# הודעה על החמרה ( מידע בטיחות) בעלון לצרכן

**תאריך \_\_02.10.2013\_\_\_\_**

**שם תכשיר באנגלית: CLEXANE, CLEXANE FORTE**

**מספר רישום:46772603700/11, 1206030007**

**שם בעל הרישום:\_\_sanofi-aventis Israel Ltd**

**טופס זה מיועד לפרוט ההחמרות בלבד !**

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| **ההחמרות המבוקשות** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **תופעות לוואי** |  | **טקסט שהוסף מסומן בצהוב , טקסט מחוק מסומן באדום עם קו חוצה, שינויי מיקום וניסוח מסומנים בירוק.**  **(יש להדגיש כי מוזכרים כאן רק תתי הסעיפים שבהם נעשו שינויים במידע בטיחות, מידע מלא ניתן למצוא בעלון המלא):**  **...................**  *נדיר (מתרחש בפחות מ -1 מתוך 1000 אנשים):* תגובה אלרגית : הסימנים יכולים לכלול: פריחה בעור, בעיות בנשימה או בבליעה, נפיחות בשפתיים, בפנים, בגרון או בלשון~~.~~ **~~המטומות בחוט השדרה או לידו שיכולות להתבטא ב~~**תחושת עקצוץ, נימול וחולשת שרירים, במיוחד בפלג גופך התחתון, ~~או~~ איבוד שליטה על הסוגרים (אינך מסוגל לשלוט על עשיית הצרכים) **~~או שיתוק~~** לאחר שעברת ניקור או הרדמה בעמוד השדרה. ~~או הרדמה בעמוד השדרה.~~  **................**  *שכיחות לא ידועה:*  תגובה של רגישות יתר (כולל שוק אנפילקטי)  כאב ראש  המטומות בחוט השדרה או בסמוך לו דווחו במקרים של שימוש בקלקסן במקביל לאלחוש אפידורלי או בחוט השדרה או בניקור מותני. תגובות אלה מתבטאות בדרגות שונות של פגיעה נוירולוגית כולל שיתוק לטווח ארוך או קבוע.  דלקת עורית או נמק של העור, בדרך כלל באיזור ההזרקה. במקרה זה יש לפנות מיד אל הרופא ולהפסיק את הטיפול.  פגיעה בכבד *ודרכי המרה*  התקרחות  אנמיה, אאוזינופיליה.( עליה בסוג מסויים של תאי דם לבנים**), היווצרות קרישי דם (thrombosis), תגובות עוריות ותת עורית**  ~~תגובה של רגישות יתר (כולל שוק אנפילקטי), כאב ראש, פגיעה בכבד~~~~, התקרחות, אנמיה, אאוזינופיליה.( עליה בסוג מסויים של תאי דם לבנים).~~  שימוש בקלקסן במשך תקופה ארוכה (יותר משלושה חודשים) עלול להגביר את הסיכון לאוסטאופורוזיס, מצב בו עולה הסיכון לשברים בעצמות.  אם אחת מתופעות הלוואי מחמירה, או נמשכת יותר ממספר ימים או כאשר אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא. |

