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Patient Health Protection

PhVWP Monthly report on safety concerns, guidelines and general matters

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The CHMP Pharmacovigilance Working Party (PhVWP) held its May 2012 plenary meeting on 21-23 May 2012.

Safety concerns

Discussions on non-centrally authorised medicinal products are summarised below in accordance with the PhVWP publication policy. The positions agreed by the PhVWP for non-centrally authorised products form recommendations to Member States. For the publication policy, readers are referred to http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500006181.pdf.

The PhVWP also provides advice to the Committee for Medicinal Products for Human Use (CHMP) on centrally authorised products and products subject to ongoing CHMP procedures at the request of the CHMP. For safety updates concerning these products, readers are referred to the meeting highlights from the CHMP published under http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid=.

Lamotrigine – Evidence does not confirm signal of increased risk of sudden unexpected death in epilepsy (SUDEP) with lamotrigine

Available evidence does not confirm a causal relationship between lamotrigine and increased risk of sudden unexpected death in epilepsy (SUDEP).

Following findings reported in the medical literature, the PhVWP reviewed the possibility of a causal relationship between increased risk of sudden unexpected death in epilepsy (SUDEP) and the use of lamotrigine. The PhVWP concluded that the available evidence did not confirm the signal of an increased risk of SUDEP with lamotrigine and that no regulatory action is currently necessary (see Annex 1 for the Summary Assessment Report).

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Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

CMDh – Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

EU – European Union

HMA – Heads of Medicines Agencies

PASS – post-authorisation safety study

PhVWP – CHMP Pharmacovigilance Working Party

PL – package leaflet

PSUR – periodic safety update report

RMP – risk management plan

SmPC – summary of product characteristics

Annex 1

Summary Assessment Report of the PhVWP May 2012

Lamotrigine – Evidence does not confirm signal of increased risk of sudden unexpected death in epilepsy (SUDEP) with lamotrigine

Key message

Available evidence does not confirm a causal relationship between lamotrigine and increased risk of sudden unexpected death in epilepsy (SUDEP).

Safety concern and reason for current safety review

Following results from an observational study investigating the possibility of a causal relationship between increased risk of sudden unexpected death in epilepsy (SUDEP) and the use of lamotrigine [1], the PhVWP agreed to review this possible risk.

The study suggested that the incidence of SUDEP was significantly higher among female epilepsy patients treated with lamotrigine than among female patients with epilepsy who were not treated with lamotrigine [1]. The study was conducted as a follow-up to a publication by the same authors which described 4 cases of SUDEP in patients using lamotrigine and recommended a formal study to investigate whether lamotrigine might increase the risk of SUDEP in subgroups of patients [2].

Clinical setting

Lamotrigine has been available in the EU since the early 1990s and is used for the treatment of several types of epilepsy and bipolar disorders.

Sudden unexpected death in epilepsy (SUDEP) refers to the sudden death of a seemingly healthy individual with epilepsy, usually occurring during or immediately after a tonic-clonic epileptic seizure. The frequency of SUDEP varies depending on the severity of the epilepsy, but overall the risk is more than 20 times higher than that of the risk of sudden death in the general population. Several different mechanisms are likely to exist, and most research has focused on mechanisms like seizure-related respiratory depression, cardiac arrhythmia, cerebral depression and autonomic dysfunction. Data from a pooled analysis of risk factors for SUDEP indicate that the higher the frequency of tonic-clonic seizures in an individual, the higher the risk of SUDEP. SUDEP usually occurs when the seizures are not witnessed and often at night [3].

Information on the data assessed

In addition to the above publications [1,2], the PhVWP reviewed data from the medical literature [3-7], and from clinical trials and in vitro studies that were submitted by the originator marketing authorisation holder.

