הודעה על החמרה - מידע בטיחות בעלון לרופא

תאריך:11.07.16.

שם תכשיר באנגלית: BINOCRIT

מספר רישום:

147-08-33360-00/ 147-09-33361-00 147-17-33370-00/ 147-11-33363-00/147-12-33364-00/ 147-13-33365-00 /147-14-33366-00/ 147-15-33367-00/ 146-16-33368-00/ 147-10-33362-00/ 147-18-33372-00

שם בעל הרישום : Pharmalogic Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד !

מסומנים בצהוב אך ורק החמרות!!

החמרות מבוקשות			
פרק בעלון		טקסט ישן	טקסט חדש
Special warnings and precautions for use			General Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal (see section 4.8:"undesirable effects").
			Treatment of symptomatic anaemia in adult and paediatric chronic renal failure patients Caution should be exercised with escalation of epoetin alfa doses in patients with chronic renal failure since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered (see section 4.2 and 5.1).

Treatment of patients with chemotherapy induced anaemia Cancer patients being treated with epoetin alfa should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter			
Medicinal products that decrease erythropoiesis may decrease the response to epoetin alfa.			**Interaction with other medicinal products and othe forms of interaction**
In female adult patients with metastatic breast cancer, subcutaneous co-administration of 40,000 IU/ml epoetin alfa with trastuzumab 6 mg/kg had no effect on the pharmacokinetics of trastuzumab.			
Tabulated List of adverse reactions Of a total 3,262 subjects in 23 randomised, double-blinded,placebo or standard of care controlled studies, the overall safety profile of epoetin alfa was evaluated in 1,992 anaemic subjects. Included were 228 epoetin alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N = 131 exposed CRF subjects] and 2 in dialysis [N = 97 exposed CRF subjects]; 1,404 exposed cancer subjects in 16 studies of anaemia due to chemotherapy; 147 exposed subjects in 2 studies for autologous blood donation; and 213 exposed subjects in 1 study in the perisurgical period. Adverse drug reactions reported by ≥1% of subjects treated with epoetin alfa in these trials are shown below.			**Undesirable effects**

Blood and lymphatic system disorders Very rare: Erythropoeitin antibody-mediated pure red cell aplasia[1,4], thrombocythaemia[1]	**Blood and lymphatic system disorders** Uncommon: Thrombocythaemia (cancer patients) Frequency not known: Erythropoeitin antibody-mediated pure red cell aplasia[1], thrombocythaemia (chronic renal failure patients)	N	**Undesirable effects**
Metabolism and nutrition disorders: **Uncommon: Hyperkalaemia[2]**			
Nervous system disorders *Common*: Headache *Uncommon*: Convulsions **Vascular disorders** *Common*: Venous and arterial thromboses[3], hypertension *Not known*: Hypertensive crisis[4]	**Nervous system disorders** Very common: Headache (cancer patients) Common: Seizures (chronic renal failure patients), headache (chronic renal failure patients~~), stroke~~ Uncommon: Cerebral haemorrhage[2], seizures (cancer patients) Frequency not known: Cerebrovascular accident[2], hypertensive encephalopathy, transient ischaemic attacks **Vascular disorders** *Common*: Deep vein thrombosis[2] (cancer patients),hypertension Frequency not known: Deep vein thrombosis[2] (chronic renal failure patients), arterial thrombosis, hypertensive crisis		
Respiratory, thoracic, and mediastinal disorders *Common*: Cough *Uncommon*: Respiratory tract congestion	**Respiratory, thoracic, and mediastinal disorders** Common: Pulmonary embolism[2] (cancer patients)		

	Frequency not known: Pulmonary embolism[2] (chronic renal failure patients)		
Gastrointestinal disorders *Very common*: Diarrhoea, nausea, vomiting	**Gastrointestinal disorders** Very common: Nausea Common: Diarrhoea (cancer patients), vomiting Uncommon: Diarrhoea (chronic renal failure patients		
Musculoskeletal and connective tissue disorders *Common*: Arthralgia, bone pain, myalgia,pain in extremity **General disorders and administration site conditions** *Very common*: Pyrexia *Common*: Chills, influenza-like illness injectionsite reaction oedema peripheral *Not known*: Drug ineffective [4]	**Musculoskeletal and connective tissue disorders** Very common: Arthralgia (chronic renal failure patients) Common: Arthralgia (cancer patients) Uncommon: Myalgia (cancer patients) Frequency not known: Myalgia (chronic renal failure patients) **General disorders and administration site conditions** Very common: Pyrexia (cancer patients), influenza like illness (chronic renal failure patients) Common: Influenza like illness (cancer patients) Frequency not known: Substance ineffective, peripheral oedema, pyrexia (chronic renal failure patients), injection site reaction		**Undesirable effects**
[1] Identified during postmarketing experience and frequencycategory estimated from spontaneous reporting rates.			
[2] Common in dialysis	Serious adverse drug reactions include venous and arterial		

