

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 46 of Regulation (EC) No1901/2006, as  
amended**

**Trileptal/Lancyl/Timox  
(Oxcarbazepine)**

**DK/W/0028/pdWS/001**

**Marketing Authorisation Holder: Novartis**

<b>Rapporteur:</b>	DK
<b>Finalisation procedure (day 90):</b>	08-06-2016

### ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Trileptal / Lancyl / Timox
INN (or common name) of the active substance(s):	Oxcarbazepine
MAH:	Novartis
Currently approved Indication(s)	<p>Trileptal is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures.</p> <p>Trileptal is indicated for use as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above.</p>
Pharmaco-therapeutic group (ATC Code):	N03A F02
Pharmaceutical form(s) and strength(s):	Film-coated tablets 150 mg, 300 mg, and 600 mg. Oral suspension 60 mg/ml.

## **I. EXECUTIVE SUMMARY**

The anti-epileptic compound Trileptal (oxcarbazepine) is currently approved via the Mutual Recognition procedure in 15 countries (RMS is Denmark) and inter alia via the National procedure in 13 additional European countries for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures, either as monotherapy or adjunctive therapy, in adults and children as of six years of age. The MAH has now submitted results from two open label paediatric clinical studies conducted in the People's Republic of China. According to the MAH the efficacy and safety results from these two studies do not warrant any change to the European MRP product information for Trileptal. Thus, no SmPC and PL changes are proposed by the MAH.

## **II. RECOMMENDATION**

The position of the MAH is supported since no new efficacy nor any new safety information has emerged from the two completed clinical studies which would change the benefit-risk ratio. No SmPC nor any PL changes are therefore proposed by the Rapporteur.

## **III. INTRODUCTION**

On November 14, 2014, the MAH submitted two completed paediatric studies for Trileptal, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Trileptal and that there is no consequential regulatory action planned by the MAH.

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the study(ies)**

The authorised formulation Trileptal oral solution 60 mg oxcarbazepine / ml was used in both clinical studies.

### **IV.2 Clinical aspects**

#### **1. Introduction**

Trileptal (INN: oxcarbazepine) is an antiepileptic drug (ATC code: N03A F02). The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite (MHD- Mono hydroxy derivative) of oxcarbazepine. The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilization of hyper excited neural membranes, inhibition of repetitive neuronal firing, and diminished propagation of synaptic impulses. In addition, increased potassium

conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects. In Europe Trileptal is approved for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures. Trileptal is indicated for use as monotherapy or adjunctive therapy in adults and in children as of 6 years of age and above.

The posology in adults for monotherapy as well as adjunctive therapy is a starting dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day in adults. For paediatric use (as of six years of age), in mono- and adjunctive therapy, Trileptal should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses. In adjunctive therapy trials, a maintenance dose of 30-46 mg/kg/day, achieved over two weeks, was shown to be effective and well tolerated in children. Therapeutic effects were seen at a median maintenance dose of approximately 30 mg/kg/day. If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day increments at approximately weekly intervals from the starting dose, to a maximum dose of 46 mg/kg/day, to achieve the desired clinical response. Plasma level monitoring of oxcarbazepine or MHD is not routinely warranted.

The MAH has now submitted final reports for:

- CTRIT476BCN04. Title: Efficacy and safety of Oxcarbazepine oral suspension in the treatment of pediatric patients with partial seizure and/or generalised tonic-clonic seizures: 26 week, single group, open-label, multi-center, observational study
- CTRIT476BCN06. Title: A multi-center, 26-weeks, single arm, observational study to evaluate the efficacy and safety of Oxcarbazepine in 2-5 years old pediatric patients with partial seizure and/ or GTCS in routine clinical practice.

## 2. Clinical study(ies)

*CTRIT476BCN04. Title: Efficacy and safety of Oxcarbazepine oral suspension in the treatment of pediatric patients with partial seizure and/or generalised tonic-clonic seizures: 26 week, single group, open-label, multi-center, observational study.*

### ➤ Description

### ➤ Methods

- Objective(s)
  - Primary objective: To evaluate the safety of oxcarbazepine (OXC) oral suspension treatment in paediatric patients with partial seizure or generalized tonic clonic seizures.
  - Secondary objectives: To evaluate the efficacy of OXC oral suspension treatment in pediatric patients with partial seizure or generalized tonic clonic seizures.
- Study design  
A 26 week, single arm, open label, multicenter, observational study.
- Study population /Sample size  
Two to 16 years old paediatric patients with partial seizure and/ or GTCS in routine clinical practice who did not receive oxcarbazepine treatment within 30 days prior to enrolment. Subjects were allowed to be on treatment with concomitant AED(s). One thousand subjects were planned to be enrolled. No formal sample size estimate was done.