Outcome of the assessment

The PhVWP considered the following:

A previous analysis of SUDEP cases recorded during clinical trials with lamotrigine estimated an incidence of 3.5 per 1,000 patient-years. This rate seemed similar to that of the other anti-epileptics levetiracetam, gabapentin and topiramate, as stated in reports available in the public domain. In the medical literature, incidence rates of SUDEP vary depending on the epilepsy population studied. Figures range from 0.09-0.35 per 1,000 person-years in unselected cohorts of incidence cases of epilepsy, 0.9-2.3 per 1,000 person-years in the general epilepsy population, 1.1-5.9 per 1,000 person-years in individuals with chronic refractory epilepsy (treated) and 6.3-9.3 per 1,000 person-years in epilepsy surgery candidates.

Given that SUDEP occurs during or immediately after a tonic-clonic epileptic seizure, it seems paradoxical that anti-epileptic medicines, including lamotrigine, may cause SUDEP. If the observed association were truly causal, this paradox might be explained by insufficient seizure control despite pharmacological treatment, which could be due to non-responding of the epileptic patient to the given treatment, irregular/insufficient plasma levels of the medication due to non-compliance or interactions with concomitant medication.

The data triggering the review [1,2] had several limitations. Both were case-only observations which did not allow adjustment for other clinical factors associated with SUDEP. The finding of study [1], that SUDEP occurred more often in female than male patients, could be due to the fact that female patients were using oral contraceptives, which are known to increase or decrease plasma levels of lamotrigine, which may affect seizure control. The study was carried out before this interaction between lamotrigine and oral contraceptives was included in the product information for lamotrigine. Furthermore, the number of SUDEP cases were small in both publications (4 cases in [2] and 26 cases in [1]). Overall, in view of these limitations, the strength of the signal in [1, 2] may have been overestimated.

A recently published pooled analysis of 112 clinical trials that compared adjunctive anti-epileptics with placebo in adult patients with uncontrolled partial or primary tonic-clonic seizures showed that treatment with adjunctive anti-epileptics at effective doses appeared to reduce the incidence of definite or probable SUDEP by more than 7 times compared with placebo in patients with previously uncontrolled seizures. This study included 16 clinical trials where lamotrigine was used as adjunctive treatment in refractory epilepsy [5].

In two other publications, data from four case-control studies of SUDEP were pooled [6,7]. All four studies included patients with epilepsy as controls. Patients with a history of heart disease were excluded. In the pooled analysis of these data, none of the anti-epileptic medicines studied were associated with an increased risk of SUDEP in monotherapy or polytherapy when frequency of generalised tonic-clonic seizures was taken into account. This implies that the risk of SUDEP increases with the number of generalised tonic-clonic seizures rather than being linked to the medication.

Clinical trial data held in the originator marketing authorisation holder's database showed that the incidence rates for SUDEP with lamotrigine treatment fall within the range of the rates observed for the chronic refractory epilepsy population. This is plausible, since in the majority of the clinical studies lamotrigine was given as adjunctive treatment, i.e. to patients with refractory epilepsy. The originator marketing authorisation holder committed to re-evaluate the estimate of the rate of SUDEP with lamotrigine in clinical trials. Results are expected to be available in the 3rd quarter of 2012.

Despite effects of lamotrigine on the IKr (rapid delayed rectifier potassium current) and the hERG channel (an ion channel that contributes to the electrical activity that coordinates the heart's beating) seen in vitro, no such effects of lamotrigine were seen in healthy humans. A prolongation of the QT

interval was seen with overdoses of lamotrigine, but this was not clinically significant. A cumulative review of tachycardia showed that lamotrigine is unlikely to be associated with an increased risk of arrhythmias.

Overall, the PhVWP concluded that the available evidence did not confirm the signal of an increased risk of SUDEP with lamotrigine and that no regulatory action is currently necessary. The principal risk factor for SUDEP seems to be poorly controlled generalised tonic-clonic seizures, while polytherapy, male gender and young age at onset of epilepsy are likely to be additional risk factors.

References

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