06/2019

רופא/ה, רוקח/ת נכבד/ה,

ניאופרם שמחה להודיעך על אישורה של תוספת התוויה לתכשירים:

לנווימה 4 מ"ג כמוסות קשיחות **Lenvima 4 mg** hard capsules

לנווימה 10 מ"ג כמוסות קשיחות **Lenvima 10 mg** hard capsules

החומר הפעיל: lenvatinib (as mesilate) 4 mg, lenvatinib (as mesilate) 10 mg

נוסח ההתוויה החדשה:

- LENVIMA is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

- LENVIMA is indicated in combination with everolimus for the treatment of adult patients with advanced clear cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

- LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.

- העלונים לרופא ולצרכן עודכן במרץ 2019
- בהודעה זו מצוינים השינויים המהווים החמרה וכן שינויים נוספים שאינם החמרה
- טקסט שהתווסף מסומן בקו תחתי, טקסט שהוסר מסומן בקו חוצה

העדכונים העיקריים בעלון לרופא נעשו בסעיפים הבאים:

4.1 Therapeutic indications

LENVIMA is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

LENVIMA is indicated in combination with everolimus for the treatment of adult patients with advanced clear cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

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4.2 Posology and method of administration

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Posology

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Hepatocellular Carcinoma (HCC):

The recommended daily dose of lenvatinib is 8 mg (two 4 mg capsules) once daily for patients with a body weight of < 60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥ 60 kg. Dose adjustments are based only on toxicities observed and not on body weight changes during treatment. The daily dose is to be modified, as needed, according to the dose/toxicity management plan.

Dose adjustments and Discontinuation for HCC
Management of some adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy. Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. Details for monitoring, dose adjustment and discontinuation are provided in Table 4.

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Table 4 Dose modifications from recommended lenvatinib daily dose in HCC patients

Starting Dose		**≥60 kg BW** **12 mg (three 4 mg capsules orally once daily)**	**<60 kg BW** **8 mg (two 4 mg capsules orally once daily)**
Persistent and Intolerable Grade 2 or Grade 3 Toxicities[a]			
Adverse Reaction	**Modification**	**Adjusted Dose[b] (≥60 kg BW)**	**Adjusted Dose[b] (<60 kg BW)**
First occurrence [c]	Interrupt until resolved to Grade 0-1 or baseline[d]	8 mg (two 4 mg capsules) orally once daily	4 mg (one 4 mg capsule) orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4 mg (one 4 mg capsule) orally once daily	4 mg (one 4 mg capsule) orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4 mg (one 4 mg capsule) orally every other day	Discontinue
Life-threatening toxicities (Grade 4): Discontinue[e]			

a. Initiate medical management for nausea, vomiting, or diarrhoea prior to interruption or dose reduction.
b. Reduce dose in succession based on the previous dose level (12 mg, 8 mg, 4 mg or 4 mg every other day).
c. Haematologic toxicity or proteinuria-no dose adjustment required for first occurrence.
d. For haematologic toxicity, dosing can restart when resolved to Grade 2; proteinuria, resume when resolves to less than 2g/24 hours
e. Excluding laboratory abnormalities judged to be nonlife-threatening, which should be managed as Grade 3.

Grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

Special populations
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HCC
Patients ≥75 years, of white race or female sex or those with worse baseline hepatic impairment (Child-Pugh A score of 6 compared to score of 5) appear to have reduced tolerability to lenvatinib.

HCC patients other than those with moderate and severe hepatic impairment or severe renal impairment should initiate treatment at the recommended starting dose of 8 mg (two 4 mg capsules) for body weight < 60 kg and 12 mg (three 4 mg capsules) for body weight ≥ 60 kg, following which the dose should be further adjusted on the basis of individual tolerability.

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Patients with hepatic impairment

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HCC

In the patient populations enrolled in the HCC study no dose adjustments were required on the basis of hepatic function in those patients who had mild hepatic impairment (Child-Pugh A). The available very limited data are not sufficient to allow for a dosing recommendation for HCC patients with moderate hepatic impairment (Child-Pugh B). Close monitoring of overall safety is recommended in these patients (see sections 4.4 and 5.2). Lenvatinib has not been studied in patients with severe hepatic imparement (Child-Pugh C) and is not recommended for use in these patients.