[4] Addressed in the subsection below and/or in section 4.4 :"Special warnings and precaution for use"). ***Paediatric population with chronic renal failure on haemodialysis*** The exposure of paediatric patients with chronic renal failure on haemodialysis in clinical trials and post-marketing experience is limited. No paediatric-specific adverse reactions not mentioned previously in the table above, or any that were not consistent with the underlying disease were reported in this population.	thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, arterial thrombosis (including myocardial infarction and ~~myocardial ischaemia)~~, retinal thrombosis, and shunt thrombosis (including dialysis equipment). Additionally, cerebrovascular accidents (including cerebral infarction and cerebral haemorrhage) and transient ischaemic attacks have been reported in clinical trials of epoetin alfa. Aneurysms have been reported.		**Undesirable effects**

Mechanism of action : Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidney in response to hypoxia and is the key regulator of red blood cell (RBC) production. EPO is involved in all phases of erythroid development, and has its principal effect at the level of erythroid precursors. After EPO binds to its cell surface receptor, it activates signal transduction pathways that interfere with apoptosis and stimulates erythroid cell proliferation. Recombinant human EPO (epoetin alfa), expressed in Chinese hamster ovary cells, has a 165 amino acid sequence identical to that of human urinary EPO; the 2 are indistinguishable on the basis of functional assays.			**PHARMACOLOGICAL PROPERTIES**
Pharmacodynamic effects ***Healthy volunteers*** After single doses (20,000 to 160,000 IU subcutaneously) of epoetin alfa, a dose-dependent response was observed for the pharmacodynamic markers investigated including: reticulocytes, RBCs, and haemoglobin. A defined concentration-time profile with peak and return to baseline was observed for changes in percent reticulocytes. A less defined profile was observed for RBCs and haemoglobin. In general, all pharmacodynamic markers increased in a linear manner with dose reaching a maximum response at the highest dose levels. Further pharmacodynamic studies explored 40,000 IU once weekly versus 150 IU/kg 3 times per week. Despite differences in concentration-time profiles the pharmacodynamic response (as measured by changes in percent reticulocytes, haemoglobin, and total RBCs) was similar between these regimens. Additional studies compared the 40,000 IU once-weekly regimen of epoetin alfa with biweekly doses ranging from 80,000 to 120,000 IU subcutaneously. Overall, based on the results of these pharmacodynamic studies in healthy subjects, the 40,000 IU once-weekly dosing regimen seems to be more efficient in producing RBCs than the biweekly regimens despite an observed similarity in reticulocyte production in the once-weekly and biweekly regimens. ***Chronic renal failure*** Epoetin alfa has been shown to stimulate erythropoiesis in anaemic patients with CRF, including dialysis and pre-dialysis patients. The first evidence of a response to epoetin alfa is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, haemoglobin and			

haematocrit, usually within 2 to 6 weeks. The haemoglobin response varies between patients and may be impacted by iron stores and the presence of concurrent medical problems. ***Chemotherapy-induced anaemia*** Epoetin alfa administered 3 times per week or once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients receiving chemotherapy. In a study comparing the 150 IU/kg, 3 times per week and 40,000 IU, once-weekly dosing regimens in healthy subjects and in anaemic cancer subjects the time profiles of changes in percent reticulocytes, haemoglobin, and total red blood cells were similar between the two dosing regimens in both healthy and anaemic cancer subjects. The AUCs of the respective pharmacodynamics parameters were similar between the 150 IU/kg, 3 times per week and 40,000 IU, once-weekly dosing regimens in healthy subjects and also in anaemic cancer subjects. ***Adult surgery patients in an autologous predonation programme*** Epoetin alfa has been shown to stimulate red blood cell production in order to augment autologous blood collection, and to limit the decline in haemoglobin in adult patients scheduled for major elective surgery who are not expected to predeposit their complete perioperative blood needs. The greatest effects are observed in patients with low haemoglobin (≤13 g/dl). ***Treatment of adult patients scheduled for major elective orthopaedic surgery*** In patients scheduled for major elective orthopaedic surgery with a pre-treatment haemoglobin of >10 to ≤13 g/dl, epoetin alfa has been shown to decrease the risk of receiving allogeneic transfusions and hasten erythroid recovery (increased haemoglobin levels, haematocrit levels, and reticulocyte counts). <u>Clinical efficacy and safety</u> ***Chronic renal failure*** Epoetin alfa has been studied in clinical trials in adult anaemic CRF patients, including haemodialysis and pre-dialysis patients, to treat anaemia and maintain haematocrit within a target concentration range of 30 to 36%. In clinical trials at starting doses of 50 to 150 IU/kg, three times per week, approximately 95% of all patients responded with aclinically significant increase in haematocrit. After approximately			

