Lamotrigine

Essential medicine status

EMLc | ATC codes: N03AX09

Indication	Epilepsy or seizures ICD11 code: 8A6Z
INN	Lamotrigine
Medicine type	Chemical agent
List type	Core
Additional notes	as adjunctive therapy for treatment-resistant partial or generalized seizures.
Formulations	**Oral > Solid:** 25 mg tablet ; 50 mg tablet ; 100 mg tablet ; 200 mg tablet ; 2 mg tablet (chewable, dispersible) ; 5 mg tablet (chewable, dispersible) ; 25 mg tablet (chewable, dispersible) ; 50 mg tablet (chewable, dispersible) ; 100 mg tablet (chewable, dispersible) ; 200 mg tablet (chewable, dispersible)
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Lamotrigine
DrugBank	Lamotrigine

Expert Committee recommendation

The Expert Committee noted that lamotrigine has been shown to be effective as an adjunctive therapy for persons with partial or generalized epileptic seizures refractory to monotherapy with one of the antiepileptic drugs already included in the EML/EMLc. The Committee also noted that lamotrigine has been reported to be a valid alternative to carbamazepine and valproate as monotherapy. Its safety profile for use in women of childbearing age and people living with HIV/AIDS appears favourable compared with other therapeutic options included in the EML/EMLc. Considering all relevant clinical outcomes, there is a net benefit, resulting primarily from the safety profile of lamotrigine. Based on the positive evaluation, the Expert Committee recommended that lamotrigine be included in the EML and EMLc as an adjunctive therapy for persons with partial or generalized epileptic seizures refractory to monotherapy with one of the antiepileptic drugs already included in the EML/EMLc. The Committee recommended that a review of the effectiveness and safety of lamotrigine in comparison with other alternatives (e.g. levetiracetam) would be informative for a future EML application.

Background

The EML currently lists nine anticonvulsant medicines: carbamazepine, diazepam, lorazepam, magnesium sulfate, midazolam, phenobarbital, phenytoin, valproic acid and ethosuximide (the last is on the complementary list only). Apart from magnesium sulfate, the same medicines are on the EMLc. These medicines are intended to treat generalized and partial epilepsy, mostly as first-line therapies. In the past, the Expert Committee has recommended a review of second-line anticonvulsants for an update of the EML, including topiramate, lamotrigine and gabapentin as second-line therapy for children and adults (1). None of the anticonvulsants that are not included in the EML and EMLc can be considered as the treatment of choice in both generalized and partial seizures; “treatment strategy should be individualized according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the child, young person or adult’s lifestyle, and the preferences of the person and their family

and/or carers as appropriate" (2). Inclusion in the EML/EMLc of suitable treatments that may be added as second-line therapies in drug-resistant epilepsy, and also used as alternative first-line options if treatments now included in the EML/EMLc are unavailable or not tolerated, is desirable. The application was preceded by an overview of recently updated guidance on epilepsy, which found that lamotrigine is generally mentioned among first-choice treatment options in generalized and focal seizures, both as monotherapy in newly diagnosed epilepsy and as an adjunctive treatment in refractory disease. Lamotrigine was therefore selected as a priority candidate for the EML, given its broad indications in children and adults, its safety profile in pregnant women, and the fact that it is generally recommended by evidence-based clinical guidelines. Lamotrigine (LTG) (3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine) is a phenyltriazine antiepileptic drug and chemically unrelated to existing antiepileptics.

