# הודעה על החמרה ( מידע בטיחות) בעלון לצרכן

# (מעודכן 05.2013)

**תאריך 10.9.2013**

**שם תכשיר באנגלית ומספר הרישום \_ Xanagis 0.5mg 063-4626908-00,**

**Xanagis 0.25mg 063-48-26906-00, Xanagis 1mg 063-47-26907-00**

**שם בעל הרישום**  **פריגו ישראל פרמצבטיקה בע"מ**

טופס זה מיועד לפרוט ההחמרות בלבד !

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| **ההחמרות המבוקשות** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **מתי אין להשתמש בתכשיר?** | אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול במקרים הבאים:  אם הינך סובל/ת מגלאוקומה חריפה מטיפוס הזוית הסגורה. | * בחולי ברקית (גלאוקומה) מטיפוס הזווית הסגורה. |
| **אזהרות מיוחדות הנוגעות לשימוש בתרופה:** | אין לשתות יינות או משקאות חריפים בתקופת הטיפול עם התרופה. | **שימוש בתרופה וצריכת אלכוהול**  אין לצרוך כלל אלכוהול במהלך השימוש בקסנאגיס, כיוון שאלכוהול מגביר את השפעת התרופה!!! אם אתה צורך אלכוהול, ספר על כך לרופא. |
| **תגובות בין תרופותיות:** |  | * תרופות לטיפול באפילפסיה. |
| **תופעות לוואי:** | יש להפסיק את הטיפול ולהתייעץ עם הרופא במקרים הבאים: חוסר מנוחה, אי שקט, עצבנות, תוקפנות, תעתועים (אשליות), כעס, סיוטי לילה, דמיונות שווא, פסיכוזה, הפרעות התנהגותיות.  אחרי הפסקת הטיפול: ישנם מקרים של תופעות גמילה, בעיקר לאחר טיפול במינונים גבוהים או לאחר טיפול ממושך (במידה שאושר ע"י הרופא) או כשהטיפול הופסק בפתאומיות. תופעות הגמילה הן כגון: כאבי ראש, כאבי שרירים, חרדה קיצונית, מתח, חוסר מנוחה, בלבול, שינויים במצבי רוח, עצבנות, קשיים בשינה, רגישות לאור או לרעש או למגע פיזי, הזיות, התקפי אפילפסיה. לכן הפסקת הטיפול חייבת להיעשות בהדרגה, בהתאם להנחיות הרופא.  מיד.  ../3  שכיח: נמנום, חוסר יציבות, סחרחורת. תופעות אלו חולפות בדרך כלל תוך זמן קצר לאחר תקופת ההסתגלות לתרופה. פחות שכיח: כאבי ראש, דיכאון, רעד, שינויים במשקל, טשטוש ראיה, בעיות בזיכרון, שיכחה, הפרעות בריכוז, בלבול, בעיות קואורדינציה, עצבנות, בעיות בעיכול. | **סיבות להפסקת הטיפול בקסנאגיס באופן מיידי:**  יש לפנות מיד לרופא להפסקת הטיפול במידה ואתה חווה את אחד מהתסמינים הבאים. הרופא ייעץ לך בנוגע לאופן הפסקת הטיפול.   * לעיתים קרובות הטיפול בקסנאגיס עלול לגרום להשפעות התנהגותיות ופסיכיאטריות חמורות כגון סערת נפש, חוסר מנוחה, תוקפנות, עצבנות, כעס אלים, אמונות שווא, סיוטים והזיות או התנהגות בלתי הולמת אחרת. * צפצופים פתאומיים בנשימה, קושי בבליעה או בנשימה, נפיחות של העפעפיים, הפנים או השפתיים, פריחה או גירוד (בעיקר כזו המשפיעה על כל הגוף).   **יש לפנות מיד לרופא אם את/ה מבחין/ה באחד מהתסמינים הבאים, כיוון שיהיה צורך בהתאמת המינון והטיפול:**   * אובדן זיכרון (שיכחה) או * הצהבה של העור והלבן של העיניים (צהבת ילודים)   **סימפטומים של תלות וגמילה:**  ".......................  תופעות אלו עלולות להתבטא בכאבי ראש, כאבי שרירים, חרדה קיצונית, מתח, חוסר מנוחה, בלבול, שינויים במצב רוח, קושי בשינה ועצבנות.  במקרים חמורים של גמילה, ייתכנו גם התסמינים הבאים: בחילות, הקאות, זיעה, התכווצויות בבטן, התכווצויות שרירים, תחושה של חוסר מציאות או ניתוק, רגישות לקול, אור או מגע, חוסר תחושה ונימול של כפות רגליים והידיים, הזיות (ראייה או שמיעה של דברים שאינם קיימים בזמן ערות), רעד או התקפי אפילפסיה.  **תופעות לוואי נוספות:**  **מופיעות לעיתים קרובות מאוד:**  **......................**   * חוסר יכולת להישאר ער, חולשה   .....................   * עצירות, יובש בפה, בחילה   **מופיעות לעיתים קרובות**:   * עצבנות, חרדה או סערת נפש * נדודי שינה (חוסר יכולת לישון או הפרעות בשינה).   ...............   * התרוממות רוח או התרגשות יתר, הגורמות להתנהגות חריגה |

