

Review of the available evidence on Lamotrigine for Epilepsy

FOR THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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1. Summary statement of the proposal

Based on currently available evidence (one large pragmatic long-term randomized controlled trial, Marson et al. (2007a,b,c), several short-term (up to 12-month follow up) randomized controlled trials, and data from pharmacovigilance registries), **it is suggested to consider a potential role for lamotrigine in the WHO Model List of Essential Medicines** (subsection *Anticonvulsants/Antiepileptics*) **as a monotherapy antiepileptic drug in specific situations, such as:**

- the treatment of new onset partial epilepsy in patients not tolerating carbamazepine.
- the treatment of new onset generalized epilepsy in women who are contemplating pregnancy and for which the severity of the disease (e.g. number and/or type of seizures threatening the patient's safety and/or seriously limiting her quality of life and/or threatening the fetus' safety) makes therapy with antiepileptic drugs strongly recommended; in this context, valproic acid, the most effective drug, is associated with the highest risk of major malformations among all antiepileptic drugs;

The proposal is based on the following evidence and considerations:

1. in new onset partial epilepsy lamotrigine is more effective than carbamazepine (the main comparator) in terms of “time to treatment withdrawal” (HR 0.78, 95% CI 0.63 to 0.97; risk difference of -6%, 95% CI -13% to +2%, after a 3-year follow up) due to a better tolerability (“time to treatment withdrawal for unacceptable adverse events”: HR 0.62, 95% CI 0.46 to 0.83; risk difference -10%, 95% CI -4% to -17%). In terms of efficacy, the outcomes “time to 12-month remission” and “time to treatment withdrawal for inadequate seizure control” show no difference, while considering the outcome “time to first seizure” carbamazepine shows a superiority over lamotrigine (HR 1.23, 95% CI 1.04 to 1.45; risk difference -7%, 95% CI 0 to -13%, after a 3-year follow up).
2. in new onset generalized epilepsy valproic acid (the main comparator) is superior to lamotrigine in terms of efficacy (“time to 12-month remission”: HR 1.31, 95% C.I 1.06 to 1.62, risk difference +7%, 95% CI +1% to +15%, after a 3-year follow up; “time to treatment withdrawal for inadequate seizure control”: HR 1.95, 95% CI 1.28 to 2.98, risk difference -13%, 95% CI -4% to -21%, after a 3-year follow up), with no difference in terms of tolerability;
3. Available data are largely consistent with the notion that monotherapy of women during pregnancy with the most commonly used AEDs is associated with an increase in risk of major congenital malformations by two to three times, and that the magnitude of risk increases in offspring exposed to polytherapy.
4. Among all antiepileptic drugs, valproic acid is associated to the highest risk of major malformations in offsprings of exposed women during pregnancy (10.73%, 95% CI 8.16-13.29 versus 3.27%, 95% CI 1.37-5.17 in unexposed women). Treatment with carbamazepine during pregnancy is associated with a risk of spina bifida in offsprings which is higher than the expected risk among women not treated with antiepileptic drugs (RR 3.84, 95% CI 1.1-10.3).
5. Available data do not allow to draw conclusions on possible risk differences in terms of offspring malformations between women exposed to lamotrigine therapy during pregnancy and women not exposed to the drug, although recent epidemiological studies suggest that the risk of orofacial cleft may be higher among offsprings of women treated with lamotrigine during pregnancy. These assumptions need further confirmation.

6. Available data on effectiveness and tolerability of lamotrigine come from clinical trials conducted in developed countries including patients affected by epileptic syndromes with a variety of etiologies. The efficacy and safety of lamotrigine has not been specifically tested in patients with symptomatic epileptic syndromes due to parasitic infections (cysticercosis, malaria, etc.), which are peculiar of developing countries, and therefore not represented in the populations mentioned above.

2. Name of the focal point in WHO submitting or supporting the application

3. Name of the organization(s) consulted and/or supporting the application

The application has been developed by CeVEAS, NHS Centre for the Evaluation of the Effectiveness of Health Care, World Health Organization Collaborating Centre for Evidence Based Research Synthesis and Guideline Development in Reproductive Health. Modena, Italy.

4. International Nonproprietary Name (INN, generic name) of the medicine:

The International Nonproprietary Name (INN) of the medicine is: lamotrigine.

