An overview of reports on lacosamide

Introduction

Lacosamide (Vimpat®) was registered for the European market on August 29th 2008. Since then Lareb has received several reports of possible adverse drug reactions, which will be summarized in this overview. Lacosamide is indicated as *adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older* [1].

The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. Two observations that may be of relevance for the observed therapeutic effects are:
In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes. Further, lacosamide binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein which is mainly expressed in the nervous system and is involved in neuronal differentiation and control of axonal outgrowth [1].

Since its introduction in the Netherlands, lacosamide has been used by only a small proportion of the patients with epilepsy [2].

Table 1. Number of lacosamide users in the Netherlands between 2008 and 2009

Drug	2008	2009
lacosamide	-	558

In this overview the reports on this new drug received by Lareb through the spontaneous reporting system will be discussed.

Reports of ADRs

On January 10, 2011 the Netherlands Pharmacovigilance Centre Lareb had received 15 reports on lacosamide (9 in 2009, 6 in 2010). These reports contained a total of 23 possible adverse drug reactions.
Of these 15 reports, six were reported as serious according to the CIOMS criteria, None of these reports were received through the marketing authorisation holder (MAH). The serious reports concerned the following ADRs: Epilepsy/status epilepticus, cardiac death, suicidal ideation, somnolence/chorea, suicide attempt, completed suicide/death.

Table 2. reported adverse events on lacosamide, grouped by system organ class received through spontaneous reporting (only the System Organ Classes containing ADRs are displayed).

System Organ Class	ADRs Lareb	ADRs in Lareb database	common and very common adverse drug reactions according to SPC
General disorders and administration site conditions	2	Death Cardiac death	Gait disturbance Asthenia Fatigue Irritability

System Organ Class	ADRs Lareb	ADRs in Lareb database	common and very common adverse drug reactions according to SPC
Investigations	3	Heart rate decreased* Respiratory rate decreased ECG QT prolonged*	-
Metabolism and nutrition disorders	1	Fluid retention	-
Musculoskeletal and connective tissue disorders	1	Arthralgia	Muscle spasms
Nervous system disorders	8	Coordination abnormal Somnolence (2x) Dizziness Epilepsy Status epilepticus Paraesthesia Chorea	Coordination abnormal Somnolence Dizziness Headache Balance disorder Memory impairment Cognitive disorder Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention
Psychiatric disorders	4	Loss of libido Suicidal ideation Suicide attempt Completed suicide	Depression Confusional state
Renal and urinary disorders	1	Nocturia	-
Skin and subcutaneous tissue disorders	3	Pruritus Alopecia Photosensitivity reaction	Pruritus Rash
Vascular disorders	0		

* Although the SmPC does not contain ADRs in the SOC “Investigations”, bradycardia and AV-block are described in the SOC “Cardiac disorders” section. The frequency of both ADRs is uncommon.

The adverse drug reactions reported via the spontaneous reporting system are in general consistent with the ADR profile of lacosamide as reported in the SmPC. However, the events related to suicidal behavior are not explicitly present in the SmPC and will be described in more detail below.

Suicidal events associated with lacosamide use

The details of reports containing suicidal events in patients using lacosamide are presented in table 3.

Table 3. Reports concerning suicidal events associated with the use of lacosamide

Patient, sex, age	Suspect Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 103082 F, 41-50 years	lacosamide 100 mg, epilepsy		suicidal ideation	3 weeks discontinued recovered
B 109198 M, 41-50 years	lacosamide 200 mg, epilepsy valproic acid	diphantoine	suicide attempt	3 months unknown not yet recovered
C 110655 F, 41-50 years	Lacosamide 200 mg, epilepsy agomelatin , depression		death, suicide	11 months no change fatal

Patient A is a female between 41 and 50 years with suicidal ideation following administration of lacosamide 100 mg daily for (difficult to treat) epilepsy with a latency of three weeks. Lacosamide was withdrawn three days after start of the complaints and the patient recovered.

Patient B is a male between 41 and 50 years with a suicide attempt following administration of lacosamide 200 mg daily for epilepsy with a latency of 3 months. The patient has a history of bifrontal low-grade astrocytoma, epilepsy and alcohol abuse with intentional overdose. It is not known whether lacosamide was withdrawn or continued. Concomitant medications were valproic acid 3000 mg daily and diphantoine 300 mg daily. According to the reporter this adverse event could be related to the frontal lobe syndrome the patient had as a result of his astrocytoma.