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Patients with renal impairment

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HCC

No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment. The available data do not allow for a dosing recommendation for patients with HCC and severe renal impairment.

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4.4 Special warnings and precautions for use

Hypertension

Hypertension has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). Blood pressure (BP) should be well controlled prior to treatment with lenvatinib and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with lenvatinib. Serious complications of poorly controlled hypertension, including aortic dissection, have been reported.

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Proteinuria

Proteinuria has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). Urine protein should be monitored regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2). Cases of nephrotic syndrome have been reported in patients using lenvatinib. Lenvatinib should be discontinued in the event of nephrotic syndrome.

Hepatotoxicity

DTC and Clear cell RCC

LLiver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase (ALT), ~~increases in~~ aspartate aminotransferase (AST), and ~~increases in~~ blood bilirubin. Hepatic failure and acute hepatitis (<1%; see section 4.8, Description of selected adverse reactions) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive metastatic liver metastases disease.

In HCC patients treated with lenvatinib in the REFLECT trial, liver-related adverse reactions including hepatic encephalopathy and hepatic failure (including fatal reactions) were reported at a higher frequency (see Section 4.8) compared to patients treated with sorafenib . Patients with worse hepatic impairment and/or greater liver tumour burden at baseline had a higher risk of developing hepatic encephalopathy and hepatic failure. Hepatic encephalopathy also occurred more frequently in patients aged 75 years and older. Approximately half of the events of hepatic failure and one third of the events of the hepatic encephalopathy were reported in patients with disease progression.

Data in HCC patients with moderate hepatic impairment (Child-Pugh B) are very limited and there are currently no data available in HCC patients with severe hepatic impairment (Child-Pugh C). Since lenvatinib is mainly eliminated by hepatic metabolism, an increase in exposure in patients with moderate to severe hepatic impairment is expected.

Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. Patients with HCC should be monitored for worsening liver function including hepatic encephalopathy. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

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Haemorrhage

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One fatal case of hepatic tumour haemorrhage in a patient with HCC has been reported.

Screening for and subsequent treatment of oesophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with lenvatinib.

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Non-Gastrointestinal fistula

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In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of fistula and pneumothorax occurred in association with tumour regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. Lung metastases may also increase the risk of pneumothorax.

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Wound Healing Complications

No formal studies of the effect of lenvatinib on wound healing have been conducted. Impaired wound healing has been reported in patients receiving lenvatinib. Temporary interruption of lenvatinib should be considered in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of lenvatinib following a major surgical procedure. Therefore, the decision to resume lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.

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4.8 Undesirable effects

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HCC

The most frequently reported adverse reactions (occurring in ≥30% of patients) are hypertension (44.0%), diarrhoea (38.1%), decreased appetite (34.9%), fatigue (30.6%), and decreased weight (30.4%).

The most important serious adverse reactions were hepatic failure (2.8%), hepatic encephalopathy (4.6%), oesophageal varices haemorrhage (1.4%), cerebral haemorrhage (0.6%), arterial thromboembolic events (2.0%) including myocardial infarction (0.8%), cerebral infarction (0.4%) and cerebrovascular accident (0.4%) and renal failure/impairment events (1.4%). There was a higher incidence of decreased neutrophil count in patients with HCC (8.7% on lenvatinib than in other non- HCC tumour types (1.4%)), which was not associated with infection, sepsis or bacterial peritonitis.

In 496 patients with HCC, dose modification (interruption or reduction) and discontinuation were the actions taken for an adverse reaction in 62.3% and 20.2% of patients, respectively. Adverse reactions that most commonly led to dose modifications (in ≥5% of patients) were decreased appetite, diarrhoea, proteinuria, hypertension, fatigue, PPE and decreased platelet count. Adverse reactions that most commonly led to discontinuation of lenvatinib were hepatic encephalopathy, fatigue, increased blood bilirubin, proteinuria and hepatic failure.