5. Formulation proposed for inclusion; including adult and pediatric (if appropriate)

Tablets 25, 50, 100, 200 mg

Tablets, chewable dispersible 2, 5, 25, 50, 100, 200 mg

6. International availability - sources, if possible manufacturers (Annex A)

A list of manufacturers that have active status in the Drug Master File of the Food and Drug Administration is available in **Annex A**. LTG is registered in many countries (US, Europe, Asia, South America). The choice of the manufacturer for LTG will depend on the price and availability at the local or national level.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the Model List of Essential Medicines as an individual medicine, to be included in the *section 5 Anticonvulsants/Antiepileptics* of the WHO EML.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment on current use, target population)

Definition of epilepsy

Epilepsy is defined as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social

consequences of this condition.” (Fisher 2005). It is also operatively defined as “a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause” (Commission 1993 – see **Annex B** for the definition of *epileptic seizure*). Epilepsy affects both sexes and all ages and usually is a chronic condition. In order to communicate the prognosis to affected people and to orientate the therapeutic decisions (i.e. whether to start the treatment with antiepileptic drugs (AEDs), and which AED is more indicated), epilepsy is usually classified according to etiology or semeiologic manifestation (see **Annex B**). However, the following categories, based both on semeiology and response to therapy, are usually considered in trials testing potential AEDs: 1) *new onset generalized epilepsy* in adults and children (i.e. the patients with primarily generalized seizures free from any drug treatment); 2) *new onset partial epilepsy* in adults and children (i.e. the patients with partial seizures, with or without secondary generalization, free from any drug treatment); 3) *drug-resistant generalized epilepsy* in adults and children (i.e. the patients with primarily generalized seizures, not controlled by a single drug treatment); 4) *drug-resistant partial epilepsy* in adults and children (i.e. the patients with partial seizures, with or without secondary generalization, not controlled by a single drug treatment).

Epidemiology of epilepsy

Incidence

The worldwide median annual incidence of epilepsy is 47.4 per 100,000 (range 24.0–190.0) (Kotsopoulos et al. 2002). In developing countries, the incidence is higher than in developed countries with a median of 68.7 per 100,000 (range 49.3–190.0) versus 43.4 per 100,000 (range 24.0–100.0) (Kotsopoulos et al. 2002). In developed countries the age specific incidence of epilepsy shows a U-shaped pattern, with higher rates for children and the elderly than for adults, whereas in developing countries incidence peaks among children and young adults (see **table 1**). This is probably due to a higher exposure to some preventable risk factors (i.e. perinatal risk factors, infections, traumas), and also reflects a different structure of the populations at risk (i.e. a predominant distribution of young individuals and a short life expectancy). Most studies report a slightly higher incidence among males, although the difference between genders rarely reaches statistical significance. In developed countries (Forsgren et al. 2005b, Zarrelli et al. 1999) partial seizure and primarily generalized seizure epilepsy are equally common in children, whilst the former accounts for the majority (about two thirds) of cases in adults. Cumulative incidence (i.e. the lifetime probability of developing epilepsy), ranges between 3.1% and 5.8% (Jallon 2002).

Table 1: incidence rates of epilepsy by age group, socioeconomic status and geographic area.

	All ages	Children	Adult	Elderly
	Incidence rates (/100,000/year)			
Developed countries*	24.0-100.0 (range)	53.0-71.5 (range)	23.0-31.8 (range)	15.0-107.3 (range)
Developing countries*	49.3–190.0 (range)	61.0-219.0 (range)	36.0-158.0 (range)	20.5-150.3 (range)
Asia [^]	28.8-60.0 (range)			
Europe [§]	43.0-47.0 (range)	70.0	30.0	100.0
Latin America [°]	77.7-190.0 (range)			
Sub-Saharan Africa**	64.0-156.0 (range)			
US [#]	52.0			

*from Kotsopoulos et al. 2002; §from Forsgren et al. 2005b; #from Zarrelli et al. 1999; °from Burneo et al. 2005; ^from Mac et al. 2007; **from Preux and Druet-Cabanac 2005.

Prevalence

Prevalence reflects severity or chronicity of epilepsy rather than its frequency. It is influenced by the interaction of several factors, such as incidence rate, death and remission rates, availability of medical care and migration (Jallon 2002). Most studies report a rate of active epilepsy (i.e. at least one seizure in the preceding five years) ranging from 4 to 8 per 1000 (ILAE Commission Report 1997) with higher rates in developing countries (see **table 2**). In developed countries the prevalence of epilepsy is lower in infancy and tends to increase thereafter, with the highest rate occurring in elderly people, whilst in developing countries age-specific prevalence rates tend to be higher in the second and third decades (WHO 2006). These differences between developed and developing countries may be explained by the shorter life expectancy in the latter, and by a different distribution of risk factors. Socioeconomic background affects the frequency of epilepsy both in developed and developing countries, and in the latter prevalence rates have been shown, with rare exceptions, to be greater in the rural compared with the urban context and in the lower compared with the higher socioeconomic classes (WHO 2006).