- **Treatments**  
Trileptal oral suspension (60mg/ml) was to be used according to the approved doses as per local (Chinese) prescribing information. According to the local prescribing information Trileptal should be initiated with a dose 8-10 mg/kg/day given in 2 divided doses as mono/adjunctive therapy; if clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day increments at least weekly interval from the starting dose to achieve the desired clinical response.
- **Outcomes/endpoints**  
Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and frequency. They also included regular assessments of vital signs and physical condition. Laboratory test were not mandatory in the study.

Efficacy was evaluated by comparison between the frequency of seizure (times/month) at baseline and at the end of study. The primary efficacy variable was the reduction in seizure frequency at the end of 26 weeks (or the end of the study) compared to baseline. No AED concentration measurements were performed for the study.

- **Statistical Methods**  
All statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05, unless otherwise specified. Summary statistics included n (number of observations), mean, standard deviation, median, minimum and maximum values for continuous variables, as well as frequencies and percentages for categorical variables.

The analysis sets were divided into following populations:

- **Full Analysis Set, (FAS):** All patients who received at least 1 dose of OXC oral suspension treatment, and had at least one post-baseline efficacy evaluation were to be included in the FAS. FAS was the primary efficacy population;
- **Per Protocol Set(PPS):** The per protocol (PP) population was is a subset of the FAS population and consisted of all subjects who had no pre-specified protocol violations during the course of the study. PPS were to be used as secondary efficacy population.
- **Safety Set (SS):** The safety population consisted of all patients who received at least one dose of oxcarbazepine and had at least one post-baseline safety assessment. SS was the primary safety population.

## ➤ **Results**

- **Recruitment / Number analysed**  
A total of 987 patients were entered into the study from 23 sites in China. First patient first visit (FPFV) was in June, 2009. The last patient last visit (LPLV) in March, 2011. Of the 987 patients, 20 patients without receiving a single dose of study drug were excluded from the SS population. Of the total 967 patients who received oxcarbazepine treatment, 4 patients only had safety evaluation, and another 31 patients violated the visit schedule, thus 932 patients (94.4%) were included into the FAS population. Overall, 75 patients (7.6%) discontinued from the study drug treatment prematurely. The most frequently reasons were: adverse events (2.2%), unsatisfactory therapeutic effect (1.8%), and lost to follow-up (1.2%).

- Baseline data

The mean age ( $\pm$  SD) of the FAS population was  $5.2 \pm 2.8$  years. A greater number of the patients were in the 2-4 years (55.3%) and  $>5$  years (44.7%) age groups. The majority of patients were male (58.4%). The mean weight ( $\pm$  SD) was  $19.6 \pm 8.4$  kg. The mean duration ( $\pm$  SD) of epilepsy was  $11.7 \pm 17.7$  months. According to classification by seizure type, 840 patients (90.1%) had partial seizures, 135 patients (14.5%) had tonic-clonic seizures.

802 patients received Oxcarbazepine as mono-therapy at baseline, with mean seizure frequency  $36.7 \pm 113.1$  times/month, median seizure frequency about 2.2 times/month. 128 patients received Oxcarbazepine as add-on therapy at baseline, with mean seizure frequency  $9.7 \pm 52.6$  times/month, median seizure frequency about 1.7 times/month.

- Efficacy results

Average seizure frequency was reduced from  $13.4 \pm 65.0$  times/month at baseline to  $1.6 \pm 19.5$  times/month at the end of 26 weeks. The median seizure frequency was reduced from 2.0 times/month at baseline to zero/month after 26 weeks of treatment ( $p < 0.0001$ ). At the last visit, 705 patients (82.4%) had 100% reduction of seizure frequency, 62 patients (7.2%) had a reduction rate between 75%- 100%, 33 patients (3.9%) had a reduction rate between 50%- 75%, and 56 patients (6.5%) had a reduction rate less than 50%.