Public health relevance

Epilepsy is a chronic disorder of the brain affecting both sexes and all ages; it is characterized by an enduring predisposition to epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition. Psychiatric and neurological disorders, including epilepsy, are among the most important contributors to the global burden of human suffering (3). Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally and a priority included in the WHO Mental Health Action Plan 2013–2020 (4). Among 105 countries responding to a worldwide survey by WHO in collaboration with the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) within the framework of the Global Campaign Against Epilepsy, the mean number of people with epilepsy per 1000 population was 8.93 (SD 8.14; median 7.59) (5). Cumulative incidence (i.e. the lifetime probability of developing epilepsy) ranged between 3.1% and 5.8% (6). In developed countries, the age-specific incidence of epilepsy showed a U-shaped pattern, with higher rates for children and the elderly (over 65 years) than for adults; in developing countries, however, incidence peaks among children and young adults. This is probably the result of greater exposure to some preventable risk factors (e.g. perinatal risk factors, infections, traumas); it may also reflect a different structure of the populations at risk (i.e. a predominant distribution of young individuals and a short life expectancy). In most population-based prevalence and incidence surveys, no cause is found and diagnosis of the type of epilepsy remains difficult. Epilepsy can be associated with significant morbidity due to the effects of seizures and/or treatment. It is associated with stigma and with psychological, social, cognitive and economic repercussions. People with epilepsy commonly encounter problems in: education; employment; driving; personal development; mental health; and social and personal relationships (2). It should also be noted that epilepsy may be the manifestation of an underlying pathology (e.g. stroke, tumour, cerebral palsy, infection). Deaths related to epilepsy may be attributable to underlying disorders (causing a symptomatic epilepsy) or to the epilepsy itself, as in chronic epilepsy. Mortality among epileptic patients, measured as a standardized mortality ratio (SMR), is 2–3 times higher than in the general population in developed countries and as much as 6 times higher in developing countries (7, 8). Diagnosis of epilepsy is primarily clinical and based on a detailed description of the events before, during and after a seizure given by the affected person and/or a witness. Seizures are generally described in two major groups – primary generalized seizures (including tonic–clonic seizures) and partial seizures. The availability of an antiepileptic agent with effectiveness in both types of seizures, and for paediatric as well as adult patients, would thus be a useful treatment option in clinical practice, since it could be offered to most people with epilepsy.

Benefits

The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs) to prevent the recurrence of epileptic seizures without adverse effects (9). Given the wide variability in the frequency and severity of epileptic seizures, defining treatment success is not easy. The ILEA has defined treatment success as a seizure-free duration that is at least three times the longest seizure-free interval before the start of treatment, with a sustained response over 12 months (10). Conversely, drug-resistant epilepsy is defined by ILAE as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom". No threshold relative to the frequency is mentioned, and a frequency of one seizure per year can therefore be regarded as treatment-resistant. "Treatment success can only be determined after the individual has remained without seizures for either 3 times the prior inter-seizure interval or 1 year, whichever is longer" (10). Drug treatment of epilepsy is usually started as monotherapy; if the first AED is ineffective or not tolerated, a trial of a second AED is recommended. It is preferable for a patient to be maintained on a single AED, since this increases the probability of compliance, provides a wider therapeutic index, and is more cost-effective than combination drug treatments. Combination therapy can be associated with drug interactions between AEDs, making it difficult to dose and monitor patients. Assessing the place in therapy of anticonvulsants is challenging: most clinical trials compare the active treatment with placebo and therefore direct comparisons between them are not always available. The relative efficacy of new compounds must be inferred by means of systematic reviews and meta-analyses, but these methods do not provide conclusive evidence of differences in efficacy or tolerability. The application searched for systematic reviews, randomized controlled trials

