יום חמישי 08 אוקטובר 2020

רופא/ה, רוקח/ת נכבד/ה,

הנדון: טרילפטין Trileptin 300mg, 600mg
[106-80-28707, 106-81-28708]

אנו מבקשים להודיעך כי העלונים לרופא ולצרכן של התכשירים בנדון עודכנו באוקטובר 2020. עלונים אלו מבוססים על העלונים המאושרים על-ידי רשות הבריאות השוויצרית.

התכשיר מתווה בישראל להתווית כדלקמן:

Treatment of primary generalised tonic-clonic seizures and partial seizures, with or without secondary generalisation.

מרכיב פעיל: oxcarbazepine 300mg, 600mg

צורות מינון: Film-coated Tablets

בעמוד העוקב מצויינים סעיפים בהם נעשה שינוי אשר מהווה החמרה או שינוי משמעותי. למידע נוסף, יש לעיין בעלונים לצרכן ולרופא המצורפים כפי שאושרו על ידי משרד הבריאות.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#!/byDrug

ניתן לקבלם מודפסים על ידי פניה לחברת נוברטיס ישראל בע"מ, תוצרת הארץ 6, ת.ד. 7126, תל אביב
טל: 03-9201111, פקס: 03-9229230

בברכה,

ברוך גבריאלי
רוקח ממונה
נוברטיס ישראל בע"מ

Novartis Israel Ltd.
6 Tozeret Haaretz street, P.O.Box 7126, Tel Aviv
Tel: 03-9201111, Fax: 03-9229230

נוברטיס ישראל בע"מ.
תוצרת הארץ 6, ת.ד. 7126, תל אביב
טל: 03-9201111, פקס: 03-9229230

להלן פירוט השינויים העיקריים (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה:)

בעלון לרופא:

4.3 Contraindications

Known hypersensitivity to the active substance oxcarbazepine, **eslicarbazepine** or any of the excipients listed in section 6.1.

4.4 Warnings and precautions

Hypersensitivity reactions

Hypersensitivity reactions, including class I reactions and other hypersensitivity reactions, have been reported under treatment with oxcarbazepine. If such symptoms develop, Trileptin should be discontinued and the patient switched to treatment with another antiepileptic drug.

Class I reactions: Symptoms ranging from rash, pruritus, urticaria, **dyspnoea, bronchospasm** and angioedema to anaphylactic shock have been reported. The cases of anaphylactic angioedema involved the larynx, ~~**glottis**~~ **tongue**, lips and eyelids; such reactions were observed both after the first dose and after subsequent doses of Trileptin.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that the cross-reaction rate for hypersensitivity reactions (e.g. serious skin reactions) with Trileptin treatment is 25-30%. **For this reason patients should be specifically asked about previous treatment with carbamazepine before starting Trileptin therapy. Patients with a history of hypersensitivity reactions to carbamazepine should generally only be treated with Trileptin if the potential benefit justifies the potential risk.** If signs or symptoms of hypersensitivity develop, Trileptin should be discontinued immediately.

Other hypersensitivity reactions, including multi-organ hypersensitivity reactions: **Such reactions have been observed both in adults and children in close temporal association (mostly within the first 3 weeks, possibly also later) with the commencement of treatment. Symptoms varied greatly. Patients normally exhibited not only fever and a rash, but also involvement of other organ systems. In this context there have been reports of asthenia, pruritus, arthralgia, joint swelling, lymphadenopathy, splenomegaly, haematological abnormalities (e.g. eosinophilia, thrombocytopenia, neutropenia), pulmonary oedema, interstitial lung changes, abnormal liver function tests, hepatitis, proteinuria, oliguria, interstitial nephritis, renal failure and hepatorenal syndrome. Symptoms in other organ systems may also occur. Some cases led to hospitalisation, with isolated cases being regarded as life-threatening.**

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*Association with the HLA-B*1502 allele*

Retrospective studies in patients of Han Chinese or Thai descent demonstrated a strong correlation between SJS/TEN skin reactions associated with the use of carbamazepine and the presence of the human leukocyte antigen (HLA)-B*1502 allele. As the chemical structure of oxcarbazepine is similar to that of carbamazepine, patients carrying the HLA-B*1502 allele are also presumed to have an increased risk of SJS/TEN skin reactions with oxcarbazepine. **Some data describe such an association for oxcarbazepine as well.**

The prevalence of carriers of this allele is around 20% in the Philippines, 13.5% in Vietnam, 2-12% in the Han Chinese population, **at least 8% in Thailand and 2-6% in Korea and India.** In contrast, the prevalence of the HLA-B*1502 allele is negligible (<1%) in the Caucasian, African, Japanese, indigenous American and Hispanic populations.

