# הודעה על החמרה (מידע בטיחות) בעלון לרופא

**(מעודכן 05.2013)**

**תאריך:** 01/06/2017

**שם תכשיר באנגלית ומספר רישום:**

Vimpat 10 mg/ml solution for infusion (33552)

**שם בעל הרישום:** Neopharm Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד !

| טקסט חדש | טקסט נוכחי | פרק בעלון |
|---|---|---|
| Vimpat is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in ~~adult~~ patients with epilepsy aged 16 years and older. | Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adult patients with epilepsy aged 16 years and older. | **Indication** |
| Posology:<br><br>Lacosamide therapy can be initiated with either oral or i.v. administration. Solution for infusion is an alternative for patients when oral administration is temporarily not feasible. The overall duration of treatment with i.v. lacosamide is at the physician's discretion; there is experience from clinical trials with twice daily infusions of lacosamide for up to 5 days in adjunctive therapy. Monitor closely patients with known cardiac conduction problems, on concomitant medications that prolong PR interval, or with severe cardiac disease (e.g. myocardial ischemia, heart failure) when lacosamide dose is higher than 400 mg/day (see Method of administration below and section 4.4).<br>Lacosamide must be taken twice a day (usually once in the morning and once in the evening).<br><br>*Monotherapy*<br>The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.<br>Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.<br>Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of | Posology:<br><br>Vimpat therapy can be initiated with either oral or i.v. administration. Solution for infusion is an alternative for patients when oral administration is temporarily not feasible. The overall duration of treatment with i.v. lacosamide is at the physician's discretion; there is experience from clinical trials with twice daily infusions of lacosamide for up to 5 days.<br><br>Vimpat must be administered twice a day (usually once in the morning and once in the evening). The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week. | **Posology, dosage and administration** |

| | | |
|---|---|---|
| 300 mg twice a day (600 mg/day).<br>In patients having reached a dose greater than 400 mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.<br><br>*Adjunctive therapy*<br>The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.<br><br>……<br><br>*Special populations*<br>*Elderly (over 65 years of age)*<br>No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'Renal impairment' and section 5.2).<br>There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8, and 5.1).<br><br>*Hepatic impairment*<br>A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.<br>The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.<br><br>…….<br><br>Method of administration<br>Product with particulate matter or discolouration should not be used.<br>The solution for infusion is infused over a period of 15 to 60 minutes twice daily. An infusion duration of at least 30 minutes for administration >200 mg per infusion (i.e. >400 mg/day) is preferred. Vimpat solution for infusion can be administered intravenously without further dilution or can be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, glucose 50 mg/ml (5%) solution for injection or lactated Ringer's solution for injection. | …..<br><br>*Special populations*<br>*Elderly (over 65 years of age)*<br>No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'Renal impairment' and section 5.2).<br><br>*Hepatic impairment*<br>No dose adjustment is needed for patients with mild to moderate hepatic impairment.<br>The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2).<br><br>…….<br><br>Method of administration<br>Product with particulate matter or discolouration should not be used.<br>The solution for infusion is infused over a period of 15 to 60 minutes twice daily. Vimpat solution for infusion can be administered intravenously without further dilution or can be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, glucose 50 mg/ml (5%) solution for injection or lactated Ringer's solution for injection. | |

