

מרץ 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא ובעלון לצרכן של התכשיר:
העדכון כולל תוספת התוויה כמפורט מטה.

Darzalex

המאושר להתוויות הבאות:

DARZALEX is indicated:

In combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

4.1 Therapeutic indications

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- ~~as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.~~
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

DARZALEX should be administered by a healthcare professional, in an environment where resuscitation facilities are available.

Pre- and post-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below “Recommended concomitant medications”, “Management of infusion-related reactions” and section 4.4.

Posology

Dosing schedule in combination with lenalidomide (4-week cycle regimen) and for monotherapy:

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide (4-week cycle dosing regimen) and monotherapy

<u>Weeks</u>	<u>Schedule</u>
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24 ^a	every two weeks (total of 8 doses)
Week 25 onwards until disease progression ^b	every four weeks

^a First dose of the every-2-week dosing schedule is given at Week 9

^b First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics

Newly diagnosed multiple myeloma

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens) ~~for patients ineligible for autologous stem cell transplant:~~

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 1~~2~~.

Table 1~~2~~: DARZALEX dosing schedule in combination with bortezomib, melphalan and prednisone (VMP); 6-week cycle dosing regimen)

<u>Weeks</u>	<u>Schedule</u>
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54 ^a	every three weeks (total of 16 doses)
Week 55 onwards until disease progression ^b	every four weeks

^a First dose of the every-3-week dosing schedule is given at Week 7

^b First dose of the every-4-week dosing schedule is given at Week 55

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. For information on the VMP dose and dosing schedule when administered with DARZALEX, see section 5.1.

Relapsed/Refractory multiple myeloma

~~Dosing schedule for monotherapy and in combination with lenalidomide (4-week cycle regimen):~~

~~The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 2.~~

Table 2: ~~DARZALEX dosing schedule for monotherapy and in combination with lenalidomide (4-week cycle dosing regimen)~~

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24^a	every two weeks (total of 8 doses)
Week 25 onwards until disease progression^b	every four weeks

^a ~~First dose of the every 2-week dosing schedule is given at Week 9~~

^b ~~First dose of the every 4-week dosing schedule is given at Week 25~~

~~For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.~~

Dosing schedule in combination with bortezomib (3-week cycle regimen):

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 3.

Table 3: DARZALEX dosing schedule in combination with bortezomib (3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24 ^a	every three weeks (total of 5 doses)
Week 25 onwards until disease progression ^b	every four weeks

^a First dose of the every-3-week dosing schedule is given at Week 10

^b First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Infusion rates

Following dilution the DARZALEX infusion should be intravenously administered at the initial infusion rate, presented in Table 4 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

Table 4: Infusion rates for DARZALEX (16 mg/kg) administration

	Dilution volume	Initial infusion rate (first hour)	Rate Increments ^a of infusion rate^a	Maximum infusion rate
<u>Week 1 Infusion</u> ^{First infusion}	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<u>Week 2 (16 mg/kg) infusion</u> ^{Second infusion^b}	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<u>Subsequent infusions (Week 3 onwards, 16 mg/kg) infusions^c</u>	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

- ^a Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.
- ^b ~~A dilution volume of 500 mL should be used only if there were no IRRs during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1,000 mL and instructions for the first infusion.~~ A dilution volume of 500 mL for the 16 mg/kg dose should be used only if there were no IRRs the previous week. Otherwise, use a dilution volume of 1,000 mL
- ^c ~~A modified initial rate for subsequent infusions (i.e. third infusion onwards) should only be used only if there were no IRRs during a final infusion rate of ≥ 100 mL/hr in the first two infusions. Otherwise, use instructions for the second infusion.~~ A modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) should only be used only if there were no IRRs during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

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Recommended concomitant medications

Pre-infusion medication

Pre-infusion medications should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of DARZALEX as follows:

- Corticosteroid (long-acting or intermediate-acting)
 - Monotherapy:
Methylprednisolone 100 mg, or equivalent, administered intravenously.
Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg).
 - Combination therapy:
Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX infusion. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on DARZALEX infusion days (see section 5.1).
Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions. Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX infusion days when patients have received dexamethasone as a pre-medication.
- Antipyretics (oral paracetamol 650 to 1,000 mg)
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

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Paediatric population

DARZALEX is not indicated for children under 18 years old.

The safety and efficacy of DARZALEX in children aged below 18 years of age have not been established.

No data are available (see section 5.1).

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4.4 Special warnings and precautions for use

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Hepatitis B virus (HBV) Reactivation

Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with DARZALEX. HBV screening should be performed in all patients before initiation of treatment with DARZALEX.