~~**The frequency of HLA-B*1502 allele ranges from 2 to 12% in Han Chinese populations, from 0 to 18% in Taiwanese populations, and is about 8% in Thai populations, 10 % in the Hong Kong (Chinese) population, and above 15% in the Philippines and some Malaysian populations.**~~

~~**Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in persons from European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (< 1%).**~~

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*Association with the HLA-A*3101 allele*
The human leukocyte antigen (HLA)-A*3101 may be a risk factor for the development of adverse skin reactions such as SJS/TEN, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) and maculopapular rash. In particular, there are data that suggest that the HLA-A*3101 allele is associated with an increased risk of carbamazepine-induced skin reactions (SJS/TEN, DRESS, AGEP) and maculopapular rash.

The prevalence of this allele varies widely in different ethnic populations. The prevalence in the European population is around 2-5% and around 10% in the Japanese population. The prevalence of this allele is estimated to be less than 5% in the majority of the Australian, Asian, African and North American populations ~~**with some exceptions within 5 to 12%. Frequency above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10% to 15% in other native ethnicities in these same regions.**~~

The values given here relate to the prevalence of homozygous allele carriers. The proportion of heterozygotes (and thus of people with a potentially increased risk of skin reactions) is nearly twice as high.

Screening for HLA-A*3101 is not recommended in population groups with a low prevalence. Similarly, screening is not appropriate in patients who have already used Trileptin for a prolonged period as SJS/TEN, DRESS, AGEP and maculopapular rash usually occur only in the first few months of therapy.

Patients of European or Japanese descent who carry the HLA-A*3101 allele may be treated with Trileptin provided that the benefits outweigh the risks.

Genetic screening results are not a substitute for appropriate monitoring of the patient, particularly as the risk of severe skin reactions may also be influenced by other factors (such as comorbidities).

~~**Genetic screening results must never substitute appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with Trileptin will not develop SJS/TEN, and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. Similarly, many patients positive for HLA-A*3101 and treated with Trileptin will not develop SJS, TEN, DRESS, AGEP or maculopapular rash, and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. The role of other possible factors in the development of, and morbidity from, these severe cutaneous adverse reactions, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.**~~

~~**Information for healthcare professionals**~~

~~**If testing for the presence of the HLA-B*1502 allele is performed, high resolution "HLA-B*1502 genotyping" is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected, and negative if no HLA-B*1502 alleles are detected. Similarly, if testing for the presence of the HLA-A*3101 allele is performed, high resolution "HLA-A*3101 genotyping" is recommended. The test is positive if either one or two HLA-A*3101 alleles are detected, and negative if no HLA-A*3101 alleles are detected.**~~

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Hyponatraemia

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Serum sodium levels should be measured prior to initiating therapy in patients with pre-existing renal conditions requiring a high fluid intake, patients with pre-existing low sodium levels (e.g. syndrome of inappropriate ADH secretion) and patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, desmopressin) **or with NSAIDs** (e.g. indomethacin). Thereafter, serum sodium levels should initially be measured after approximately two weeks and then at monthly intervals for the first three months of treatment or according to clinical need. The aforementioned risk factors are particularly present in elderly patients. For patients on Trileptin therapy in whom treatment with sodium-lowering medicinal products is being initiated the same approach should be followed to determine serum sodium levels. In general, if clinical symptoms suggestive of hyponatraemia occur during Trileptin treatment, serum sodium measurement should be considered. In all other patients it is sufficient to assess serum sodium levels as part of routine laboratory tests.
Very rarely, clinically relevant hyponatraemia (Na <125 mmol/l) can develop during Trileptin therapy. This generally occurred during the first 3 months of treatment, although there were patients who first developed a serum sodium level <125 mmol/l one year following initiation of therapy. Cases were also

observed involving seizures, disorientation, depressed level of consciousness, encephalopathy, visual disturbances (e.g. blurred vision), vomiting, nausea and folic acid deficiency.
In isolated cases syndrome of inappropriate ADH secretion (SIADH) may occur under Trileptin therapy.