Patient C is a female between 41 and 50 years with a completed suicide following administration of lacosamide 200 mg daily for epilepsy with a latency of 11 months. The patient has a history of depression, suicide attempts, alcohol abuse, drug abuse and was diagnosed with epilepsy in February 2008. Levetiracetam had been withdrawn on a previous occasion due to suicidal ideations. Concomitant medication was agomelatin 25 mg daily for depression. According to the reporter the suicide is probably not directly related to lacosamide use, but due to failing of the anti-depression medication. Patient might have used additional concomitant medication, however, this could not be confirmed.

Other sources of information regarding suicidal events associated with lacosamide use

SmPC
The SmPC of Vimpat® contains the following information regarding suicidal events (section 4.4 Special warnings and precautions for use):

"Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge."

Although it is mentioned above that there might be an increased risk of suicidal events when using lacosamide, none of these events are mentioned in section 4.8 of the SmPC.

Literature

Although the SmPC contains warnings regarding the use of lacosamide in patients with suicidal ideations and behaviour, no reports of these events occurring while using lacosamide can be found in publicly available literature sources. In a recent review where the possibility of an increased risk of suicidal thoughts or behaviour is mentioned, the source referenced is the Vimpat® package insert [3].

Databases

For the determination of disproportionality, the MedDRA® HLT "Suicidal and self-injurious behaviour" was used in all three databases referenced.

As described above, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of suicidal / self-injurious behaviour associated with the use of lacosamide, which was reported disproportionally (ROR = 42.4, 95% CI: 11.9 - 150.6).

The WHO database of the Uppsala Monitoring Centre contained 25 reports with a total of 27 events of suicidal / self-injurious behaviour (see table 4). It concerns 16 females and 7 males. In two cases, the sex of the patient involved was not reported. The median age of the patients was 42.5 years (range 18 - 83). All of the events were reported disproportionally with the exception of "completed suicide". The overall disproportionality was statistically significant (ROR = 5.2, 95% CI: 3.5 - 7.7).

Table 4. Reports of Suicidal and self-injurious behaviour associated with lacosamide in the WHO database (MedDRA HLT: Suicidal and self-injurious behaviour)

ADR (MedDRA PT)	Number of events	ROR (95% CI)
Suicide attempt	12	6.9 (3.9 – 12.2)
Suicidal ideation	11	6.9 (3.8 – 12.1)
Self injurious ideation	2	25.4 (6.3 – 102.1)
Suicidal behaviour	1	24.6 (3.4 – 175.3)
Completed Suicide	1	0.6 (0.1 – 4.4)
TOTAL	**27**	**5.2 (3.6 – 7.7)**

On January 11th 2011, the Eudravigilance database contained 39 reports of suicidal and self-injurious behaviour associated with the use of lacosamide which was reported disproportionally (ROR = 4.2, 95% CI: 3.1 - 5.8). It concerns 24 females and 11 males. In four cases, the sex of the patient involved was not reported. The median age of the patients was 43 years (range 18 - 83). All events were classified as 'serious' and in one case, the reaction reported resulted in death.

Mechanism

Although the mechanism of lacosamide-induced suicidal events remains unclear, there seems to be a role for CRMP-2, a protein that binds to lacosamide [4]. CRMP-2 is involved in the signalling pathway of axon formation, and disturbance

of this pathway is believed to have a role in several psychiatric disorders, such as paranoid-type schizophrenia, bipolar disorder and major depressive disorder [5].

Discussion and conclusion

The aim of this report was to give an overview of the ADRs associated with the use of lacosamide using information from the spontaneous reporting system. Spontaneous reporting is based on concerned reporting i.e when a health professional or patient see an ADR which they find worrying, they will report it. The chance of receiving reports with rare and serious ADRs through spontaneous reporting is therefore relatively high.

The overall safety profile presented in this report is quite consistent with the information provided in the SmPC of lacosamide. When analyzing the data, a new possible signal for lacosamide and suicidal events has been identified.

- Possible new signal of lacosamide associated with suicidal events

References
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