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Table ~~5~~6 Adverse reactions reported in patients treated with lenvatinib ~~in clinical trials~~

System Organ Class (MedDRA terminology*)	**Very Common**	**Common**	**Uncommon**	**Not known**
Infections and infestation	Urinary tract infection		Perineal abscess	
Blood and lymphatic disorders	Thrombocytopenia[a] Leukopenia[a] Neutropenia[a]	Lymphopenia[a]	Splenic infarction	
Endocrine disorders	Hypothyroidism** Increased ~~B~~blood thyroid stimulating hormone ~~increased~~‡**			

System Organ Class (MedDRA terminology[*])	**Very Common**	**Common**	**Uncommon**	**Not known**
Metabolism and nutrition disorders	Hypocalcaemia‡ Hypercholesterolaemia[b,**] Hypokalaemia Decreased appetite Decreased ~~W~~weight ~~decreased~~	Dehydration Hypomagnesaemia[b]		
Psychiatric disorders	Insomnia			
Nervous system disorders	Dizziness Headache Dysgeusia	Cerebrovascular accident [†]	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	
Cardiac disorders		Myocardial infarction[c,†] Cardiac failure Prolonged e~~E~~lectrocardiogram QT ~~prolonged~~ Decreased ~~E~~ejection fraction ~~decreased~~		
Vascular disorders	Haemorrhage[d, †,‡] Hypertension[e,‡] Hypotension		Aortic Dissection[***]	
Respiratory, thoracic and mediastinal disorders	Dysphonia	Pulmonary embolism[†,]	Pneumothorax	
Gastrointestinal disorders	Diarrhoea[‡,**] Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth	Anal fistula Flatulence Increased lipase Increased amylase	Pancreatitis [i,†]	

System Organ Class (MedDRA terminology*)	**Very Common**	**Common**	**Uncommon**	**Not known**
Hepatobiliary disorders	Increased ~~B~~blood bilirubin ~~increased~~[j, ‡] Hypoalbuminaemia[j, ‡] Increased ~~A~~alanine aminotransferase ~~increased~~[‡] Increased a~~A~~spartate aminotransferase ~~increased~~[‡]	Hepatic failure[k,‡,†] Hepatic encephalopathy[l,‡,†] ~~Aspartate aminotransferase increased~~[‡] H~~ypoalbuminaemia~~[‡] ~~Alanine aminotransferase increased~~[‡] Increased ~~B~~blood alkaline phosphatase ~~increased~~ Hepatic function abnormal Increased ~~G~~gamma-glutamyltransferase ~~increased~~[e] B~~lood bilirubin increased~~[‡]Cholecystitis	Hepatocellular damage/hepatitis[‡m]	
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome Palmar erythema Rash Alopecia	Hyperkeratosis		
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain			
Renal and urinary disorders	Proteinuria[‡]	Renal failure cases[‡n, †, ‡] Renal impairment[‡] Increased ~~B~~blood creatinine ~~increased~~ Increased ~~B~~blood urea ~~increased~~	Nephrotic syndrome	
General disorders and administration site conditions	Fatigue Asthenia O~~edema~~ P~~p~~eripheral Oedema	Malaise	Impaired healing[***]	Non-gastrointestinal fistula[‡o]

*: Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. Preferred terms have been reassigned to the SOC most relevant to the target organ.

**: These adverse reactions occur more frequently with combination therapy compared to lenvatinib monotherapy.

***: Identified from post-marketing use of lenvatinib

†: Includes cases with a fatal outcome.

‡: See section 4.8 Description of selected adverse reactions for further characterisation.