Table 2: Prevalence of lifetime and active epilepsy by geographic area.

	lifetime epilepsy prevalence (/1000)	active epilepsy prevalence (/1000)
Asia [^]	1.5-14.0 (range)	-
Europe [§]	-	3.3-7.8 (range)
Latin America [°]	6.0-43.2 (range)	5.1-57.0 (range)
Sub-Saharan Africa ^{**}		5.2-74.4 (range)
US ^{***}	10.7	7.0

§from Forsgren et al. 2005b; °from Burneo et al. 2005; ^from Mac et al. 2007; **from Preux and Druet-Cabanac 2005, not specified if lifetime or active epilepsy prevalence; ***from Jallon 2002.

Etiology

Aetiology of epilepsy depends on patient's age (WHO 2005). Cryptogenic epilepsy (i.e. when no clear abnormality or putative risk factor is identified for what is presumed to be a symptomatic or acquired epileptic condition) is the more common condition across all ages (up to 40% of all cases). The most common causes of epilepsy among young infants are perinatal hypoxia and trauma, metabolic disturbances, congenital brain malformations, and infections. In young children and adolescents idiopathic epilepsies (i.e. a genetically determined conditions) account for the majority of cases, although trauma and infection play an important role. Febrile seizures are also common in children under the age of five. The causes of adult onset epilepsy are variable. Both idiopathic and birth-trauma associated epilepsy may start in early adulthood. Other important causes of seizures in adulthood are head injury, alcohol abuse, cerebrovascular disease, and brain tumours. Cerebrovascular and neurodegenerative disorders account for the majority of cases in older age (Annegers 2004). Peculiar etiologies in developing countries are infection by parasites - mostly cysticercosis, but also malaria, filariasis, trypanosomiasis, toxoplasmosis and toxocariasis - and genetic epilepsies due to high occurrence of consanguinity are common in some African and Asian communities and cultures (Preux and Druet-Cabanac 2005, Mac et al. 2007).

Recurrence of seizures after a first seizure and after diagnosis of epilepsy

In general, diagnosis of epilepsy is possible only after recurrent seizures. Most studies on epilepsy rely on the prognosis of the first seizure, which is the clinical event bringing the patient to medical observation, compelling a choice on whether to start a drug treatment. Observational studies and 2 randomized controlled trials (RCT) conducted in developed countries show that after a first seizure about 40 to 50% of patients, if untreated, will have a recurrent seizure within 2 years (Berg 2008).

Immediate treatment with AEDs may reduce this risk by as much as 50%, which means a recurrence risk of 20 to 25%.

Only one published RCT investigates the recurrence risk among epileptic patients (i.e. after recurrent seizures allow a proper diagnosis of epilepsy) showing a 69% risk at 5 years among untreated patients (Marson et al. 2005). Immediate treatment with AEDs reduces the risk to 57% (12% absolute risk reduction, 95% CI not reported). Considering as an outcome a 2-year seizure-free period, 87% of untreated and 91% of treated epileptic patients will attain the outcome within 5 years (4% absolute risk reduction, 95% CI not reported).

These data suggest that, regardless of treatment, about 10% of patients diagnosed as epileptic will develop a chronic epilepsy and that treatment is useful in obtaining an earlier remission of seizures (Berg 2008).

Abnormal EEG, identifiable neurological condition or seizures consistent with a possible hidden organic cause appear to be associated with the highest risk of recurrence.

Morbidity

Epilepsy can be associated with significant morbidity due to the effects of seizures and/or treatment (Stokes et al. 2004). Epilepsy may sometimes result in significant disability, social exclusion and stigmatisation. People with epilepsy commonly experience problems in education, employment, driving, personal development, and social and personal relationships. In addition, it has to be noted that epilepsy may be the manifestation of an underlying pathology (e.g. stroke, tumour, cerebral palsy, infection, etc.).

Mortality

Deaths related to epilepsy may be attributable to underlying disorders (causing a symptomatic epilepsy), or to the epilepsy itself, as in chronic epilepsy. In developed countries, mortality among epileptic patients measured as a standardized mortality ratio (SMR) is 2–3 times higher than in the general population and, being higher in childhood, is inversely correlated with age. This finding may be partly explained considering that:

- “symptomatic” epileptic syndromes (seizures caused by underlying pathologic conditions) are more common among children
- competing causes of death are less common during childhood.
- The main epilepsy-related causes of death are (Gaitatzis and Sander 2004, Forsgren et al. 2005a):
 - the so-called “sudden unexpected, unexplained death in epilepsy” (SUDEP) (2–18% of all deaths in epilepsy),
 - death in status epilepticus (12.5%)
 - suicide (0–2%)

Scanty data suggest that mortality rate among epileptic patients in developing countries is higher (up to six-fold) than in developed countries (Carpio et al. 2005, Diop et al. 2005). The causes of death may be epilepsy-related in up to 50% of patients (e.g., status epilepticus, drowning, burns, traumas, SUDEP) (Diop et al. 2005).

The global burden of epilepsy

At least 43,000,000 of peoples are affected by epilepsy all over the world (WHO 2005). Around 85% of people with epilepsy live in developing countries (WHO 2006).