two months of therapy, virtually all patients were transfusion independent. Once the target haematocrit was achieved, the maintenance dose was individualised for each patient.

In the three largest clinical trials conducted in adult patients on dialysis, the median maintenance dose necessary to maintain the haematocrit between 30 to 36% was approximately 75 IU/kg given 3 times per week.

In a double-blind, placebo-controlled, multicentre, quality of life study in CRF patients on haemodialysis, clinically and statistically significant improvement was shown in the patients treated with epoetin alfa compared to the placebo group when measuring fatigue, physical symptoms, relationships and depression (Kidney Disease Questionnaire) after six months of therapy. Patients from the group treated with epoetin alfa were also enrolled in an openlabel extension study which demonstrated improvements in their quality of life that were maintained for an additional 12 months.

Adult patients with renal insufficiency not yet undergoing dialysis.

In clinical trials conducted in patients with CRF not on dialysis treated with epoetin alfa, the average duration of therapy was nearly five months. These patients responded to epoetin alfa therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dosedependent and sustained increase in haematocrit when epoetin alfa was administered by either an intravenous or subcutaneous route. Similar rates of rise of haematocrit were noted when epoetin alfa was administered by either route. Moreover, epoetin alfa doses of 75 to 150 IU/kg per week have been shown to maintain haematocrits of 36 to 38% for up to six months.

In 2 studies with extended interval dosing of epoetin alfa (3 times per week, once weekly, once every 2 weeks, and once every 4 weeks) some patients with longer dosing intervals did not maintain adequate haemoglobin levels and reached protocol-defined haemoglobin withdrawal criteria (0% in once weekly, 3.7% in once-every-2-weeks, and 3.3% in the once-every-4-weeks groups).

A randomised prospective trial evaluated 1,432 anaemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to epoetin alfa treatment targeting a maintenance haemoglobin level of 13.5 g/dl (higher than the recommended haemoglobin concentration level) or 11.3 g/dl. A major cardiovascular event (death, myocardial infarction,

stroke or hospitalisation for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03). ***Treatment of patients with chemotherapy-induced anaemia*** Epoetin alfa has been studied in clinical trials in adult anaemic cancer patients with lymphoid and solid tumors, and patients on various chemotherapy regimens, including platinum and nonplatinum- containing regimens. In these trials, epoetin alfa administered 3 times per week and once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients. In some studies, the double-blind phase was followed by an openlabel phase during which all patients received epoetin alfa and a maintenance of effect was observed. Available evidence suggests patients with haematological malignancies and solid tumours respond equivalently to epoetin alfa therapy, and that patients with or without tumour infiltration of the bone marrow respond equivalently to epoetin alfa therapy. Comparable intensity of chemotherapy in the epoetin alfa and placebo groups in the chemotherapy trials was demonstrated by a similar area under the neutrophil time curve in patients treated with epoetin alfa and placebo-treated patients, as well as by a similar proportion of patients in groups treated with epoetin alfa and placebo-treated groups whose absolute neutrophil counts fell below 1,000 and 500 cells/µl. ***Autologous predonation programme*** The effect of epoetin alfa in facilitating autologous blood donation in patients with low haematocrits (≤39% and no underlying anaemia due to iron deficiency) scheduled for major orthopaedic surgery was evaluated in a double-blind, placebo-controlled study conducted in 204 patients, and a single-blind placebo-controlled study in 55 patients. In the double-blind study, patients were treated with epoetin alfa 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). On average, patients treated with			