- Safety results

One or more adverse events (AEs) were experienced by a total of 7.6% (74 patients) of the safety population, 75 cases (57 patients) had suspected relationship to study drug. In terms of outcome, 82 cases recovered completely, six cases were recovering, 13 cases without change and four cases with unknown outcome. One patient experienced skin rashes as serious adverse events (SAE) and was recovered after oxcarbazepine dechallenge. The event was suspected to be related to oxcarbazepine. Skin and subcutaneous tissue disorders were the most frequently reported AEs and occurred in 33 patients (3.4%) with 34 cases; followed by nervous system disorders, which occurred in 23 patients (2.4%) with 24 cases; Gastrointestinal disorders were reported as AEs in 1.3% of patients (13 patients). No relevant changes were seen in vital signs. Seven patients experienced hyponatraemia (sodium  $< 135$ mmol/L) during the study, no clinically significant hyponatraemia (sodium  $< 125$  mmol/L) were developed. ALT and AST increase were reported in 6 patients and 16 patients, respectively. Most of them were slightly increased without clinical significance.

The initial dose of Oxcarbazepine was  $10.6 \pm 4.0$  mg/kg/d; the median time to achieve the maintenance dose was 28 days, the average time to achieve the maintenance dose was  $40.1 \pm 34.7$  days. At week 26, for the 885 patients who remained on the oxcarbazepine treatment, the average dose was  $25.2 \pm 10.5$  mg/kg/d; the mean dose was 24.6 mg/kg/d.

CTRIT476BCN06. Title: A multi-center, 26-weeks, single arm, observational study to evaluate the efficacy and safety of Oxcarbazepine in 2-5 years old pediatric patients with partial seizure and/ or GTCS in routine clinical practice.

➤ **Description**

➤ **Methods**

- **Objective(s)**  
The study was conducted to evaluate the efficacy and safety of Trileptal oral suspension within 26 weeks treatment in young children in routine clinical practice
- **Study design**  
A 26 week, single arm, open label, multicenter, observational study.
- **Study population /Sample size**  
Children of either sex 2-5 years old with confirmed diagnosis as partial seizure and/or GTCS with a baseline seizure frequency of  $\geq 2$  times/month were included in the study. Subjects were allowed to be on treatment with concomitant AED(s). Based on the previous studies a sample size of 550 patients was estimated to have more than 90% power to detect a 55% seizure improve rate at 26 weeks treatment. Allowing for a 10% rate of lost to follow up patients, 600 patients were to be included in this study. However, the actual total sample size would be based on the site enrolling availability.
- **Treatments**  
Trileptal oral suspension (60mg/ml) was to be used according to the approved doses as per local (Chinese) prescribing information. According to the local prescribing information Trileptal should be initiated with a dose 8-10 mg/kg/day given in 2 divided doses as mono/adjunctive therapy; if clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day increments at least weekly interval from the starting dose to achieve the desired clinical response.
- **Outcomes/endpoints**  
Standard efficacy and safety parameters for this indication / patient population were selected. Efficacy was evaluated by comparison between the frequency of seizure (times/month) at baseline and at the end of study. The primary efficacy variable was the percentage of pediatric patients treated by Trileptal oral suspension who achieve  $\geq 50\%$  seizure reduction at the end of study (week 26) comparing to baseline. Secondary efficacy assessment was the percentage of pediatric patients who become seizure free, significantly improved, no change or worsening at 26 weeks compared to baseline.  
  
Safety assessments consisted of collecting all adverse events (AEs and serious adverse events (SAEs), with their severity and frequency. They also included regular assessments of vital signs and physical condition. No AED concentration measurements were performed for the study. Laboratory test were not mandatory in the study.
- **Statistical Methods**  
As for study CTRIT476BCN04.

## ➤ Results

- Recruitment / Number analysed

A total of 606 patients were entered into the study from 11 sites in China. FPFV was in August 2012 and LPLV was in January 2014. All the 606 patients were included in the safety analysis set (SS). Of the 606 patients who received Oxcarbazepine treatment, 23 patients did not have a primary or secondary efficacy variable record after baseline visit, thus 583 patients (96.2%) were included into the full analysis set (FAS) population. Overall, 75 patients (12.38%) discontinued from the study drug treatment prematurely. The most frequently reasons were: lost to follow-up (3.63%), lack of efficacy (2.97%), adverse events (2.81%), others (1.65%), and upon patients' requests (0.99%).