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Hypothyroidism

Hypothyroidism is a very rare adverse effect of oxcarbazepine. In view of the importance of thyroid hormones for childhood development after birth it is advisable to carry out a thyroid function test before initiating Trileptin therapy in the paediatric age group, particularly in children aged 2 years and under. In the paediatric age group it is also recommended to monitor thyroid function during Trileptin therapy. **In patients with hypothyroidism monitoring of thyroid function is recommended to determine the dose for hormone replacement therapy.**

Suicidality

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic drugs in several indications. A meta-analysis of randomised, placebo-controlled studies with antiepileptic drugs also showed a slightly increased risk of suicidal ideation and behaviour. The mechanism triggering this adverse effect is not known **and the available data do not rule out the possibility of an increased risk when taking Trileptin.**

Therefore, patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and their carers) should be advised to seek medical advice if signs of suicidal ideation or behaviour emerge.

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Hepatic function

Very rare cases of hepatitis have been reported, which in most cases resolved spontaneously. In case of suspected hepatic impairment; **hepatic function should be assessed** and discontinuation of Trileptin treatment should be considered. Caution is advised when treating patients with severe hepatic impairment (see "Dosage/Administration" and "Properties/Actions").

Renal function

In patients with renal impairment (creatinine clearance below 30 ml/min) caution is advised during Trileptin treatment, especially concerning the starting dose and up-titration of the dose (see "Dosage/Administration" and "Pharmacokinetics").
There have been reports of reduced bone mineral density through to overt osteoporosis with the occurrence of fractures during long-term use of Trileptin. The precise mechanism by which oxcarbazepine affects bone metabolism is not yet known.

Withdrawal effects

As with other antiepileptic drugs, sudden withdrawal of Trileptin must be avoided. The dosage should be reduced gradually to minimise the risk of triggering seizures**, i.e. aggravation of seizures or status epilepticus. If abrupt withdrawal of Trileptin is unavoidable – due to severe adverse effects, for example – a suitable drug (e.g. i.v. or rectal diazepam; i.v. phenytoin) should be administered during the changeover period to another antiepileptic drug and the patient monitored closely.**

Oxcarbazepine has a weaker enzyme-inducing effect than carbamazepine. The dose of other co-administered antiepileptic drugs may need to be lowered (see "Interactions").

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Interactions

Hormonal contraceptives: Patients of childbearing age should be advised that the concomitant use of Trileptin with hormonal contraceptives may render the contraception ineffective (see "Interactions"). Additional, non-hormonal contraceptive measures should be recommended to patients treated with Trileptin.

Vitamin B12 deficiency should either be ruled out or treated.
Alcohol: Patients treated with Trileptin should avoid alcohol due to a possible additive sedative effect.

4.5 Interactions

The following table provides an overview of the interactions of oxcarbazepine with other antiepileptic drugs. See the text below the table for details.

Summary of antiepileptic drug interactions with Trileptin		
Antiepileptic drug Co-administered:	Influence of Trileptin on antiepileptic drug C_{min}:	Influence of antiepileptic drug on MHD (**) AUC:
Carbamazepine	0-22% decrease **(30% increase in carbamazepine epoxide)**	40% decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Lamotrigine	**No influence (*)**	**No influence**
Phenobarbital	14-15% increase	30-31% decrease
Phenytoin	0-40% increase	29-35% decrease
Valproic acid	No influence	0-18% decrease

(*: No effect on C_{min}, AUC or C_{max})
(**: MHD: Monohydroxy derivative (pharmacologically active metabolite of oxcarbazepine))

Influence of other medicinal products on oxcarbazepine pharmacokinetics

Strong inducers of cytochrome P450 such as **rifampicin,** carbamazepine, phenytoin or phenobarbital decrease plasma/serum levels of MHD by 29-40%. **Therefore, monitoring of plasma levels and/or dose adjustment should be considered if one or more of these medicinal products are co-administered with oxcarbazepine.**

Cimetidine, erythromycin, viloxazine, warfarin and dextropropoxyphene had no effect on the pharmacokinetics of MHD. ~~**viloxazine produced minor changes in the MHD plasma levels (about 10% higher after repeated co-administration**~~

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4.6 Pregnancy/Breast-feeding

Pregnancy

General risks associated with epilepsy and the use of antiepileptic drugs

It has been shown that the rate of malformations in the children of women with epilepsy is two to three times higher than the rate of approximately 3% in the general population. **In women receiving treatment an increase in malformations was seen particularly in those receiving combination therapy; however, the extent to which the relevant treatment and/or the condition itself were responsible could not be established.** Effective antiepileptic treatment should not be interrupted during pregnancy since aggravation of the illness is associated with risks to both the mother and the fetus.

Risks due to oxcarbazepine

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Animal studies demonstrated an increased incidence of embryo mortality, delayed growth and isolated cases of malformations at high, maternally toxic doses (see "Preclinical data").