**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................**

⮽ 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: Xanax eMC Patient Information leaflet PIL.3725 (22/11/2012),,

FDA Patient Information Leaflet Reference ID: 3004871 (06/2011, עלון ישראלי של XANAX XR

**האסמכתא מצ"ב.**

⮽ השינוי הנ"ל אושר על ידי רשויות הבריאות באנגליה וארה"ב

⮽אני, הרוקח הממונה של חברת פריגו פרמצבטיקה 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 (שם וחתימה) :\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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| **ההחמרות המבוקשות** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **Posology, dosage & administration** | The optimum dosage of Xanagis (alprazolam) should be determined individually based on the severity of the symptoms and individual patient response. In the event of severe adverse effects with initial dose, a dose reduction is necessary. It is advisable to review treatment regularly and to discontinue use as soon as possible.  The recommended daily dose will be sufficient in most patients. In the few patients who require a higher dose, the dosage should be increased gradually, starting with a higher dose in the evening, to avoid adverse effects. In general, patients who have not previously taken psychotropic agents will require a lower dose compared to those who have previously been treated with tranquillizers, antidepressants or hypnotics or compared to chronic alcoholics.  In order to prevent ataxia and oversedation, it is advisable to use the lowest effective dose. This is particularly important in elderly and/or debilitated patients.  **SYMPTOMATIC TREATMENT OF ANXIETY**  Recommended starting dose: varies from 0.25 mg to 0.5 mg three times daily. Recommended dose: The dose can be increased to suit the patient's needs to a maximal daily dose of 4 mg divided over the day.  **SYMPTOMATIC TREATMENT OF PANIC DISORDERS**  Recommend starting dose: varies from 0.5 to 1 mg at bedtime.  Recommended dose: The dose should be adjusted according to the patient's response. The maximal dose increase should be 1 mg every three to four days. Additional doses may be given to reach 3 or 4 administrations daily.  In clinical studies the mean dose was 6 ± 2 mg. Exceptionally, a maximum dose of 10 mg daily was required in a few patients.  **TREATMENT OF GERIATRIC OR DEBILITATED PATIENTS**  Recommended starting dose: 0.25 mg twice to three times daily.  Recommended dose: If necessary, the dose can be increased gradually depending on tolerance.  The starting dose should be reduced if side-effects occur.  Paediatric patients: Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore use of alprazolam is not recommended | Treatment should be as short as possible. It is recommended that the patient be reassessed at the end of no longer than 4 weeks' treatment and the need for continued treatment established, especially in case the patient is symptom free. The overall duration of treatment should not be more than 8-12 weeks, including a tapering off process.  In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re­evaluation of the patient's status with special expertise. As with all benzodiazepines, physicians should be aware that long-term use might lead to dependence in certain patients.  The optimum dosage of alprazolam should be based upon the severity of the symptoms and individual patient response. The lowest dose which can control symptoms should be used. Dosage should be reassessed at intervals of no more than 4 weeks. The usual dosage is stated below; in the few patients who require higher doses, the dosage should be increased cautiously to avoid adverse effects. When higher dosage is required, the evening dose should be increased before the daytime doses. In general, patients who have not previously received psychotropic medications will require lower doses than those so treated, or those with a history of chronic alcoholism.  Anxiety: 0.25 mg to 0.5 mg three times daily increasing if required to a total of 3 mg daily.  The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3 to 4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment………………."    Panic Disorder: The successful treatment of many panic disorder patients has required the use of alprazolam at doses greater than 4 mg daily.  Treatment may be initiated with a dose of 0.5 mg three times daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg per day. Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (i.e., a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage.  Paediatric patients: Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore use of alprazolam is not recommended.  Geriatric patients or in the presence of debilitating disease: 0.25 mg two to three times daily to be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses.  If side-effects occur, the dose should be lowered. It is advisable to review treatment regularly and to discontinue use as soon as possible. Should longer term treatment be necessary, then intermittent treatment may be considered to minimize the risk of dependence. |
| **contraindications** |  | . Alprazolam may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.  Alprazolam is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A). |
| **Special Warnings and Precautions for Use** | In patients presenting with major depression or anxiety associated with depression benzodiazepines and benzodiazepinelike agents should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide.  ***Dependence***  Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products The risk of dependence increases with dose and duration of treatment. Addiction and emotional/physical dependence can occur with the use of benzodiazepines, including alprazolam. Caution is required, in particular when benzodiazepines are prescribed for patients who are prone to drug abuse (e.g. alcoholics, drug addicts), since these patients are predisposed to addiction and dependence.  Panic disorders or related conditions have been associated with major primary or secondary depressions in untreated patients and with an increase in the number of suicide cases. Consequently, the same precautions are required as with the use of other psychotropic agents for the treatment of patients suffering from depression or in patients suspected of harbouring occult suicide ideas or plans.  .  .  s. | In patients presenting with major depression or anxiety associated with depression benzodiazepines and benzodiazepine-­like agents should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.  …………….  . There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam.  Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (See section 4.5 Interactions with other medicinal products and other form of interactions). A decreased systemic alprazolam elimination rate (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam.  Dependence  Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and drug abuse. Pharmacodependency may occur at therapeutic doses and/or in patients with no individualized risk factor. There is an increased risk of pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Cases of abuse have also been reported.  The importance of dose and the risks of alprazolam as a treatment for panic disorder: Because the management of panic disorder often requires the use of average daily doses of alprazolam above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety.  Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with alprazolam compared to placebo-treated patients.  Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.  …………………………..  Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually by no more than 0.5 mg every three days. Some patients may require an even slower dose reduction. (See section 4.2 Posology and method of administration)  ………………………….  Interdose Symptoms  Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam have been reported in patients with panic disorder taking prescribed maintenance doses of alprazolam. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations  …………………..  Uricosuric Effect  Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam |
| Interaction with other medicinal products and other forms of interaction | CYP3A4 Inducers  …………However, after prolonged ritonavir exposure this inhibition is counteracted by CYP3A induction. The interaction requires dose adjustment or discontinuation of treatment with alprazolam.  Mean increases of respectively 31% and 20% of the steady-state plasma levels of imipramine and desipramine have been reported during concurrent administration of Xanagis up to 4 mg daily. The clinical significance of these changes has not yet been established.  Interactions with isoniazide or rifampicin have not been evaluated. No changes in alprazolam kinetics have been noted during concurrent administration of propranolol or disulfiram.  Alprazolam does not affect the plasma levels of phenytoin, but the effect of phenytoin on the levels of alprazolam has not been studied.  Although it has never been described with alprazolam, there is an increased risk of psychosis when benzodiazepines are used in combination with valproic acid.  Theophyllin antagonizes the effect of benzodiazepines. | 1. *Fluoxetine* — Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance. 2. *Propoxyphene* — Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%. 3. *Oral Contraceptives* — Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.   Caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with Cimetidine—Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.  CYP3A4 Inducers  …….However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam. Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.  Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from an in vivo drug interaction study involving a single dose of alprazolam 1 mg and steady state dose of sertraline (50 to 150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from in vitro studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam. |
| Fertility, pregnancy and lactation | When alprazolam is prescribed to a woman of childbearing age, she should be warned to notify her physician if she wishes to become pregnant or if she is pregnant, so the physician can decide to discontinue treatment.  The data concerning teratogenicity and effects on postnatal development and behavior following benzodiazepine treatment are inconsistent. A large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found a twofold increased risk of oral clefts. | Pregnancy  The data concerning teratogenicity and effects on postnatal development and behavior following benzodiazepine treatment are inconsistent. A large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found a twofold increased risk of oral clefts. |
| **Undesirable effects** |  | Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.  Post Introduction Reports:  Various adverse drug reactions have been reported in association with the use of alprazolam since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of alprazolam cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, angioedema, peripheral edema, hyperprolactinemia, gynecomastia, and galactorrhea. |
| Overdose | Although a benzodiazepine overdose is not usually life-threatening, it is always necessary to bear in mind the possibility that agents such as alcohol and barbiturates have been taken and the potential underlying pathology should be considered. Treatment should be adapted accordingly.  Treatment of overdosage consists mainly in supporting respiratory and cardiovascular functions. In case of coma, treatment is mainly symptomatic, hereby avoiding complications such as asphyxiation due to ptosis of the tongue or aspiration pf gastric contents. Intravenous fluid administration is required to prevent dehydration.  When other sedatives have been taken in combination, it is of primordial importance to support vital functions. Shortly after ingestion, gastric lavage and/or activated charcoal can be indicated. Afterwards, an osmotic laxative can be administered. It is known that the effect due to ingestion of a very large dose can persist for a long time. Forced diuresis or haemodialysis is of limited use. | As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). In the management of overdose with any medicinal product, it should be borne in mind that multiple agents have been taken.  Following overdose with oral benzodiazepines, vomiting may be induced (within 1 hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.  Special attention should be paid to respiratory and cardiovascular functions in intensive care.  Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. |

**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................**

⮽ 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 לצרכן והוא מעודכן בהתאם.

⮽אסמכתא לבקשה: Xanax eMC Patient Information leaflet PIL.3725 (22/11/2012),,

FDA Patient Information Leaflet Reference ID: 3004871 (06/2011

**האסמכתא מצ"ב**.

⮽ השינוי הנ"ל אושר על ידי רשויות הבריאות באירופה וארה"ב

⮽ אני, הרוקח הממונה של חברת 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 (שם וחתימה)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_