(RCTs) not covered by the reviews, and guidelines, up to October 2016. Systematic reviews and clinical trials considered patients affected by a variety of epileptic syndromes (new-onset generalized epilepsy, new-onset partial epilepsy, drug-resistant generalized epilepsy and drug-resistant partial epilepsy). RCTs were conducted in developed countries where the etiology of epilepsy and the characteristics of patients at risk are different from those in developing countries. Lamotrigine as add-on (versus placebo) in drug-resistant epilepsy Available evidence comes from RCTs testing the addition of lamotrigine to current therapy against addition of placebo. Specifically, in drug-resistant generalized epilepsy addition of lamotrigine to current anticonvulsant therapy was found to be “likely to be beneficial” (GRADE quality of evidence: moderate); it was superior to addition of placebo in reducing seizure frequency in three placebo-controlled RCTs (11). Studies included both adults and children but did not report outcomes separately. There was no meta-analysis of the three studies because of differences in study design. For patients with generalized tonic–clonic or absence seizures, adding lamotrigine significantly increased the proportion of those who experienced a 50% or greater reduction in seizure rate in all three RCTs. In the two RCTs that reported between-group comparisons, the proportion of people with at least a 50% reduction in seizure rate was clinically relevant. In one trial, over dose-escalation and maintenance phase, 64% achieved this seizure rate reduction with lamotrigine compared with 39% with placebo, $P < 0.05$; (intention-to-treat analysis) (12). In the second trial, a reduction in seizure rate of at least 50% was achieved in 75% of patients given lamotrigine compared with 32% given placebo, $P < 0.0001$ (13). A Cochrane review exploring the effectiveness of adjunctive lamotrigine for refractory primary generalized tonic¬–clonic seizures, and including two RCTs, found very similar results (14). In drug-resistant focal epilepsy, a Cochrane systematic review found that addition of lamotrigine to current anticonvulsant therapy was superior to addition of placebo in reducing seizure frequency (GRADE quality of evidence: high). The review included 14 RCTs that involved both adults and children (38 infants, 199 children and 1721 adults) (15). The overall risk ratio (RR) for participants with 50% or greater reduction in seizure frequency was 1.80 (95% confidence interval (CI) 1.45–2.23) for 12 studies (n = 1322, adults and children), indicating that lamotrigine was significantly more effective than placebo in reducing seizure frequency in patients already on at least two seizure medications. Lamotrigine versus other anticonvulsants as monotherapy In monotherapy, available evidence comes from both head-to-head and placebo-controlled RCTs. One systematic review informing NICE (National Institute for Health and Care Excellence) guidelines (updated 2014) synthesized data from head-to-head RCTs and an individual patient data (IPD) meta-analysis testing lamotrigine versus other anticonvulsants in focal or generalized epilepsy (2, 16). Focal seizures data from direct and indirect comparisons show that lamotrigine and carbamazepine provided the best combination of seizure control and treatment failure. Lamotrigine was clinically superior to all other drugs for treatment failure but was less effective than carbamazepine in delaying time to first seizure (GRADE quality of evidence: low). Results for generalized epilepsy suggest that valproate might be the best choice: time to 12-month remission significantly favoured sodium valproate over lamotrigine monotherapy (hazard ratio (HR) 1.41; 95% CI 1.10–1.80) (moderate-quality evidence). These results overlap with the SANAD (Standard and New Antiepileptic Drugs) trial (17). A Cochrane systematic review published in 2016 compared lamotrigine and carbamazepine; it included individuals with partial-onset seizures and showed mixed results. Carbamazepine was significantly better than lamotrigine for time to first seizure (hazard ratio (HR) 1.22; 95% CI 1.09–1.37) and for time to 6-month remission (HR 0.84; 95% CI 0.74–0.94), but there was a significant advantage for lamotrigine for withdrawal of allocated treatment (HR 0.72; 95% CI 0.63–0.82) (18). A network meta-analysis published in 2016 made multiple comparisons between AEDs and found that lamotrigine did not differ from other new AEDs (e.g. levetiracetam, oxcarbazepine, sultiam, topiramate) or from carbamazepine in terms of efficacy profile (19). One subsequent RCT compared the effectiveness of valproate and lamotrigine in 60 newly diagnosed adults with idiopathic generalized tonic–clonic seizures. At the last observation, after 12 months’ follow-up, 23 patients (76.67%) taking valproic acid and 17 (56.67%) taking lamotrigine were seizure-free. Statistical analyses were doubtful: re-analysis of data provided non-significant differences between groups (RR 1.22; 95% CI 0.86–1.73) (20). Another subsequent large RCT, which compared the effectiveness of lamotrigine with that of controlled-released carbamazepine and levetiracetam in 359 patients over 60 years of age with newly diagnosed focal epilepsy found that retention of lamotrigine was not significantly different between comparators, and seizure freedom rates at week 58 were no different across the groups (21).