For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of DARZALEX treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

In patients who develop reactivation of HBV while on DARZALEX, suspend treatment with DARZALEX and institute appropriate treatment. Resumption of DARZALEX treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

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4.5 Interaction with other medicinal products and other forms of interaction

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Clinical pharmacokinetic assessments of daratumumab in combination with lenalidomide, pomalidomide, thalidomide, and bortezomib and dexamethasone indicated no clinically-relevant drug-drug interaction between DARZALEX and these combination therapies small molecule medicinal products.

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4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions ($\geq 20\%$) were infusion reactions, fatigue, nausea, diarrhoea, constipation, ~~muscle spasms~~, pyrexia, dyspnoea, cough, back pain, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea, and atrial fibrillation.

Tabulated list of adverse reactions

Table 5 summarises the adverse drug reactions that occurred in patients receiving DARZALEX.

The data reflects exposure to DARZALEX (16 mg/kg) in 1530 patients with multiple myeloma including 1374 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. ~~1166 patients with multiple myeloma including 872 patients from three Phase III active-controlled trials who received DARZALEX in combination with either lenalidomide and dexamethasone (DRd; n = 283; Study MMY3003), bortezomib and dexamethasone (DvD; n = 243; Study MMY3004) or bortezomib, melphalan and prednisone (D-VMP; n = 346; Study MMY3007), and five open-label, clinical trials in which patients received DARZALEX either in combination with pomalidomide and dexamethasone (DPd; n = 103), in combination with lenalidomide and dexamethasone (n = 35) or as monotherapy (n = 156).~~ Post-marketing adverse reactions are also included.

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 4: — Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

System-Organ-Class	Adverse-reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Pneumonia ^a	Very Common	16	11
	Bronchitis ^a		17	2
	Upper respiratory tract infection ^a		50	5
	Influenza	Common	4	1*
Blood and lymphatic system disorders	Neutropenia ^a	Very Common	46	38
	Thrombocytopenia ^a		40	27
	Anaemia ^a		30	16
	Lymphopenia		10	8
Immune system disorders	Anaphylactic reaction ^b	Rare	-	-
Nervous system disorders	Peripheral sensory neuropathy	Very Common	22	2
	Headache		11	<1*
Cardiac disorders	Atrial fibrillation	Common	4	1
Vascular disorders	Hypertension ^a	Very Common	10	5
	Cough ^a	Very Common	27	<1*
	Dyspnoea ^a		19	3
	Pulmonary oedema ^a	Common	1	1
Gastrointestinal disorders	Diarrhoea	Very Common	31	3
	Nausea		22	1*
	Vomiting		15	1*
Musculoskeletal and connective tissue disorders	Muscle spasms	Very Common	13	<1*
General disorders and administration site conditions	Fatigue	Very Common	28	5
	Pyrexia		21	1*
	Oedema peripheral ^a		19	1
Injury, poisoning and procedural complications	Infusion related reaction ^c	Very common	42	5

*—No Grade 4

^a—Indicates grouping of terms

^b—Post-marketing adverse reaction

^c—Infusion related reaction includes terms determined by investigators to be related to infusion, see below