The expected global burden of epilepsy for year 2005 measured by the disability-adjusted life years (DALYs – see **Annex C** for definition) is more than seven millions DALYs (0,5% of the global burden of disease), representing about 8% of the burden of all neurological disorders, that in turn account for the 6% of the global burden disease (WHO 2006). The burden of neurological disorders parallels that of HIV/AIDS and of malignant neoplasm (each slightly over 5% of global burden),

and is higher than ischaemic heart disease and respiratory diseases (each about 4% of global burden).

Across the different neurological categories, epilepsy ranks as the fourth in terms of DALYs after cerebrovascular disease, Alzheimer/dementias and migraine (see the **table 3**). The burden is usually inversely correlated to income category (see **Annex C** for specifications) as estimates for 2005 show (see **Table 4**).

Table 3: Projection for 2005 of global burden of neurological disorders, by cause category (adapted from WHO 2006).

Cause category	No. of DALYs (000)	Percentage of total DALYs
Cerebrovascular disease	50 785	3.46
Alzheimer and other dementias	11 078	0.75
Migraine	7 660	0.52
<i>Epilepsy</i>	7 308	0.50
Tetanus	6 423	0.44
Meningitis	5 337	0.36
Parkinson's disease	1 617	0.11
Multiple Sclerosis	1 510	0.10
...
Total neurological disorders	92 392	6.29

Table 4: Projection for 2005 of global burden of neurological disorders, by income category; values are DALYs per 100,000 population (adapted from WHO 2006).

Cause category	World	Income category			
	(/100 000 population)	Low	Lower middle	Upper middle	High
Cerebrovascular disease	788.4	662.5	1 061.2	612.2	592
Alzheimer and other dementias	172	90.7	150.7	166.9	457.3
Migraine	118.9	114	106.8	147.1	146.3
<i>Epilepsy</i>	113.4	158.3	80	139.2	51.3
Tetanus	99.7	228.6	10.8	1.3	0.1
Meningitis	82.9	143.2	51.2	39.7	10.7
Parkinson's disease	25.1	15.1	19.7	17.5	70.8
Multiple Sclerosis	23.4	20.1	23.3	24.9	32.5
...
Total neurological disorders	1 434.3	1 448.1	1 514.3	1 150.1	1 362.2

Treatment of epilepsy

The primary focus of care for patients with epilepsy is the prevention of further seizures which may, in turn, lead to additional morbidity or even mortality. The treatment goal should be the maintenance of a normal, preferably seizure-free lifestyle, with minimal AED-associated side-effects. Up to 90% of people with epilepsy could become seizure free with AED treatment, while at least in 10% of epileptic patients seizures won't be completely controlled by drugs. Epilepsy surgery is a safe and effective alternative treatment in selected cases.

Assessment on current use of AEDs

According to the Global Campaign Against Epilepsy (WHO 2005), the most commonly used AED is phenobarbital, which has been included in the list of essential drugs in 95.4% of countries (96.0% of low-income countries), followed by carbamazepine (CBZ) (93.1%; 82.6% of low-income countries) phenytoin (86.1%; 68.2% of low-income countries) and valproic acid (VPA) (86.7%; 62.5% of low-income countries).

Treatment gap

The concept of *seizure treatment gap* was developed in order to face the problem that a large number of people with epilepsy in developing countries are not actually being treated. (Meinardi et al. 2001). *Seizure treatment gap* is defined as “*the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given time, expressed as a percentage*” (see **Annex C** for the complete definition). According to a recent systematic review (SR) (Mbuba et al. 2008), the treatment gap prevalence in the developing countries can be estimated around 56.0% (95% CI 31.1–100.0 %), with small differences across the continents (Latin America 55.4%, 95% CI 39.0–78.6%, Asia 64.0%, 95% CI 24.3–100.0%, Africa 49.0%, 95% CI 14.0–100.0%) but wider differences across urban and rural settings (46.8%, 95% CI 34.1–64.8% and 73.3%, 95% CI 49.5–100.0%, respectively). Cost of drugs is the main cause of treatment gap, while unavailability of trained health care personnel, traditional alternative non medical treatments, superstitions and cultural beliefs and long distance to health facilities are other possible although less frequent causes.

A recent cost-effectiveness analysis by Chrisholm on behalf of WHO-CHOICE (2005) found that in developing countries older first-line AEDs phenobarbital or phenytoin are more cost-effective than CBZ (the main comparator for new onset partial epilepsy) and than VPA (the main comparator for new onset generalized epilepsy), because of their roughly similar efficacy and their lower cost in comparison with other AEDs. Nevertheless, in several developing countries even the cheapest AED is proportionately too costly in relation with low annual average incomes. For example in India in 1988 the cost of a year’s supply of phenobarbital was 20 to 30 US\$, while the average annual income was around US\$ 110 (Scott et al. 2001).