The following terms have been combined:

a: Thrombocytopenia includes thrombocytopenia and decreased platelet count. Neutropenia includes neutropenia and decreased neutrophil count decreased. Leukopenia includes leukopenia and decreased white blood cell count. Lymphopenia includes lymphopenia and decreased lymphocyte count.

b: Hypomagnesaemia includes hypomagnesaemia and decreased blood magnesium. Hypercholesterolaemia includes hypercholesterolaemia and increased blood cholesterol.

c: Myocardial infarction includes myocardial infarction and acute myocardial infarction.
d: Includes all haemorrhage terms.
Haemorrhage terms that occurred in 5 or more subjects with DTC were: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechial, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma and vaginal haemorrhage.
Haemorrhage terms that occurred in 5 or more subjects with HCC were: epistaxis, haematuria, gingival bleeding, haemoptysis, oesophageal varices haemorrhage, haemorrhoidal haemorrhage, mouth haemorrhage, rectal haemorrhage and upper gastrointestinal haemorrhage.~~Haemorrhage includes: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechiae, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma, vaginal haemorrhage, conjunctival haemorrhage, haemorrhoidal haemorrhage, intracranial tumour haemorrhage, laryngeal haemorrhage, ecchymosis, increased tendency to bruise, post procedural haemorrhage, purpura, skin haemorrhage, aneurysm ruptured, arterial haemorrhage, eye haemorrhage, gastric haemorrhage, gastroduodenitis haemorrhagic, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhagic stroke, melaena, metrorrhagia, nail bed bleeding, haemothorax, postmenopausal haemorrhage, proctitis haemorrhagic, renal haematoma, splenic haemorrhage, splinter haemorrhages, subarachnoid haemorrhage, tracheal haemorrhage, tumour haemorrhage.~~
e: Hypertension includes: hypertension, hypertensive crisis, increased diastolic blood pressure ~~diastolic~~, orthostatic hypertension, and increased blood pressure.
f: Gastrointestinal and abdominal pain includes: abdominal discomfort, abdominal pain, ~~lower~~ abdominal pain lower, ~~upper~~ abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
g: Oral inflammation includes: aphthous stomatitis, aphthous ulcer, gingival erosion, gingival ulceration, oral mucosal blistering, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.
h: Oral pain includes: oral pain, glossodynia, gingival pain, oropharyngeal discomfort, ~~and~~ oropharyngeal pain and tongue discomfort.
i: Pancreatitis includes: pancreatitis and acute pancreatitis.
j: Hyperbilirubinaeamia includes: hyperbilirubinaemia, increased blood bilirubin, jaundice and increased bilirubin conjugated. Hypoalbuminaemia includes hypoalbuminaemia and decreased blood albumin.
k: Hepatic failure includes: hepatic failure, acute hepatic failure and chronic hepatic failure.
l: Hepatic encephalopathy includes: hepatic encephalopathy, coma hepatic, metabolic encephalopathy and encephalopathy.
im: ~~—~~Hepatocellular damage and hepatitis includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.
jn: Renal failure cases includes: acute prerenal failure, renal failure, renal failure acute, acute kidney injury, and renal tubular necrosis.
ko: Non-gastrointestinal fistula includes cases of fistula occurring outside of the stomach and intestines such as tracheal, tracheo-oesophageal, oesophageal, female genital tract fistula, and cutaneous fistula.

העדכונים בעלון לצרכן נעשו בסעיפים הבאים:

1. <u>למה מיועדת התרופה?</u>

- ~~–~~לטיפול במבוגרים עם סרטן מתקדם של בלוטת התריס כאשר הטיפול ביוד רדיואקטיבי לא סייע בבלימת המחלה.
- ~~–~~בשילוב עם אברולימוס, לטיפול במבוגרים עם סרטן כליה מתקדם מסוג תאים בהירים, כאשר טיפולים אחרים [הנקראים "טיפול ממוקד נגד גורם הגדילה של אנדותל כלי הדם – VEGF (Vascular endothelial growth factor)"] לא סייעו בעצירת המחלה.
- כטיפול יחידני לטיפול בסרטן הכבד *(hepatocellular carcinoma)* במבוגרים שלא טופלו בעבר בטיפול סיסטמי בתרופה אחרת נגד סרטן. אנשים מקבלים טיפול בלנווימה כאשר סרטן הכבד שלהם ~~התפשט~~בשלב מתקדם או שלא ניתן להסירו בניתוח.