Table 5: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

<u>System Organ Class</u>	<u>Adverse reaction</u>	<u>Frequency</u>	<u>Incidence (%)</u>	
			<u>Any Grade</u>	<u>Grade 3-4</u>
<u>Infections and infestations</u>	<u>Pneumonia^a</u>	<u>Very Common</u>	<u>18</u>	<u>12</u>
	<u>Bronchitis^a</u>		<u>16</u>	<u>2</u>
	<u>Upper respiratory tract infection^a</u>		<u>46</u>	<u>3</u>
	<u>Urinary tract infection</u>	<u>Common</u>	<u>9</u>	<u>2</u>
	<u>Influenza</u>		<u>5</u>	<u>1*</u>
	<u>Hepatitis B Virus reactivation^b</u>	<u>Uncommon</u>	<u>-</u>	<u>-</u>
<u>Blood and lymphatic system disorders</u>	<u>Neutropenia^a</u>	<u>Very Common</u>	<u>48</u>	<u>41</u>
	<u>Thrombocytopenia^a</u>		<u>35</u>	<u>22</u>
	<u>Anaemia^a</u>		<u>32</u>	<u>15</u>
	<u>Lymphopenia^a</u>		<u>12</u>	<u>10</u>
	<u>Leukopenia^a</u>		<u>14</u>	<u>8</u>
<u>Immune system disorders</u>	<u>Anaphylactic reaction^b</u>	<u>Rare</u>	<u>-</u>	<u>-</u>
<u>Metabolism and nutrition disorders</u>	<u>Decreased appetite</u>	<u>Very Common</u>	<u>14</u>	<u>1*</u>
	<u>Hyperglycemia</u>	<u>Common</u>	<u>9</u>	<u>4</u>
	<u>Hypocalcemia</u>		<u>7</u>	<u>2</u>
	<u>Dehydration</u>		<u>3</u>	<u>1*</u>
<u>Nervous system disorders</u>	<u>Peripheral sensory neuropathy</u>	<u>Very Common</u>	<u>23</u>	<u>2</u>
	<u>Headache</u>		<u>13</u>	<u>< 1*</u>
	<u>Paraesthesia</u>	<u>Common</u>	<u>7</u>	<u>< 1</u>
<u>Cardiac disorders</u>	<u>Atrial fibrillation</u>	<u>Common</u>	<u>4</u>	<u>2</u>
<u>Vascular disorders</u>	<u>Hypertension^a</u>	<u>Very Common</u>	<u>11</u>	<u>5</u>
<u>Respiratory, thoracic and mediastinal disorders</u>	<u>Cough^a</u>	<u>Very Common</u>	<u>28</u>	<u>< 1*</u>
	<u>Dyspnoea^a</u>		<u>22</u>	<u>3</u>
	<u>Pulmonary oedema^a</u>	<u>Common</u>	<u>1</u>	<u>1</u>
<u>Gastrointestinal disorders</u>	<u>Diarrhoea</u>	<u>Very Common</u>	<u>37</u>	<u>4</u>
	<u>Constipation</u>		<u>27</u>	<u>1</u>
	<u>Nausea</u>		<u>24</u>	<u>1*</u>
	<u>Vomiting</u>		<u>16</u>	<u>1*</u>
<u>Musculoskeletal and connective tissue disorders</u>	<u>Back pain</u>	<u>Very Common</u>	<u>21</u>	<u>2</u>
	<u>Muscle spasms</u>		<u>17</u>	<u>< 1*</u>
<u>General disorders and administration site conditions</u>	<u>Fatigue</u>	<u>Very Common</u>	<u>31</u>	<u>5</u>
	<u>Oedema peripheral^a</u>		<u>25</u>	<u>1</u>
	<u>Pyrexia</u>		<u>21</u>	<u>1*</u>
	<u>Asthenia</u>		<u>17</u>	<u>2</u>
	<u>Chills</u>	<u>Common</u>	<u>9</u>	<u>< 1*</u>
<u>Injury, poisoning and procedural complications</u>	<u>Infusion-related reaction^c</u>	<u>Very Common</u>	<u>42</u>	<u>5</u>

* No Grade 4

^a Indicates grouping of terms^b Post-marketing adverse reaction^c Infusion-related reaction includes terms determined by investigators to be related to infusion, see below

Infusion-related reactions

In clinical trials (monotherapy and combination treatments; N=~~1166~~1530) the incidence of any grade infusion-related reactions was 40% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the ~~second~~ Week 2 infusion, and ~~cumulatively~~ 4% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction with ~~second-the~~ Week 2 or subsequent infusions. ~~Grade 4 infusion reactions were reported in 2/1166 (0.2%) of patients.~~

The median time to onset of a reaction was 1.4~~5~~ hours (range: 0 to 72.8 hours). The incidence of infusion modifications due to reactions was 37%. Median durations of 16 mg/kg infusions for the 1st Week, 2nd Week and subsequent infusions were ~~approximately~~ 7, 4.3 and 3.4 hours respectively.

Severe infusion-related reactions included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse infusion-related reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea (see section 4.4)

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported ~~with DARZALEX combinations and background therapies as follows:~~

~~(Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%;~~

~~D-VMP:23%, VMP:15%; DPd: 28%).~~

~~Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%.~~

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. ~~In the active controlled studies, discontinuations from treatment due to infections (1-4%)~~

~~Discontinuations from treatment due to infections were reported in 1% to 5% of patients. Fatal~~ and fatal infections were generally ~~infrequent and~~ balanced between the DARZALEX containing regimens and active control arms. ~~(<2%) in the controlled studies, and Fatal infections~~ were primarily due to pneumonia and sepsis.

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השינויים המהותיים בעלון לצרכן מופיעים בסעיפים הבאים:

למה מיועדת התרופה?