| | | |
|---|---|---|
| *Cardiac rhythm and conduction*<br>Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems,severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.<br>In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400 mg/day and after lacosamide is titrated to steady-state. | *Rhythm and conduction*<br>Prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems or severe cardiac disease such as a history of myocardial infarction or heart failure. Caution should especially be exerted when treating elderly patients as they may be at an increased risk of cardiac disorders or when lacosamide is used in combination with products known to be associated with PR prolongation. | **Special warnings and special precautions for use** |
| Nervous system disorders<br>(Very common) Dizziness, Headache<br>(Common) Balance disorder, Coordination abnormal, Memory impairment, Cognitive disorder, Somnolence, Tremor, Nystagmus Hypoesthesia, Dysarthria, Disturbance in attention, Paraesthesia<br>(Uncommon) Syncope<br><br>Hepatobiliary disorders<br>(Uncommon) Liver function test abnormal<br>Hepatic enzyme increased (> 2x ULN)<br><br>…..<br><br>Elderly population<br>In the monotherapy study comparing lacosamide to carbamazepine CR, the types of adverse reactions related to lacosamide in elderly patients (≥ 65 years of age) appear to be similar to that observed in patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients. The most frequent cardiac-related adverse reaction reported in elderly compared to the younger population was first degree AV block. This was reported with lacosamide in 4.8% (3/62) in elderly patients versus 1.6% (6/382) in younger adult patients. The discontinuation rate due to adverse events observed with lacosamide was 21.0% (13/62) in elderly patients versus 9.2% (35/382) in younger adult patients. These differences between elderly and younger patients were similar to those observed in the active comparator group. | Nervous system disorders<br>(Very common) Dizziness, Headache<br>(Common) Balance disorder, Coordination abnormal, Memory impairment, Cognitive disorder, Somnolence, Tremor, Nystagmus Hypoesthesia, Dysarthria, Disturbance in attention, Paraesthesia<br><br>Hepatobiliary disorders<br>(Uncommon) Liver function test abnormal | **Adverse events** |
| **4.9 Overdose**<br><br>Symptoms<br><br>Symptoms observed after an accidental or intentional overdose of lacosamide are primarily associated with CNS and gastrointestinal system.<br><br>• The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were | **4.9 Overdose**<br><br>Symptoms<br>In clinical trials<br>The types of adverse events experienced by patients exposed to supratherapeutic doses were not clinically different from those of patients administered recommended doses of lacosamide.<br><br>Following doses of 1,200 mg/day, | **Overdose** |

| | | |
|---|---|---|
| not clinically different from those of patients administered recommended doses of lacosamide.<br>• Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of lacosamide.<br><br>~~Following doses of 1,200 mg/day, symptoms related to the central nervous system (e.g. dizziness) and the gastrointestinal system (e.g. nausea, vomiting) were observed and resolved with dose adjustments.~~<br><br>~~The highest reported overdose in the clinical development program for lacosamide was 12000 mg taken in conjunction with toxic doses of multiple other antiepileptics drugs. The subject was initially comatose with AV block and then fully recovered without permanent sequelae.~~<br><br>~~In post-marketing experience:~~<br>~~Following acute single overdose ranging between 1000 mg and 12000 mg, seizures (generalized tonic-clonic seizures, status epilepticus) and cardiac conduction disorders were observed. Fatal cardiac arrest was reported after an acute overdose of 7000 mg of lacosamide in patient with cardiovascular risk factor.~~ | symptoms related to the central nervous system (e.g. dizziness) and the gastrointestinal system (e.g. nausea, vomiting) were observed and resolved with dose adjustments.<br><br>The highest reported overdose in the clinical development program for lacosamide was 12000 mg taken in conjunction with toxic doses of multiple other antiepileptics drugs. The subject was initially comatose with AV block and then fully recovered without permanent sequelae.<br><br>In post-marketing experience:<br>Following acute single overdose ranging between 1000 mg and 12000 mg, seizures (generalized tonic-clonic seizures, status epilepticus) and cardiac conduction disorders were observed. Fatal cardiac arrest was reported after an acute overdose of 7000 mg of lacosamide in patient with cardiovascular risk factor. | |
| …<br>Clinical efficacy and safety<br>*Monotherapy*<br>Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in 886 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial onset seizures with or without secondary generalization. The patients were randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 1200 mg/day for carbamazepine CR and from 200 to 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.<br>The estimated 6-month seizure freedom rates were 89.8% for lacosamide-treated patients and 91.1% for carbamazepine CR treated patients using the Kaplan-Meier survival analysis method. The adjusted absolute difference between treatments was -1.3% (95 % CI: -5.5, 2.8). The Kaplan- | | **5.1 Pharmacodynamic properties** |

| | | |
|---|---|---|
| Meier estimates of 12-month seizure freedom rates were 77.8% for lacosamide-treated patients and 82.7% for carbamazepine CR treated patients.<br>The 6-month seizure freedom rates in elderly patients of 65 and above (62 patients in lacosamide, 57 patients in carbamazepine CR) were similar between both treatment groups. The rates were also similar to those observed in the overall population. In the elderly population, the maintenance lacosamide dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to over 400 mg/day in 1 patient (1.6%).<br><br>*Conversion to monotherapy*<br>The efficacy and safety of lacosamide in conversion to monotherapy has been assessed in a historical-controlled, multicentre, double-blind, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400 mg/day or 300 mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.<br><br>... | | |