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! אזהרות מיוחדות הנוגעות לשימוש בתרופה

- **לפני התחלת הטיפול בלנווימה ספר לרופא אם:**

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- אתה צריך לעבור הליך כירורגי. רופאך עשוי לשקול להפסיק את הטיפול בלנווימה אם אתה עתיד לעבור הליך כירורגי רציני מכיוון שלנווימה עשויה להשפיע על ריפוי פצעים. ניתן להתחיל את הטיפול בלנווימה מחדש לאחר שהושלם ריפוי הפצע כראוי

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2. <u>תופעות לוואי:</u>

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יש לפנות לרופא מיד אם אתה סובל מאחת מתופעות לוואי הבאות – ייתכן ותצטרך טיפול רפואי דחוף:

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- כאב או לחץ בחזה, כאב בזרועות, בגב, בצוואר או בלסת, קוצר נשימה, דופק מהיר או לא סדיר, שיעול, שפתיים או אצבעות כחלחלות, תחושת עייפות יתר – אלו עלולים להיות סימנים לבעיה לבבית, ~~או~~לקריש דם בריאה או לדליפת אוויר מהריאה לתוך החזה כך שהריאה לא יכולה להתנפח.
- כאב חזק בבטן - עלול להיגרם כתוצאה מחור בדופן המעיים או פיסטולה (חור במעיים היוצר מעבר דמוי צינור אל חלק אחר בגוף או בעור).
- צואה שחורה, דמוית זפת או דמית או שיעול דמי – אלו עלולים להיות סימנים של דימום פנימי.
- עור צהוב או הצהבה של הלבן בעיניים (צהבת) או נמנום, בלבול, ריכוז ירוד – אלה עשויים להיות סימנים לבעיות בכבד.

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תופעות לוואי שכיחות מאוד: (משפיעות על יותר מ-1 מתוך 10 מטופלים)

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- תת פעילות של בלוטת התריס (עייפות, עלייה במשקל, עצירות, תחושת קור, עור יבש)
- שינויים בתוצאות בדיקת דם - רמות אשלגן (נמוכות), רמות סידן (נמוכות), כולסטרול (גבוה) ורמת ההורמון הממריץ של בלוטת התריס (TSH) (גבוהה)
- ירידה במספר תאי הדם הלבנים
- שינויים בתוצאות בדיקת דם לתפקוד הכבד

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תופעות לוואי שכיחות: (משפיעות על עד 1 מתוך 10 מטופלים)

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- כשל בכבד
- נמנום, בלבול, ריכוז ירוד, ואובדן הכרה שעשויים להיות סימנים לכשל בכבד
- תחושה כללית רעה
- דלקת בכיס המרה
- שבץ מוחי
- פיסטולה בפי הטבעת (תעלה קטנה שנוצרת בין פי הטבעת לבין העור שמסביב)
- שינויים בתוצאות בדיקת דם עבור ~~אנזימי כבד, רמת תאי דם לבנים (נמוכה), רמת נתרן ו~~רמות מגנזיום ~~בדם~~ (~~נמוכה~~נמוכות), רמות כולסטרול (גבוהות), ורמות הורמון מעורר בלוטת התריס (TSH, גבוהות).
- שינויים בתוצאות בדיקת דם עבור תפקודי כליות ואי ספיקת כליות
- עליה בליפאז ועמילאז (אנזימים המעורבים בעיכול)

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תופעות לוואי שאינן שכיחות: (משפיעות על עד 1 מתוך 100 מטופלים)

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- כאב חזק בחלק העליון השמאלי של הבטן שעלול להיות מלווה בחום, צמרמורות, בחילות והקאות (אוטם של הטחול)
- דלקת בלבלב
- בעיות בריפוי פצעים
- כאב חמור בגב, בחזה או בבטן הקשור לקרע בדופן אבי העורקים ודימום פנימי

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מצ"ב העלון לרופא ולצרכן כפי שאושרו על ידי משרד הבריאות הישראלי.

העלונים לרופא ולצרכן נשלחו למשרד-הבריאות לצורך העלאתם למאגר התרופות שבאתר משרד-הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום: ניאופרם סיינטיפיק בע"מ, רח' השילוח 6, ת.ד. 7063 פתח-תקווה,
טל: 03-9373753.

בברכה,

עוז וולך
מנהל רגולציה ורוקח ממונה
ניאופרם סיינטיפיק בע"מ