9. Treatment details

LTG is a phenyltriazine derivative initially developed as an antifolate agent based on the incorrect idea that reducing folate would effectively combat seizures. Structure–activity studies indicate that its effectiveness as an antiseizure drug is unrelated to its antifolate properties.

Pharmacodynamics

The precise mechanism(s) by which LTG exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, LTG was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. LTG also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known. One proposed mechanism of action of LTG, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that LTG inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate). The mechanisms by which LTG exerts its therapeutic action in Bipolar Disorder have not been established.

Although the relevance for human use is unknown, the following data characterize the performance of LTG in receptor binding assays. LTG had a weak inhibitory effect on the serotonin 5-HT₃ receptor (IC₅₀ = 18 μM). It does not exhibit high affinity binding (IC₅₀>100 μM) to the following neurotransmitter receptors: adenosine A₁ and A₂; adrenergic α₁, α₂, and β; dopamine D₁ and D₂; γ-aminobutyric acid (GABA) A and B; histamine H₁; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT₂. Studies have failed to detect an effect of LTG on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC₅₀ = 145 μM). LTG did not inhibit the uptake of norepinephrine, dopamine, or serotonin, (IC₅₀>200 μM) when tested in rat synaptosomes and/or human platelets in vitro.

Effect of LTG on N-Methyl d-Aspartate-Receptor Mediated Activity: LTG did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP formation in

immature rat cerebellum, nor did LTG displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The IC₅₀ for LTG effects on NMDA-induced currents (in the presence of 3 μ M of glycine) in cultured hippocampal neurons exceeded 100 μ M.

Folate Metabolism: In vitro, LTG was shown to be an inhibitor of dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of LTG were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis. Folate concentrations were also reduced in male rats given repeated oral doses of LTG. Reduced concentrations were partially returned to normal when supplemented with folic acid.

Accumulation in Kidneys: LTG was found to accumulate in the kidney of the male rat, causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed to α -2 microglobulin, a species- and sex-specific protein that has not been detected in humans or other animal species.

Melanin Binding: LTG binds to melanin-containing tissues, e.g., in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

Cardiovascular: In dogs, LTG is extensively metabolized to a 2-N-methyl metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of LTG dose) have been found in human urine (see Drug Disposition). However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate LTG (e.g., in patients with liver disease).

Pharmacokinetics

The pharmacokinetics of LTG have been studied in patients with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure.

Absorption: LTG is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration. The LTG chewable/dispersible tablets were found to be equivalent, whether they were administered as dispersed in water, chewed and swallowed, or swallowed as whole, to the LTG compressed tablets in terms of rate and extent of absorption.

Distribution: Estimates of the mean apparent volume of distribution (Vd/F) of LTG following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Protein Binding: Data from in vitro studies indicate that LTG is approximately 55% bound to human plasma proteins at plasma LTG concentrations from 1 to 10 mcg/mL (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy trials). Because LTG is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of LTG to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or VPA. LTG did not displace other AEDs (CBZ, phenytoin, phenobarbital) from protein binding sites.

Metabolism: LTG is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of ¹⁴C-LTG (15 μ Ci) to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged LTG (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

It slightly induces its own metabolism and the half-life at steady state is reported to be about 24 hours. LTG is distributed into breast milk.

The pharmacokinetics of LTG are affected by other antiepileptics

Drug Interactions: The apparent clearance of LTG is affected by the coadministration of certain medications. Because LTG is metabolized predominantly by glucuronic acid conjugation, drugs that induce or inhibit glucuronidation may affect the apparent clearance of LTG. CBZ, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of LTG. Most clinical experience is derived from patients taking these AEDs. Estrogen-containing oral contraceptives and rifampin have also been shown to increase the apparent clearance of LTG. VPA decreases the apparent clearance of LTG (i.e., more than

doubles the elimination half-life of LTG), whether given with or without CBZ, phenytoin, phenobarbital, or primidone. Accordingly, if LTG is to be administered to a patient receiving VPA, LTG must be given at a reduced dosage, of no more than half the dose used in patients not receiving VPA, even in the presence of drugs that increase the apparent clearance of LTG. The following drugs were shown not to increase the apparent clearance of LTG: felbamate, gabapentin, levetiracetam, oxcarbazepine, pregabalin, and topiramate. Zonisamide does not appear to change the pharmacokinetic profile of LTG. In vitro inhibition experiments indicated that the formation of the primary metabolite of LTG, the 2-N-glucuronide, was not significantly affected by co-incubation with clozapine, fluoxetine, phenelzine, risperidone, sertraline, or trazodone, and was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. In addition, bufuralol metabolism data from human liver microsomes suggested that LTG does not inhibit the metabolism of drugs eliminated predominantly by CYP2D6. LTG has no effects on the pharmacokinetics of lithium. The pharmacokinetics of LTG were not changed by coadministration of bupropion.