epoetin alfa were able to predeposit significantly more units of blood (4.5 units) than placebo-treated patients (3.0 units). In the single-blind study, patients were treated with epoetin alfa 300 IU/kg or 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). Patients treated with epoetin alfa were also able to predeposit significantly more units of blood (epoetin alfa 300 IU/kg = 4.4 units; epoetin alfa 600 IU/kg = 4.7 units) than placebo-treated patients (2.9 units). Epoetin alfa therapy reduced the risk of exposure to allogeneic blood by 50% compared to patients not receiving epoetin alfa. ***Major elective orthopaedic surgery*** The effect of epoetin alfa (300 IU/kg or 100 IU/kg) on the exposure to allogeneic blood transfusion has been evaluated in a placebocontrolled, double-blind clinical trial in non-iron deficient adult patients scheduled for major elective orthopaedic hip or knee surgery. Epoetin alfa was administered subcutaneously for 10 days prior to surgery, on the day of surgery, and for four days after surgery.Patients were stratified according to their baseline haemoglobin (≤10 g/dl, >10 to ≤13 g/dl and >13 g/dl). Epoetin alfa 300 IU/kg significantly reduced the risk of allogeneic transfusion in patients with a pretreatment haemoglobin of >10 to ≤13 g/dl. Sixteen percent of epoetin alfa 300 IU/kg, 23% of epoetin alfa 100 IU/kg and 45% of placebo-treated patients required transfusion. An open-label, parallel-group trial in non-iron deficient adult subjects with a pre-treatment haemoglobin of ≥10 to ≤13 g/dl who were scheduled for major orthopaedic hip or knee surgery compared epoetin alfa 300 IU/kg subcutaneously daily for 10 days prior to surgery, on the day of surgery and for four days after surgery to epoetin alfa 600 IU/kg subcutaneously once weekly for 3 weeks prior to surgery and on the day of surgery. From pre-treatment to pre-surgery, the mean increase in haemoglobin in the 600 IU/kg weekly group (1.44 g/dl) was twice than that observed in the 300 IU/kg daily group (0.73 g/dl). Mean haemoglobin levels were similar for the two treatment groups throughout the postsurgical period. The erythropoietic response observed in both treatment groups resulted in similar transfusion rates (16% in the 600 IU/kg weekly group and 20% in the 300 IU/kg daily group). ***Paediatric population***			

Chronic renal failure Epoetin alfa was evaluated in an open-label, non-randomised, open dose-range, 52-week clinical study in paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 to 20.1 years). Epoetin alfa was administered at 75 IU/kg/week intravenously in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dl/month increase in haemoglobin. The desired haemoglobin concentration range was 9.6 to 11.2 g/dl. Eighty-one percent of patients achieved the haemoglobin concentration level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a 3 times-per-week dosing regimen. After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week. Pooled post-hoc analyses of clinical studies of ESAs have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed (see section 4.2 and section 4.4).			
Absorption Following subcutaneous injection, serum levels of epoetin alfa reach a peak between 12 and 18 hours post-dose. There was no accumulation after multiple dose administration of 600 IU/kg administered subcutaneously weekly.			**Pharmacokinetic properties**
Distribution The mean volume of distribution was 49.3 ml/kg after intravenous doses of 50 and 100 IU/kg in healthy subjects. Following intravenous administration of epoetin alfa in subjects with chronic renal failure, the volume of distribution ranged from 57-			