Harms

Lamotrigine as add-on (versus placebo) in drug-resistant epilepsy Cochrane reviews found that the addition of lamotrigine to current anticonvulsant therapy increased side-effects. The adverse events significantly associated with lamotrigine were: ataxia (RR 3.34; 99% CI 2.01–5.55; 12 RCTs; n = 1524); dizziness (RR 2.00; 99% CI 1.51–2.64; 13 RCTs; n = 1767); diplopia (RR 3.79; 99% CI 2.15–6.68; 3 RCTs; n = 943); and nausea (RR 1.81; 99% CI 1.22–2.68; 12 RCTs; n = 1486) (15). In addition to these adverse events, another review found rash and headaches were also commonly reported. Skin reactions were confirmed by open-label studies, also in children (22, 23). Lamotrigine versus other anticonvulsants as monotherapy In monotherapy, a NICE systematic review (updated in 2014) showed that lamotrigine was better tolerated than carbamazepine, phenobarbital, gabapentin (except for skin rash) and topiramate (GRADE quality of evidence from very low to moderate) (2). A Cochrane systematic review published in 2016 specifically compared lamotrigine and carbamazepine, mostly in individuals with partial-

onset seizures, and showed a significant advantage for lamotrigine for time to withdrawal (HR 0.72; 95% CI 0.63–0.82; 9 RCTs; GRADE quality of evidence moderate) (18). This result was confirmed by a network meta-analysis of RCTs, published in 2016, which showed that lamotrigine was associated with fewer withdrawals due to adverse events than carbamazepine (OR 0.41; 95% CI 0.29–0.55) (19). Other harms Lamotrigine and other antiepileptic drugs have been associated with an increased risk of suicidal behaviour and ideation (24). Lamotrigine during pregnancy A Cochrane systematic review published in 2016 assessed congenital malformation outcomes in cases of monotherapy treatment of epilepsy in pregnancy. It included prospective cohort-controlled studies, cohort studies set within pregnancy registries and randomized controlled trials (25). Children exposed to lamotrigine in utero were not found to be at increased risk of major malformation compared with children born to women without epilepsy and to women with untreated epilepsy. As for drug–drug comparisons, children exposed to lamotrigine (LTG) were at lower risk than children exposed to valproic acid (VPA) (n = 4164 vs 2021; RR for VPA vs LTG 3.56; 95% CI 2.77–4.58), to carbamazepine (CBZ) (n = 4164 vs 3385; RR for CBZ vs LTG 1.34; 95% CI 1.01–1.76), to phenobarbital (PB) (n = 1959 vs 282; RR for PB vs LTG 3.13; 95% CI 1.64–5.88), to phenytoin (PHE) (n = 4082 vs 624; RR for PHE vs LTG 1.89; 95% CI 1.19–2.94) and to topiramate (TPM) (n = 3975 vs 473; RR for TPM vs LTG 1.79; 95% CI 1.06–2.94). These data are reassuring, showing that lamotrigine is safer than most other AEDs. Additionally, more observations are available for lamotrigine than for other AEDs: gabapentin, levetiracetam, oxcarbazepine, primidone and zonisamide were not associated with an increased risk, but there were substantially fewer data for these agents. By contrast, children exposed to carbamazepine, phenytoin and valproic acid were at greater risk of malformation than children born to women without epilepsy or with untreated epilepsy. Similarly, children exposed to phenobarbital and topiramate were at greater risk of malformation than children born to women without epilepsy. For example, children exposed to valproic were at greater risk of malformation than children born to women without epilepsy (n = 467 vs 1936; RR 5.69; 95% CI 3.33–9.73) and those born to women with untreated epilepsy (n = 1923 vs 1259; RR 3.13; 95% CI 2.16–4.54). A concurrent population-based case-malformed control study, based on 21 EUROCAT registries covering 10.1 million births in Europe (1995–2011) and a total of 226 806 babies with congenital anomalies, suggested that orofacial cleft (which had been previously hypothesized following a pooled analysis from five pregnancy registries including 1623 pregnancies) and other congenital anomalies – with the possible exception of clubfoot (adjusted odds ratio (ORadj) 1.83; 95% CI 1.01–3.31) – were not significantly associated with lamotrigine monotherapy (26). Lamotrigine in paediatrics A systematic review of RCTs (27) assessed safety of lamotrigine in paediatric patients aged up to 18 years (78 articles involving 3783 paediatric patients; 2222 adverse events reported). Rash was the most commonly reported adverse event, occurring in 7.3% of the patients. Stevens–Johnson syndrome was reported rarely, with a risk of 0.09 per 100 patients. Treatment was discontinued in 72 children (1.9% of treated patients) because of an adverse drug reaction. These data are quite reassuring, although the possibility of Stevens–Johnson syndrome) should be carefully considered. Persons with HIV/AIDS and epilepsy The occurrence of seizure disorders is increased among people infected with HIV; incidence is about 6% (28). Clinically significant drug interactions can occur when antiretroviral agents are combined with enzyme-inducing AEDs such as carbamazepine, phenytoin and phenobarbital. Such interactions may result in altered serum levels of both AEDs and antiretrovirals and can lead to higher rates of HIV treatment failure compared with use of antiretroviral agents with non-enzyme-inducing AEDs. In persons with HIV/AIDS treated with antiretroviral agents, the use of non-enzyme-inducing anticonvulsants (such as lamotrigine and other “newer” AEDs) is preferable (29, 30). Drug safety alert A drug safety alert has been issued by the FDA on the risk of aseptic meningitis associated with lamotrigine. A total of 40 cases of aseptic meningitis in adults and paediatric patients taking lamotrigine were reported from 1994 to 2009; more than 46 million prescriptions were dispensed over that period (31).