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Neonates

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Rare cases of hypocalcaemia have been observed in neonates whose mothers were treated with antiepileptic drugs during pregnancy. These cases were due to disorders of calcium phosphate metabolism and bone mineralisation.

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4.8 Adverse effects

Endocrine disorders
Common: Increased weight.

Metabolism and nutrition disorders
Common: Hyponatraemia**, more frequently in elderly patients** (see "Warnings and precautions").

Nervous system disorders
Very common: **Light-headedness (22.6%),** dizziness (22.6%), somnolence (22.5%), headache (14.6%).

~~**Ear and labyrinth disorders**~~
~~**Common: vertigo**~~

Hepatobiliary disorders
Uncommon: Increased transaminases and/or alkaline phosphatase.

בעלון לצרכן:

2. לפני שימוש בתרופה

אין להשתמש בתרופה אם:
יש לך רגישות יתר (אלרגיה) ידועה לאוקסקרבזפין (החומר הפעיל של טרילפטין), **אסליקרבזפין (חומר פעיל דומה לאוקסקרבזפין)** או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה. (ראה סעיף 6 'מידע נוסף').
אם זה נכון לגביך, ידע את הרופא לפני נטילת טרילפטין.
אם אתה חושב שיתכן שאתה אלרגי, היוועץ ברופא.

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

לפני הטיפול בטרילפטין, ספר לרופא אם:
אי פעם פיתחת פריחה לא רגילה בעור או סימנים אחרים של אלרגיה במהלך טיפול קודם באוקסקרבזפין (טרילפטין), **אסליקרבזפין (חומר פעיל דומה לאוקסקרבזפין)**, קרבמזפין או כל תרופה אחרת
...
התוצאות של בדיקות הדם שעברת היו חריגות
...
לפני כל טיפול חירום רפואי או כל סוג של ניתוח או טיפול שיניים עליך ליידע את הרופא האחראי עליך שאתה נוטל טרילפטין.
...
שימוש בטרילפטין ומזון
ניתן ליטול את התרופה **במהלך או לאחר הארוחה** ~~**עם או בלי אוכל**~~.
...
נהיגה ושימוש במכונות
...
היכולת שלך לנהוג ולהשתמש במכשירים או במכונות עלולה להיות מושפעת גם מהמחלה שלך. פנה לרופא שלך למידע נוסף.

3. כיצד תשתמש בתרופה?

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צורת הנטילה
לטבליות המצופות יש קו חצייה כך שניתן לחצות אותן לשני חצאים וכך להקל על בליעתן. יש לבלוע את הטבליות המצופות עם כמות קטנה של נוזל.
אסור לכתוש או ללעוס את הטבליות מכוון שהינן טבליות מצופות.
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4. תופעות לוואי

אם אתה מרגיש באחת או יותר מתופעות הלוואי הבאות, פנה מיד לרופא או וודא שמישהו אחר עושה זאת עבורך מיד.
תסמינים אלה עשויים להיות הסימנים הראשונים לתופעת לוואי חמורה הדורשת טיפול מיידי:
...
בלבול רב, נמנום, כאבי ראש או קשיים בהנעת הזרועות או הרגליים.

סימנים לתסמינים חמורים המשפיעים על העור או על רקמות ריריות כגון שלפוחיות, **התקלפות העור** ותגובות אלרגיות חמורות.
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פנה לרופא שלך בהקדם האפשרי אם אתה מרגיש באחת או יותר מתופעות הלוואי הבאות:

כאב ראש, רעד, **תחושת עקצוץ בכפות הידיים וכפות הרגליים**, הקאות, פריחה בעור, מחזורי ווסת לא סדירים, **צלילים באוזניים שאין להם הסבר, הפרעות בתאום התנועות (קואורדינציה), תנודות במצב הרוח באופן תדיר, חרדה, דכאון, הפרעות בדיבור.**

מחלות של העצמות כגון אוסטאופניה (צפיפות עצם נמוכה) ואוסטאופורוזיס (דלדול העצם) דווחו במטופלים המקבלים טיפול ממושך כמו גם שברים בעצמות.

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תופעות הלוואי הבאות עשויות להתרחש בנטילת טרילפטין:

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תופעות לוואי שכיחות (מופיעות ב- 1 עד 10 משתמשים מתוך 100):
עלייה במשקל, שלשול, עצירות, כאב בטן, הפרעות בראייה, ראייה מעורפלת,, אקנה, נשירת שיער, חולשה, הפרעות בזכרון, **חוסר מנוחה גופני (אגיטציות).**

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תופעות לוואי נוספות:
הפרעות שינה, ירידה במשקל, ירידה בלחץ הדם,

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