

<b>Skin and subcutaneous disorders</b>	Very common	Hair colour change	404 (35%)	1 (<1%)	0
		Palmar-plantar erythrodysesthesia syndrome	206 (18%)	39 (3%)	0
		Alopecia	130 (11%)	0	0
		Rash	129 (11%)	7 (<1%)	0
	Common	Skin hypopigmentation	52 (5%)	0	0
		Dry skin	50 (4%)	0	0
		Pruritus	29 (3%)	0	0
		Erythema	25 (2%)	0	0
		Skin depigmentation	20 (2%)	0	0
		Hyperhidrosis	17 (1%)	0	0
	Uncommon	Nail disorders	11 (<1%)	0	0
		Skin exfoliation	10 (<1%)	0	0
		Photosensitivity reaction	7 (<1%)	0	0
		Rash erythematous	6 (<1%)	0	0
		Skin disorder	5 (<1%)	0	0
		Rash macular	4 (<1%)	0	0
		Rash pruritic	3 (<1%)	0	0
		Rash vesicular	3 (<1%)	0	0
		Pruritus generalised	2 (<1%)	1 (<1%)	0
		Rash generalised	2 (<1%)	0	0
Rash papular		2 (<1%)	0	0	
Plantar erythema		1 (<1%)	0	0	
Skin ulcer†		Not known	Not known	Not Known	
<b>Musculoskeletal and connective tissue disorders</b>		Common	Arthralgia	48 (4%)	8 (<1%)
	Myalgia		35 (3%)	2 (<1%)	0
	Muscle spasms		25 (2%)	0	0
	Uncommon	Musculoskeletal pain	9 (<1%)	1 (<1%)	0
<b>Renal and urinary disorders</b>	Very Common	Proteinuria	135 (12%)	32 (3%)	0
	Uncommon	Haemorrhage urinary tract	1 (<1%)	0	0
<b>Reproductive system and breast disorders</b>	Uncommon	Menorrhagia	3 (<1%)	0	0
		Vaginal haemorrhage	3 (<1%)	0	0
		Metrorrhagia	1 (<1%)	0	0
<b>General disorders and administration site conditions</b>	Very common	Fatigue	415 (36%)	65 (6%)	1 (<1%)
	Common	Mucosal inflammation	86 (7%)	5 (<1%)	0
		Asthenia	82 (7%)	20 (2%)	1 (<1%)
		Oedema <sup>b</sup>	72 (6%)	1 (<1%)	0
		Chest pain	18 (2%)	2 (<1%)	0
	Uncommon	Chills	4 (<1%)	0	0
Mucous membrane disorder		1 (<1%)	0	0	
<b>Investigations</b>	Very common	Alanine aminotransferase increased	246 (21%)	84 (7%)	14 (1%)
		Aspartate aminotransferase increased	211 (18%)	51 (4%)	10 (<1%)
	Common	Weight decreased	96 (8%)	7 (<1%)	0
		Blood bilirubin increased	61 (5%)	6 (<1%)	1 (<1%)

		Blood creatinine increased	55 (5%)	3 (<1%)	0
		Lipase increased	51 (4%)	21 (2%)	7 (<1%)
		White blood cell count decreased <sup>d</sup>	51 (4%)	3 (<1%)	0
		Blood thyroid stimulating hormone increased	36 (3%)	0	0
		Amylase increased	35 (3%)	7 (<1%)	0
		Gamma-glutamyltransferase increased	31 (3%)	9 (<1%)	4 (<1%)
		Blood pressure increased	15 (1%)	2 (<1%)	0
		Blood urea increased	12 (1%)	1 (<1%)	0
		Liver function test abnormal	12 (1%)	6 (<1%)	1 (<1%)
	Uncommon	Hepatic enzyme increased	11 (<1%)	4 (<1%)	3 (<1%)
		Blood glucose decreased	7 (<1%)	0	1 (<1%)
		Electrocardiogram QT prolonged	7 (<1%)	2 (<1%)	0
		Transaminase increased	7 (<1%)	1 (<1%)	0
		Thyroid function test abnormal	3 (<1%)	0	0
		Blood pressure diastolic increased	2 (<1%)	0	0
		Blood pressure systolic increased	1 (<1%)	0	0

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).

\*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.