Additional evidence

N/A

Cost / cost effectiveness

In developed countries, the price of antiepileptics varies considerably. Branded drugs are generally more expensive. According to data from HAI (National Price Sources of Health Action International), the cost per defined daily dose (DDD) of lamotrigine is higher of that of phenobarbital but comparable to that of carbamazepine. Based on a cost–effectiveness analysis, the NICE guideline published in 2012 (updated February 2016) (2) recommended the following as cost-effective treatments for the United Kingdom National Health Service (NHS): • lamotrigine and oxcarbazepine for adjunctive treatment in children, young people and adults with refractory focal seizures; • lamotrigine for newly diagnosed focal seizures requiring treatment; • lamotrigine, with the lowest total cost, is likely to be cost-effective for first-line treatment in children, young people and adults with newly diagnosed generalized tonic–clonic seizures. Considering that no other relevant comparative economic evidence was found, and although they refer to the NHS, these analyses suggest that lamotrigine may be a cost-effective anticonvulsant drug in different clinical scenarios compared with the available alternatives.

WHO guidelines

Lamotrigine is included in WHO's 2015 Update of the Mental Health Gap Action Programme (mhGAP) guidelines for mental, neurological and substance use disorders as a recommended option for add-on therapy in patients with medication-resistant convulsive epilepsy (conditional recommendation, moderate-quality evidence) (32).

Availability

Lamotrigine was approved by the FDA in 1994 for use in partial-onset seizures. It was ultimately approved for monotherapy in 1998. Lamotrigine as monotherapy in generalized seizures has been licensed by the EMA but not the FDA.

Other considerations

Topiramate and lamotrigine are the two AEDs with the broadest indications, both in paediatric and adult populations. Authorized indications – lamotrigine (EMA, FDA) Monotherapy Adjunctive therapy Generalized Partial Generalized Partial EMA A, Ad>=13y A, Ad>=13y A, Ad, C>=2y A, Ad, C>=2y FDA NO A, Ad>=16y* A, Ad, C>=2y A, Ad, C>=2y A = adults; Ad = adolescents; C = children; y = years of age *Conversion to monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone or valproate as the single AED.

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