~~דארזלקס כטיפול יחיד (מונתרפיה) מיועדת לטיפול בחולים מבוגרים (מעל גיל 18) הסובלים ממיאלומה נפוצה, שהינה סרטן של מח העצם. הטיפול מיועד לחולים עם מחלה נשנית או עמידה, בהם למרות הטיפול הקודם) הכולל תרופות מקבוצת מעכבי פרוטאזום והאימונומודולטורים (המחלה התקדמה.~~

~~דארזלקס בשילוב עם לנאלידומיד ודקסאמתזון, או בשילוב עם בורטוזומיב ודקסאמתזון, מיועדת לטיפול בחולים מבוגרים הסובלים ממיאלומה נפוצה וקיבלו לפחות טיפול קודם אחד~~

~~דארזלקס בשילוב עם לנאלידומיד ודקסאמתזון או בשילוב עם בורטוזומיב, מלפלאן ופרדיניזון מיועדת לטיפול בחולים מבוגרים הסובלים ממיאלומה נפוצה אשר אובחנה לאחרונה ואשר אינם מיועדים להשתלה עצמית של תאי אב.~~

~~דארזלקס בשילוב עם לנאלידומיד ודקסאמתזון, או בשילוב עם בורטוזומיב ודקסאמתזון, מיועדת לטיפול בחולים מבוגרים הסובלים ממיאלומה נפוצה וקיבלו לפחות טיפול קודם אחד~~

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התרופה מיועדת למבוגרים מעל גיל 18

אזהרות מיוחדות הנוגעות בשימוש בתרופה:

הפאטיסיס B

ספר לרופא אם הנך סובל או שסבלת בעבר מזיהום בהפאטיסיס B, זאת מכיוון שדארזלקס עלולה לגרום לוירוס ההפאטיסיס B להיות פעיל שוב. יתכן והרופא יבדוק אותך לתסמיני זיהום זה לפני, במהלך ותקופה מסוימת לאחר הטיפול בדארזלקס. ספר לרופא מיד אם הבחנת בהחמרה בעייפות או בהצהבה של העור או של לובן העיניים.

ילדים ומתבגרים

אין לתת דארזלקס לילדים או מתבגרים מתחת לגיל 18, היות ואין מידע כיצד תשפיע התרופה על אוכלוסייה זו. תרופה זו אינה מיועדת לילדים ומתבגרים מתחת לגיל 18. לא קיים מידע לגבי בטיחות ויעילות השימוש בתכשיר זה בילדים ומתבגרים.

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נהיגה ושימוש במכונות

לאחר הטיפול בדארזלקס אתה עלול להרגיש עייפות, אשר עלולה להשפיע על היכולת שלך לנהוג או להפעיל מכונות.

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2. כיצד תשתמש בתרופה:

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אם קיבלת מינון יתר של דארזלקס

דארזלקס תינתן לך על ידי רופא או אחות, לכן קיים סיכוי נמוך שתקבל מינון יתר. במידה ותקבל מינון יתר, הרופא יבדוק אותך לאיתור תופעות לוואי.

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3. תופעות לוואי

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תופעות לוואי אחרות

תופעות לוואי שכיחות מאד – (very common) תופעות שמופיעות ביותר ממשתמש אחד מעשרה

- חום
- תחושת עייפות מוגברת
- שפעת
- שלשול
- עצירות
- ירידה בתאבון
- כאב ראש

- נזק עצבי העלול לגרום לתחושה של דקירות קלות, נמלול או כאב

Kibbutz Shefayim, 6099000
ISRAEL

Phone: 09-9591111 Fax: 09-9583636

- לחץ דם גבוה
 - התכווצויות שרירים
 - נפיחות בידים, בקרסוליים או רגליים
 - חולשה
 - כאב גב
 - צמרמורות
 - דלקת ריאות
 - ברונכיטיס
 - דלקת בדרכי הנשימה – באף, סינוסים או דלקת גרון
 - ספירה נמוכה של תאי דם אדומים הנושאים חמצן בדם (אנמיה)
 - ספירה נמוכה של תאי דם לבנים המסייעים להילחם בזיהומים (נוטרופניה, לימפופניה, לינקופניה)
 - ספירת נמוכה של טסיות דם, תאי דם המסייעים בקרישת הדם (טרומבוציטופניה)
- תופעות לוואי שכיחות – (common) תופעות שמופיעות ב-10-1 משתמשים מתוך 100
- הפרעות בקצב הלב (פרפור פרודוריים)
 - צבירת נוזלים בריאות אשר גורמת לקוצר נשימה
 - שפעת
 - זיהום בדרכי השתן
 - התייבשות
 - רמה גבוהה של סוכר בדם
 - רמה נמוכה של סידן בדם
 - תחושה לא רגילה בעור (כמו עקצוץ או תחושת מחטים וסיכות בעור)
- תופעות לוואי שאינן שכיחות – (common) תופעות שמופיעות ב-10-1 משתמשים מתוך 1000
- דלקת בכבד (הפאטיטיס)

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העלון לרופא והעלון לצרכן נשלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלם מודפסים בפניה אלינו לטלפון 09-9591111.

בברכה,
צפריר כהן
רוקח ממונה