107 ml/kg after single dosing (12 IU/kg) to 42–64 ml/kg after multiple dosing (48–192 IU/kg), respectively. Thus, the volume of distribution is slightly greater than the plasma space.			
Elimination The mean CL/F for the 150 IU/kg 3 times-per-week and 40,000 IU once-weekly regimens in healthy subjects were 31.2 and 12.6 ml/h/kg, respectively. The mean CL/F for the 150 IU/kg, 3 times-per week and 40,000 IU, once-weekly regimens in the anaemic cancer subjects were 45.8 and 11.3 ml/h/kg, respectively. In most anaemic subjects with cancer receiving cyclic chemotherapy, CL/F was lower after subcutaneous doses of 40,000 IU once weekly and 150 IU/kg, 3 times per week compared with the values for healthy subjects. ***Linearity/Non-linearity*** In healthy subjects, a dose-proportional increase in serum epoetin alfa concentrations was observed after intravenous administration of 150 and 300 IU/kg, 3 times per week. Administration of single doses of 300 to 2,400 IU/kg subcutaneous epoetin alfa resulted in a linear relationship between mean c_{max} and dose and between mean AUC and dose. An inverse relationship between apparent clearance and dose was noted in healthy subjects. In studies to explore extending the dosing interval (40,000 IU once weekly and 80,000, 100,000, and 120,000 IU bi-weekly), a linear but non- dose-proportional relationship was observed between mean c_{max} and dose, and between mean AUC and dose at steady state. ***PK/PD relationships*** Epoetin alfa exhibits a dose-related effect on haematological parameters which is independent of route of administration.			
<u>Paediatric population</u> The pharmacokinetic profile of epoetin alfa in children and adolescents appears to be similar to that of adults.			
In cell cultures of human bone marrow cells, epoetin alfa stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of epoetin alfa on bone marrow cells could not be detecte			**Preclinical safety data**

מצ"ב העלון ,שבו מסומנות ההחמרות המבוקשות על רקע צהוב.
שינויים שאינם בגדר החמרות סומנו(בעלון)בצבע שונה .יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך .11.07.16

☒כל השינויים עולים בקנה אחד עם תנאי הרישום(תעודת הרישום ,תעודת האיכות וטופס פרטי התכשיר העדכני.)
☒כל הכתוב בהצעת העלון ,תואם את תנאי הרישום

☐קיים עלון לרופא והוא מעודכן בהתאם
☒אסמכתא לבקשה: **הצעת העלון אומצה מ- EMEA**
BINOCRIT-EPAR-PRODUCT INFORMATION –LAST UPDATE 21/09/2015

האסמכתא מצ"ב.

☒השינוי הנ"ל אושר על ידי רשויות הבריאות- **EUROPEAN MEDICINES AGENCY**

☒אני ,הרוקח הממונה של חברת פארמלוג'יק מצהיר בזה כי אין שינויים נוספים ,מלבד אלה שסומנו בהצעת העלון.

☒אני מצהיר כי השינויים אינם יוצרים סתירה פנימית במידע בעלון .

☒עלון זה לא מטופל במקביל במסגרת אחרת(כגון :עדכון עלון במסגרת בקשה לתוספת התוויה ,החמרה וכו')
במידה וקיים טיפול מקביל במסגרת אחרת -יש לציין זאת.

חתימת הרוקח הממונה : פרידה שוד Frida Shud

הודעה על החמרה בעלון לצרכן- (מידע בטיחות)

תאריך 22.03.16

שם תכשיר באנגלית ומספר הרישום : BINOCRIT

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שם בעל הרישום :PHARMALOGIC Ltd

טופס זה מיועד לפרוט ההחמרות בלבד !

בירוק מסומנים הקלות

ההחמרות המבוקשות		
פרק בעלון	טקסט נוכחי	טקסט חדש
תופעות לוואי	<u>תופעות לוואי נפוצות מאוד (משפיעות על יותר מ-1 מתוך 10 מטופלים:)</u> תסמינים דמויי שפעת ,כגון כאב ראש ,כאבים בפרקים ,חום , חולשה ,עייפות וסחרחורת . תופעות אלו שכיחות יותר בתחילת הטיפול. אם תסמינים אלו מופיעים במהלך מתן תוך-ורידי ,מתן איטי יותר של ההזרקה עשוי למנוע תסמינים אלו בעתיד. גודש בדרכי הנשימה ,כגון גודש באף וכאב גרון דווחו בחולי כליה שטרם	<u>תופעות לוואי נפוצות מאוד (משפיעות על יותר מ-1 מתוך 10 מטופלים:)</u> שלשולים, הקאות, בחילות גודש בדרכי הנשימה ,כגון גודש באף וכאב גרון דווחו בחולי כליה שטרם עברו דיאליזה.