The following terms have been combined:

<sup>a</sup> Abdominal pain, abdominal pain upper and abdominal pain lower

<sup>b</sup> Oedema, oedema peripheral, eye oedema, localised oedema and face oedema

<sup>c</sup> Dysgeusia, ageusia and hypogeusia

<sup>d</sup> White cell count decreased, neutrophil count decreased and leukocyte count decreased

<sup>e</sup> Decreased appetite and anorexia

<sup>f</sup> Cardiac dysfunction, left ventricular dysfunction, cardiac failure and restrictive cardiomyopathy

<sup>g</sup> Venous thromboembolic event, deep vein thrombosis, pulmonary embolism and thrombosis

**Table 3 Treatment-related adverse reactions reported in STS studies (n=382) or during post-marketing period**

System Organ Class	Frequency (all grades)	Adverse reactions	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
<b>Infections and infestations</b>	Common	Gingival infection	4 (1%)	0	0
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	Very common	Tumour pain	121 (32%)	32 (8%)	0
<b>Blood and lymphatic system disorders<sup>f</sup></b>	Very common	Leukopenia	106 (44%)	3 (1%)	0
		Thrombocytopenia	86 (36%)	7 (3%)	2 (<1%)
		Neutropenia	79 (33%)	10 (4%)	0
	Uncommon	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)	1 (<1%)	1 (<1%)	0
<b>Endocrine disorders</b>	Common	Hypothyroidism	18 (5%)	0	0
<b>Metabolism and nutrition disorders</b>	Very common	Decreased appetite	108 (28%)	12 (3%)	0
		Hypoalbuminemia <sup>f</sup>	81 (34%)	2 (<1%)	0
	Common	Dehydration	4 (1%)	2 (1%)	0
	Uncommon	Hypomagnesaemia	1 (<1%)	0	0
	Not known	Tumour lysis syndrome*	not known	not known	not known
<b>Psychiatric disorders</b>	Common	Insomnia	5 (1%)	1 (<1%)	0
<b>Nervous system disorders</b>	Very common	Dysgeusia <sup>c</sup>	79 (21%)	0	0
		Headache	54 (14%)	2 (<1%)	0
	Common	Peripheral sensory neuropathy	30 (8%)	1 (<1%)	0
		Dizziness	15 (4%)	0	0
	Uncommon	Somnolence	3 (<1%)	0	0
		Paresthesia	1 (<1%)	0	0
		Cerebral infarction	1 (<1%)	0	1 (<1%)
<b>Eye disorders</b>	Common	Vision blurred	15 (4%)	0	0
<b>Cardiac disorders</b>	Common	Cardiac dysfunction <sup>g</sup>	21 (5%)	3 (<1%)	1 (<1%)
		Left ventricular dysfunction	13 (3%)	3 (<1%)	0
		Bradycardia	4 (1%)	0	0
	Uncommon	Myocardial infarction	1 (<1%)	0	0
<b>Vascular disorders</b>	Very common	Hypertension	152 (40%)	26 (7%)	0
	Common	Venous thromboembolic event <sup>d</sup>	13 (3%)	4 (1%)	5 (1%)
		Hot flush	12 (3%)	0	0
		Flushing	4 (1%)	0	0
	Uncommon	Haemorrhage	2 (<1%)	1 (<1%)	0
	<b>Rare</b>	Aneurysms and artery dissections	not known	not known	not known
<b>Respiratory, thoracic and mediastinal disorders</b>	Common	Epistaxis	22 (6%)	0	0
		Dysphonia	20 (5%)	0	0
		Dyspnoea	14 (4%)	3 (<1%)	0
		Cough	12 (3%)	0	0
		Pneumothorax	7 (2%)	2 (<1%)	1 (<1%)