Coadministration of olanzapine did not have a clinically relevant effect on LTG pharmacokinetics.

Enzyme Induction: The effects of LTG on the induction of specific families of mixed-function oxidase isozymes have not been systematically evaluated. Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, LTG induced its own metabolism, resulting in a 25% decrease in $t_{1/2}$ and a 37% increase in Cl/F at steady state compared to values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by LTG may not occur when LTG is given as adjunctive therapy in patients receiving CBZ, phenytoin, phenobarbital, primidone, or rifampin.

Special Populations:

Patients With Renal Insufficiency: Twelve volunteers with chronic renal failure (mean creatinine clearance = 13 mL/min; range = 6 to 23) and another 6 individuals undergoing hemodialysis were each given a single 100-mg dose of LTG. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of LTG present in the body was eliminated by hemodialysis during a 4-hour session.

Hepatic Disease: The pharmacokinetics of LTG following a single 100-mg dose of LTG were evaluated in 24 subjects with mild, moderate, and severe hepatic dysfunction (Child-Pugh Classification system) and compared with 12 subjects without hepatic impairment. The patients with severe hepatic impairment were without ascites ($n = 2$) or with ascites ($n = 5$). The mean apparent clearance of LTG in patients with mild ($n = 12$), moderate ($n = 5$), severe without ascites ($n = 2$), and severe with ascites ($n = 5$) liver impairment was 0.30 ± 0.09 , 0.24 ± 0.1 , 0.21 ± 0.04 , and 0.15 ± 0.09 mL/min/kg, respectively, as compared to 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-life of LTG in patients with mild, moderate, severe without ascites, and severe with ascites liver impairment was 46 ± 20 , 72 ± 44 , 67 ± 11 , and 100 ± 48 hours, respectively, as compared to 33 ± 7 hours in healthy controls.

Age:

Pediatric Patients:

The pharmacokinetics of LTG following a single 2-mg/kg dose were evaluated in 2 studies of pediatric patients ($n = 29$ for patients aged 10 months to 5.9 years and $n = 26$ for patients aged 5 to 11 years). Forty-three patients received concomitant therapy with other AEDs and 12 patients received LTG as monotherapy. LTG pharmacokinetic parameters for pediatric patients are summarized in Table 2. Population pharmacokinetic analyses involving patients aged 2 to 18 years demonstrated that LTG clearance was influenced predominantly by total body weight and concurrent AED therapy. The oral clearance of LTG was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized LTG clearance was higher in those subjects weighing less than 30 kg, compared with those weighing greater than 30 kg. Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response, as compared with subjects weighing more than 30 kg being administered the same AEDs. These analyses also revealed that, after accounting for body weight, LTG clearance was not significantly influenced by age. Thus, the same weight-adjusted doses should be administered to children irrespective of differences in age. Concomitant AEDs which influence LTG clearance in adults were found to have similar effects in children.

Elderly:

The pharmacokinetics of LTG following a single 150-mg dose of LTG were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min, range = 33 to 108 mL/min). The mean half-life of LTG in these subjects was 31.2 hours (range, 24.5 to 43.4 hours), and the mean clearance was 0.40 mL/min/kg (range, 0.26 to 0.48 mL/min/kg).

Gender: The clearance of LTG is not affected by gender. However, during dose escalation of LTG in one clinical trial in patients with epilepsy on a stable dose of VPA (n = 77), mean trough LTG concentrations, unadjusted for weight, were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

Race: The apparent oral clearance of LTG was 25% lower in non-Caucasians than Caucasians.

9.1 Indications for use

LTG is used in the treatment of epilepsy, with a wide spectrum of indications (new onset generalized and partial epilepsy in children and adults, and drug-resistant epilepsy), and in the treatment of bipolar disorders (Goodman et al. 2006). Available evidence suggests that LTG is ineffective in the treatment of neuropathic pain (Goodman et al. 2006).

The following indications are reported as available from the FDA

(www.fda.gov/cder/foi/label/2006/020241s10s21s25s26s27.020764s3s14s18s19s20lbl.pdf).

Epilepsy:

Adjunctive use: LTG is indicated as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adults and pediatric patients (≥2 years of age).

Monotherapy use: LTG is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with CBZ, phenytoin, phenobarbital, primidone, or VPA as the single AED.

Safety and effectiveness of LTG have not been established (1) as initial monotherapy, (2) for conversion to monotherapy from AEDs other than CBZ, phenytoin, phenobarbital, primidone, or VPA, or (3) for simultaneous conversion to monotherapy from 2 or more concomitant AEDs

Bipolar Disorder

LTG is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.