- Baseline data

The mean age ( $\pm$  SD) of the FAS population was  $3.32 \pm 1.09$  years. The majority of patients were male (60.38%). The mean weight ( $\pm$  SD) was  $16.47 \pm 3.90$  kg. The mean disease history ( $\pm$  SD) was  $9.73 \pm 11.68$  months. According to classification by seizure type, 533 patients (91.4%) had partial seizures, 56 patients (9.6%) had tonic-clonic seizures. At baseline, average seizure frequency was  $18.31 \pm 61.18$  times/month, the median was about 3.33 times/month;

- Efficacy results

At the end of 26 weeks, 544(93.31%, 95% CI: 90.97%,95.20% ) paediatric patients responded to OXC oral suspension treatment with a 50-100% seizure frequency reduction from baseline, which was the primary endpoint; 39(6.69%) patients did not respond to OXC oral suspension treatment. The average seizure frequency was reduced from  $18.31 \pm 61.18$  times/month at baseline to  $1.6 \pm 19.5$  times/month at the end of 26 weeks. The median seizure frequency was reduced from 3.33 times/month at baseline to zero/month after 26 weeks of treatment ( $p < 0.0001$ ). A total of 477 patients (81.82%) had 100% reduction of seizure frequency (seizure free), 41 patients (7.03%) had a reduction rate between 75% - 100% (significantly improved), 26 patients (4.46%) had a reduction rate between 50%- 75% (improved), 14 patients (2.40%) had a reduction rate less than 50% (No change) and 25 patients (4.29%) had a worsening of seizure.

- Safety results

One or more adverse events (AEs) were experienced by a total of 8.09% (49 patients) of the safety population, of which 5.45% (33 patients) of those events had suspected relationship to the study drug. In terms of outcome, 40 cases recovered completely, nine cases with partial recovery, one case recovered with sequel, two cases without change and four cases with unknown outcome. 17 patients discontinued from the study due to an AE. Three patient experienced skin rashes as serious adverse events (SAE). Two of them recovered after Trileptal dechallenge and giving symptomatic treatment and one remained unchanged. Skin and subcutaneous tissue disorders were the most frequently reported AEs and occurred in 19 patients (3.14%); following were the nervous system disorders and occurred in 14 patients (2.31%); Psychiatric disorders were reported as AEs in 0.99% of patients (6 patients), followed by general disorders reported in 5 patients (0.83%). The adverse events seen in the study were as expected for this population and this class of drug. They were mostly mild and transient, and did not seem to be dose-related and gave no indication of target organ toxicity. Three patients experienced hyponatraemia (sodium  $< 135$ mmol/L) during the study. No clinically significant hyponatraemia (sodium  $< 125$  mmol/L) was developed. ALT and AST increase were reported in 4 patients. Most of them were slightly increased without clinical significance. Four patients had abnormal EEG after treatment. A total of 103 patients with previously abnormal EEG had normal EEG after treatment with OXC, while 58 still stayed abnormal.



The initial dose of Oxcarbazepine was  $3.21 \pm 1.74$  ml/day and the maintenance dose of Oxcarbazepine was  $7.58 \pm 2.77$  ml/day. The median time to achieve the maintenance dose was 28 days and the average time was  $43.50 \pm 35.09$  days. Approximately 20 per cent of the subjects used concomitant AEDs.

### **3. Discussion on clinical aspects**

The two paediatric phase IV post-marketing surveillance studies conducted in China were done in accordance with the local therapeutic use indication but differed from the SmPC in Europe in the sense that the age group two to five (inclusive) years and subjects with primarily generalised tonic-clonic seizures were enrolled into the studies. The studies also, somewhat unusually, used a mixed study population of subjects requiring AED monotherapy and adjunctive therapy, respectively, which however resonates with the SmPC in Europe.

The outcome of the studies does not allow for any firm efficacy conclusions due to the design of the studies (i.e. lack of randomisation and active control group for the purpose of demonstrating superiority or non-inferiority), albeit the MAH stated that the studies reiterated the existing data that oxcarbazepine is effective in the population studied. However, there is nothing in the study results that question the overall benefit of oxcarbazepine treatment for the therapeutic use indications in the SmPC in Europe.

No unexpected safety findings were reported for the two studies conducted, which is also the MAH's conclusion. No changes of the EU SmPC are therefore planned by the MAH based on the results of these paediatric studies. This position of the MAH is supported.

## **V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**

### **➤ Overall conclusion**

The position of the MAH is supported since no new efficacy nor any new safety information has emerged from the two completed clinical studies which would change the benefit-risk ratio. No SmPC nor any PL changes are therefore proposed by the Rapporteur.

### **➤ Recommendation**

No further action required.