	עברו דיאליזה. <u>תופעות לוואי נפוצות(משפיעות על 1-10 מטופלים מתוך 100)</u> עלייה בלחץ הדם בחולי סרטן וחולי כליות עם אנמיה סימפטומטית .כאבי ראש ,בעיקר פתאומיים ,כאבי ראש דמויי מיגרנה חדה ,תחושת בלבול או התקפים אפילפטים ,עשויים להיות סימנים של עלייה פתאומית בלחץ הדם .מצב זה דורש טיפול דחוף .עלייה בלחץ הדם עשויה לדרוש טיפולעם תרופות אחרות (או התאמת התרופות הנלקחות לטיפול בלחץ דם גבוה .)כאבים בחזה ,קוצר נשימה ,נפיחות כואבת ברגל היכולה להוות סימן לקריש דם ,שלשול(בחולי סרטן ,) פריחות בעור ונפיחות סביב העיניים (בצקת ,)שעשויות להיגרם מתגובה אלרגית. אם הנך מטופל בהמודיאליזה : קרישי דם עלולים להיווצר בדלף (שאנט) הדיאליזה .מצב זה סביר יותר אם הנך סובל מלחץ דם נמוך או במקרה של סיבוכים בפיסטולה שלך. קרישי דם עלולים להיווצר גם במערכת ההמודיאליזה שלך . ייתכן ורופאך יחליט להעלות את מינון ההפרין במהלך הדיאליזה	<u>תופעות לוואי נפוצות(משפיעות על 1-10 מטופלים מתוך 100)</u> תסמינים דמויי שפעת ,כגון כאב ראש ,כאבים בפרקים ,חום , חולשה ,עייפות וסחרחורת . תופעות אלו שכיחות יותר בתחילת הטיפול. אם תסמינים אלו מופיעים במהלך מתן תוך-ורידי ,מתן איטי יותר של ההזרקה עשוי למנוע תסמינים אלו בעתיד. צמרמורות, שיעול, כאבי עצמות ושרירים. עלייה בלחץ הדם בחולי סרטן וחולי כליות עם אנמיה סימפטומטית .כאבי ראש ,בעיקר פתאומיים ,כאבי ראש דמויי מיגרנה חדה ,תחושת בלבול או התקפים אפילפטים ,עשויים להיות סימנים של עלייה פתאומית בלחץ הדם .מצב זה דורש טיפול דחוף .עלייה בלחץ הדם עשויה לדרוש טיפולעם תרופות אחרות (או התאמת התרופות הנלקחות לטיפול בלחץ דם גבוה .)כאבים בחזה ,קוצר נשימה ,נפיחות כואבת ברגל היכולה להוות סימן לקריש דם ,שלשול(בחולי סרטן ,) פריחות בעור ונפיחות סביב העיניים (בצקת ,)שעשויות להיגרם מתגובה אלרגית. אם הנך מטופל בהמודיאליזה : קרישי דם עלולים להיווצר בדלף (שאנט) הדיאליזה .מצב זה סביר יותר אם הנך סובל מלחץ דם נמוך או במקרה של סיבוכים בפיסטולה שלך. קרישי דם עלולים להיווצר גם במערכת ההמודיאליזה שלך . ייתכן ורופאך יחליט להעלות את מינון ההפרין במהלך הדיאליזה. אם הנך מטופל בהמודיאליזה ,

		עלייה ברמות טסיות הדם במיוחד בהתחלת הטיפול ,אודם ,צריבה וכאב באזור ההזרקה.

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.

שינויים שאינם בגדר החמרות סומנו בעלון בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך 11.07.16

☒כל השינויים עולים בקנה אחד עם תנאי הרישום (תעודת הרישום, תעודת האיכות וטופס פרטי התכשיר העדכני).

☒כל הכתוב בהצעת העלון, תואם את תנאי הרישום.

☒קיים עלון לרופא והוא מעודכן בהתאם.

☒אסמכתא לבקשה:

☐ **הצעת העלון אומצה מ- EMEA**

☐ **BINOCRIT-EPAR-PRODUCT INFORMATION –LAST UPDATE 21/09/2015**

☐

האסמכתא מצ"ב.

☒השינוי הנ"ל אושר על ידי רשויות הבריאות ב-- **EUROPEAN MEDICINES AGENCY**

☒אני, הרוקח הממונה של חברת פרמלוגיק בע"מ מצהיר בזה כי אין שינויים נוספים, מלבד אלה שסומנו בהצעת העלון.

☒אני מצהיר כי השינויים אינם יוצרים סתירה פנימית במידע בעלון.

☒עלון זה לא מטופל במקביל במסגרת אחרת (כגון: עדכון עלון במסגרת בקשה לתוספת התוויה, החמרה וכו') במידה וקיים טיפול מקביל במסגרת אחרת- יש לציין זאת.

חתימת הרוקח הממונה: Frida Shud