9.2 Dosage regimen

The dosage recommendations for epilepsy are the following (from Martindale: The Complete Drug Reference, 35th Edition by Sean Sweetman (Editor):

Adults

*Dose for use as **monotherapy** is 25 mg once daily by mouth for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 50 to 100 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily, given as a single dose or in 2 divided doses. Some patients have required up to 500 mg daily.*

*The initial adult dose of LTG for use **as an adjunct to therapy** with enzyme-inducing antiepileptics (but not with VPA) is 50 mg once daily for 2 weeks followed by 50 mg twice daily for 2 weeks;*

thereafter the dose is increased by a maximum of 100 mg every 1 to 2 weeks to usual maintenance doses of 200 to 400 mg daily given in 2 divided doses. Some patients have required up to 700 mg daily.

In adults taking VPA the initial dose of LTG is 25 mg every other day for 2 weeks followed by 25 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 25 to 50 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily given as a single dose or in 2 divided doses.

The doses above are also permitted in children over 12 years of age; the use of LTG as monotherapy is not recommended for children under 12 years of age.

Children

For children aged 2 to 12 years the initial dose of LTG **as an adjunct** to therapy with enzyme-inducing antiepileptics (but not with VPA) is 600 micrograms/kg daily in 2 divided doses for 2 weeks followed by 1.2 mg/kg daily in 2 divided doses for 2 weeks; thereafter the dose is increased by a maximum of 1.2 mg/kg every 1 to 2 weeks to usual maintenance doses of 5 to 15 mg/kg daily given in 2 divided doses.

In children taking VPA, the initial dose of LTG is 150 micrograms/kg once daily for 2 weeks followed by 300 micrograms/kg once daily for 2 weeks; thereafter the dose is increased by a maximum of 300 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 5 mg/kg, which may be given once daily or in 2 divided doses.

If the calculated daily dose for children lies between 1 and 2 mg then 2 mg may be given on alternate days for the first 2 weeks of therapy. LTG should not be administered if the calculated dose is less than 1 mg daily.

If the potential for interaction with adjunctive antiepileptics is unknown, treatment with LTG should be started with lower doses such as those used with VPA.

Withdrawal of therapy

As with other antiepileptics, withdrawal of LTG therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed drug information recommends that regardless of indication the withdrawal of LTG should be tapered over at least 2 weeks.

9.3 Duration of therapy

As reported in a previous section of this document (*Recurrence of seizures after a first seizure and after diagnosis of epilepsy, page 8*), at least 10% of epileptic patients will develop a chronic epileptic syndrome, and will never attain a complete seizure remission despite chronic treatment with AEDs (Berg 2008).

The choice about the optimal timing for the discontinuation of therapy in the remaining 90% of epileptic patients who will attain a 2-year seizure free condition after 5 years of treatment with AEDs is controversial. Among these patients discontinuation of treatment is associated with a seizure recurrence pooled risk of 29% (95% CI 24-34%) in a 2-year follow up (Berg and Shinnar 1994). Factors associated with a higher-than-average risk of seizure recurrence are adolescent-onset epilepsy, partial seizures, an associated underlying neurological condition and abnormal EEG findings at the time of AED withdrawal in children (Specchio and Beghi 2004). Therefore the decision to withdraw AEDs must be considered after a seizure-free period of at least 2 years, and taking into account the average risk of relapse, the presence of individual factors determining a higher risk of recurrence, and the treatment-related benefit-risk balance in individual patients.

9.4 Reference to existing WHO and other clinical guidelines

Existing WHO relevant documents with related web links or reference (3 documents in total) were identified:

- Chisholm D, on behalf of WHO-CHOICE. Cost-effectiveness of first-line antiepileptic drug treatments in the developing world: a population-level analysis. *Epilepsia* 2005; 46:751-9.
- World Health Organization (WHO). Atlas: Epilepsy care in the world. 2005. ISBN 92 4 156303 6 (NLM classification: WL 385). - www.who.int/mental_health/neurology/epilepsy/en/index.html
- World Health Organization (WHO). Neurological disorders : public health challenges. 2006. ISBN 92 4 156336 2 (NLM classification: WL 140). - www.who.int/mental_health/neurology/neurodiso/en/index.html

Relevant guidelines

The following documents were identified:

- from the American Academy of Neurology (www.aan.com/go/practice/guidelines):
 - French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004a;62:1252-60.
 - French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004b;62:1261-73.
- from the International League Against Epilepsy (ILAE) (www.ilae.org/Visitors/Centre/Guidelines.cfm):
 - Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2006; 47:1094-120.
 - Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T, Perucca E. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008; 49:1239-76.
- from the National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk/Guidance/CG20):
 - National Collaborating Centre for Primary Care. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE Clinical Guideline 20. October 2004.
- from the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/guidelines/published/index.html):
 - Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline 2003.
 - Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in children and young people. A national clinical guideline 2005.