# הודעה על החמרה ( מידע בטיחות) בעלון לרופא

**תאריך \_\_08.2013\_\_\_\_**

**שם תכשיר באנגלית:**

**CLEXANE, CLEXANE FORTE, CLEXANE MULTI- DOSE VIAL**

**מספרי רישום:46772603700/11, 1206030007, 1414132031**

**שם בעל הרישום: sanofi aventis Israel ltd**

**טופס זה מיועד לפרוט ההחמרות בלבד !**

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| **ההחמרות המבוקשות** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **Posology and method of administration**  **Special warnings and special precautions for use**  **Undesirable effects**  **PHARMACOLOGICAL PROPERTIES** |  | **טקסט שהוסף מסומן בצהוב , טקסט מחוק מסומן באדום עם קו חוצה, שינויי מיקום וניסוח מסומנים בירוק.**  **(יש להדגיש כי מוזכרים כאן רק תתי הסעיפים שבהם נעשו שינויים במידע בטיחות, מידע מלא ניתן למצוא בעלון המלא):**  **4.2 Posology and method of administration**  **.......**  ~~LMWH dosage has not been evaluated in terms of bodyweight in patients weighing more~~  ~~than 100 kg or less than 40 kg. The efficacy of LMWH treatment may be slightly lower in~~  ~~patients weighing more than 100 kg, and the risk of hemorrhage may be higher in patients~~  ~~weighing less than 40 kg. Specific clinical monitoring must be carried out in these patients.~~  **Body weight:**  ~~No dosage adjustments are recommended in obesity or low body weight~~  **Low weight**  An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients.  **Obese Patients**  **Obese patients** are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism (see also section 4.4 Special warnings and precautions for use~~: Low body weight and Monitoring;~~ and section 5.2 Pharmacokinetic properties).  **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**  **4.4 Special warnings and special precautions for use**  **……..**  *Low weight*  An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients  *Obese Patients*  Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism (see Section 5.2- Pharmacokinetic properties- Weight).  (see Section 4.2 Posology and method of administration and section 5.2 Pharmacokinetic properties- Weight).  ……….  **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**   * 1. **Undesirable effects**   The adverse reactions observed in clinical studies and reported in post-marketing experience are detailed below.  Frequencies are defined as follows: very common (Description: GREATER-THAN OR EQUAL TO (8805) 1/10); common (Description: GREATER-THAN OR EQUAL TO (8805) 1/100 to < 1/10); uncommon (Description: GREATER-THAN OR EQUAL TO (8805) 1/1000 to < 1/100); rare (Description: GREATER-THAN OR EQUAL TO (8805) 1/10,000 to <1/1,000); ~~and~~ very rare  (< 1/10,000) or not known (cannot be estimated from available data). Post-marketing adverse reactions are designated with a frequency “Not known”.  ~~Adverse events which have not been observed in clinical trials, but were reported in post-marketing experience are ranked under the frequency “Rare”.~~  **Haemorrhages**  **……..**  ~~In addition, in post marketing experience:~~  **~~Rare:~~** ~~Cases of spinal haematoma (or neuraxial haematoma) have been reported with the concurrent use of enoxaparin sodium as well as spinal/epidural anaesthesia or spinal puncture and post operative indwelling catheters. These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see section 4.4 Special warnings and precautions for use).~~  **……..**  **Thrombocytopenia and thrombocytosis**  **……..**  ~~In addition, in post marketing experience:~~  **~~Rare~~**~~: Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see section 4.4 Special warnings and precautions for use: Monitoring).~~  **Other clinically relevant adverse reactions**  These reactions are presented below, whatever the indications, by system organ class, frequency grouping and decreasing order of seriousness.   |  |  | | --- | --- | | MedDRA system organ class | All indications | | Immune system disorders | *Common:* Allergic reaction  *Rare:* Anaphylactic / anaphylactoid reaction (see also Postmarketing experience) | | Hepatobilary disorders | *Very common:* Hepatic enzymes increase (mainly transaminases \*\*) | | Skin and subcutaneous tissue disorders | *Common:* Urticaria, pruritus, erythema,  *Uncommon:* Bullous dermatitis | | General disorders and administration site conditions | *Common:* Injection site haematoma, injection site pain, other injection site reaction\*  *Uncommon:* Local irritation; skin necrosis at injection site | | Investigations | *Rare:* Hyperkaliemia |   \*: such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction (NOS)    \*\*: transaminases levels > 3 times the upper limit of normality  **~~In addition, in post marketing experience:~~**  • ~~Skin and subcutaneous disorders~~  **~~Rare:~~**  ~~- Cutaneous vasculitis, skin necrosis usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful). Treatment with enoxaparin sodium must be discontinued.~~  ~~- Injection site nodules (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.~~  הועבר לסוף סעיף **Post marketing experience:**  ~~Valve thrombosis in patients with prosthetic heart valves have been reported rarely, usually associated with inadequate dosing (see section 4.4 Special warnings and precautions for use).~~  ~~Long term treatment with heparin has been associated with a risk of osteoporosis. Although this has not been observed with enoxaparin the risk of osteoporosis cannot be excluded.~~  הועבר לסוף סעיף **Post marketing experience:**  ~~Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalaemia may occur particularly in patients with chronic renal failure and diabetes mellitus (see section 4.4 Special warnings and precautions for use).~~  **Post marketing experience**  The following adverse reactions have been identified during post-approval use.  The adverse reactions are derived from spontaneous reports and therefore, the frequency is “not known” (cannot be estimated from the available data).   * **Immune System Disorders** * Anaphylactic / anaphylactoid reaction including shock * **Nervous System Disorders** * Headache * **Vascular Disorders** * Cases of spinal haematoma (or neuraxial haematoma) have been reported with the concurrent use of enoxaparin sodium as well as spinal/epidural anaesthesia or spinal puncture. These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see Section 5: Spinal/epidural anesthesia). * **Blood and Lymphatic System Disorders***:* * Haemorrhagic anemia * Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see Section 6: Monitoring of platelet counts). * Eosinophilia * **Skin and subcutaneous disorders** * Cutaneous vasculitis, skin necrosis usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful).   Treatment with enoxaparin sodium must be discontinued.   * Injection site nodules (inflammatory nodules, which were not cystic enclosure of   enoxaparin).  They resolve after a few days and should not cause treatment discontinuation.   * **Alopecia** * **Hepatobilary disorders** * Hepatocellular liver injury * Cholestatic liver injury * **Musculoskeletal and connective tissue disorders** * Osteoporosis following long-term therapy (greater than 3 months) * Valve thrombosis in patients with prosthetic heart valves have been reported rarely, usually associated with inadequate dosing (see section 4.4 Special warnings and precautions for use). * Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalaemia may occur particularly in patients with chronic renal failure and diabetes mellitus (see section 4.4 Special warnings and precautions for use).   **5.2 Pharmacokinetic properties**  **…………………….**  **Weight**  After repeated subcutaneous 1.5 mg/kg once daily dosing, mean AUC of anti-Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m2) compared to non-obese control subjects, while Amax is not increased.197 There is a lower weight-adjusted clearance in obese subjects with subcutaneous dosing.  When non-weight adjusted dosing was administered, it was found after a single-subcutaneous 40 mg dose, that anti-Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects (see Section 4.4-Special warnings and special precautions for use). |