		Hiccups	4 (1%)	0	0
		Pulmonary haemorrhage	4 (1%)	1 (<1%)	0
	Uncommon	Oropharyngeal pain	3 (<1%)	0	0
		Bronchial haemorrhage	2 (<1%)	0	0
		Rhinorrhoea	1 (<1%)	0	0
		Haemoptysis	1 (<1%)	0	0
Rare	Interstitial lung disease/pneumonitis†	not known	not known	not known	
<b>Gastrointestinal disorders</b>	Very common	Diarrhoea	174 (46%)	17 (4%)	0
		Nausea	167 (44%)	8 (2%)	0
		Vomiting	96 (25%)	7 (2%)	0
		Abdominal pain <sup>a</sup>	55 (14%)	4 (1%)	0
		Stomatitis	41 (11%)	1 (<1%)	0
	Common	Abdominal distension	16 (4%)	2 (1%)	0
		Dry mouth	14 (4%)	0	0
		Dyspepsia	12 (3%)	0	0
		Mouth haemorrhage	5 (1%)	0	0
		Flatulence	5 (1%)	0	0
		Anal haemorrhage	4 (1%)	0	0
	Uncommon	Gastrointestinal haemorrhage	2 (<1%)	0	0
		Rectal haemorrhage	2 (<1%)	0	0
		Enterocutaneous fistula	1 (<1%)	1 (<1%)	0
		Gastric haemorrhage	1 (<1%)	0	0
		Melaena	2 (<1%)	0	0
		Oesophageal haemorrhage	1 (<1%)	0	1 (<1%)
		Peritonitis	1 (<1%)	0	0
		Retroperitoneal haemorrhage	1 (<1%)	0	0
		Upper gastrointestinal haemorrhage	1 (<1%)	1 (<1%)	0
Ileal perforation		1 (<1%)	0	1 (<1%)	
<b>Hepatobiliary disorders</b>	Uncommon	Hepatic function abnormal	2 (<1%)	0	1 (<1%)
	Not known	Hepatic failure*	not known	not known	not known
<b>Skin and subcutaneous disorders</b>	Very common	Hair colour change	93 (24%)	0	0
		Skin hypopigmentation	80 (21%)	0	0
		Exfoliative rash	52 (14%)	2 (<1%)	0
	Common	Alopecia	30 (8%)	0	0
		Skin disorder <sup>c</sup>	26 (7%)	4 (1%)	0
		Dry skin	21 (5%)	0	0
		Hyperhidrosis	18 (5%)	0	0
		Nail disorder	13 (3%)	0	0
		Pruritus	11 (3%)	0	0
		Erythema	4 (1%)	0	0
	Uncommon	Skin ulcer	3 (<1%)	1 (<1%)	0
		Rash	1 (<1%)	0	0
		Rash papular	1 (<1%)	0	0
		Photosensitivity reaction	1 (<1%)	0	0
Palmar-plantar erythrodysesthesia syndrome		2 (<1%)	0	0	
<b>Musculoskeletal and connective tissue disorders</b>	Common	Musculoskeletal pain	35 (9%)	2 (<1%)	0
		Myalgia	28 (7%)	2 (<1%)	0
		Muscle spasms	8 (2%)	0	0

	Uncommon	Arthralgia	2 (<1%)	0	0
<b>Renal and urinary disorders</b>	Uncommon	Proteinuria	2 (<1%)	0	0
<b>Reproductive system and breast disorder</b>	Uncommon	Vaginal haemorrhage	3 (<1%)	0	0
		Menorrhagia	1 (<1%)	0	0
<b>General disorders and administration site conditions</b>	Very common	Fatigue	178 (47%)	34 (9%)	1 (<1%)
	Common	Oedema <sup>b</sup>	18 (5%)	1 (<1%)	0
		Chest pain	12 (3%)	4 (1%)	0
		Chills	10 (3%)	0	0
	Uncommon	Mucosal inflammation <sup>c</sup>	1 (<1%)	0	0
Asthenia		1 (<1%)	0	0	
<b>Investigations<sup>h</sup></b>	Very common	Weight decreased	86 (23%)	5 (1%)	0
	Common	Ear, nose and throat examination abnormal <sup>c</sup>	29 (8%)	4 (1%)	0
		Alanine aminotransferase increased	8 (2%)	4 (1%)	2 (<1%)
		Blood cholesterol abnormal	6 (2%)	0	0
		Aspartate aminotransferase increased	5 (1%)	2 (<1%)	2 (<1%)
		Gamma glutamyltransferase increased	4 (1%)	0	3 (<1%)
	Uncommon	Blood bilirubin increased	2 (<1%)	0	0
		Aspartate aminotransferase	2 (<1%)	0	2 (<1%)
		Alanine aminotransferase	1 (<1%)	0	1 (<1%)
		Platelet count decreased	1 (<1%)	0	1 (<1%)
		Electrocardiogram QT prolonged	2 (<1%)	1 (<1%)	0

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).

\*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.

The following terms have been combined:

<sup>a</sup> Abdominal pain, abdominal pain upper and gastrointestinal pain

<sup>b</sup> Oedema, oedema peripheral and eyelid oedema

<sup>c</sup> The majority of these cases were Palmar-plantar erythrodysesthesia syndrome

<sup>d</sup> Venous thromboembolic events – includes Deep vein thrombosis, Pulmonary embolism and Thrombosis terms

<sup>e</sup> The majority of these cases describe mucositis

<sup>f</sup> Frequency is based on laboratory value tables from VEG110727 (N=240). These were reported as adverse events less frequently by investigators than as indicated by laboratory value tables.

<sup>g</sup> Cardiac dysfunction events – includes Left ventricular dysfunction, Cardiac failure and Restrictive cardiomyopathy

<sup>h</sup> Frequency is based on adverse events reported by investigators. Laboratory abnormalities were reported as adverse events less frequently by investigators than as indicated by laboratory value tables.

העלונים לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום.

בברכה,  
יעל לוי טל  
רוקחת ממונה