Recommendations by the guidelines listed above

Several international guidelines deal with the pharmacological treatment of epilepsy (French et al. 2004a, French et al. 2004b, Glauser et al. 2006, NICE 2004, SIGN 2003, SIGN 2005), trying to provide recommendations on the following topics:

- 1) which is/are the first choice drug/s for treatment of new onset generalized epilepsy in adults and in children?
- 2) which is/are the first choice drug/s for treatment of new onset partial epilepsy in adults and in children?
- 3) which is/are the first choice drug/s to add to monotherapy for treatment of drug-resistant generalized/partial epilepsy in adults and in children?

A summary of the guidelines recommendations can be found in **Annex D**.

Briefly, guidelines agreed on the following recommendations:

- 1) **LTG** and **VPA** can be considered both as first AED to initiate therapy in new onset generalized epilepsy in adults and in children, moreover **CBZ** and **topiramate** can be also the first choice in new onset generalized epilepsy in children;
- 2) **CBZ** and **VPA** can be considered both as first AED to initiate therapy in new onset partial epilepsy in adults and in children, moreover, **oxcarbazepine** can be also the first choice in new onset partial epilepsy in children;
- 3) **gabapentin**, **LTG**, **levetiracetam**, **oxcarbazepine**, **tiagabine**, **topiramate** can considered each as first add-on therapy for drug-resistant partial epilepsy in adults, and **gabapentin** for drug-resistant partial epilepsy in children. For drug-resistant generalized epilepsy in adults and children there is no consensus in recommending AEDs.

LTG in particular, is by consent recommended (together with **VPA**) as a first choice in new onset generalized epilepsy, in adults and children. Its role in partial epilepsy is more controversial: some guidelines (AAN 2004, NICE 2004, SIGN 2003, SIGN 2005) but not others (ILAE 2006) consider **LTG** as a possible first choice.

9.5 Need for special diagnostic or treatment facilities and skills

LTG does not require special diagnostic facilities with respect to other AEDs. According to ILAE (Patsalos et al. 2008), therapeutic drug monitoring by means of serum concentrations measurement is a valuable diagnostic procedure in the management of patients treated with any AED (see **table 5**). No specific recommendation is provided for any AED in regard of therapeutic drug monitoring, with the exception for phenytoin, which relationship between dose and serum concentration is unpredictable, due to its non-linear pharmacokinetics.

Table 5 (adapted from Patsalos et al. 2008)

General situations in which serum concentration measurement of AEDs is indicated:
1) when a person has attained the desired clinical outcome, to establish an individual therapeutic concentration which can be used at subsequent times to assess potential causes for a change in drug response;
2) as an aid in the diagnosis of clinical toxicity;
3) to assess compliance, particularly in patients with uncontrolled seizures or breakthrough seizures;
4) to guide dosage adjustment in situations associated with increased pharmacokinetic variability (e.g., children, the elderly, patients with associated diseases, drug formulation changes);
5) when a potentially important pharmacokinetic change is anticipated (e.g., in pregnancy, or when an interacting drug is added or removed);
6) to guide dose adjustments for AEDs with dose-dependent pharmacokinetics, particularly phenytoin.

The treatment with any AEDs should be prescribed and monitored, if possible, by a physician or a neurologist skilled in the treatment of epilepsy. With respect to other AEDs, **LTG** does not require specific competences.

10. Summary of comparative effectiveness in a variety of clinical settings

The statements reported below are based on data from available clinical trials, which enrolled 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) which, in clinical practice, often require an accurate diagnostic definition to allow prognostic evaluation and therapeutical planning. The main source of evidence, though, is a long-term pragmatic RCT including most generalized and partial epileptic syndromes (Marson et al. 2007a,b,c see below)

which conclusions were considered to be transferable to the majority of individual patients observed in clinical practice.

Although available data come from RCTs conducted in developed countries (where the distribution of the etiology of epilepsy and of the characteristics of patients at risk is different from that of developing countries), with the exception of symptomatic epilepsy due to parasitic infections (cysticercosis, malaria, etc.), that are specific of developing countries, all other etiologies are shared by both settings.

In **new onset generalized epilepsy** VPA (the main comparator in this condition) was found to be superior to LTG in the long term (median follow up 3.5 years) in the following efficacy outcomes (see below **table 6**, and also **10.2 Section** and **AnnexF_01** for details):

- time to 12-month remission: HR 1.31 (95% C.I 1.06-1.62)
- time to treatment withdrawal for inadequate seizure control: HR 1.95 (95% C.I 1.28-2.98)
- time to first seizure: HR 1.41 (95% C.I 1.14-1.75)

without difference in tolerability outcomes (time to treatment withdrawal for unacceptable adverse events (AEs): HR 0.72, 95% C.I 0.46-1.14).

The evidence supporting these results is 1 pragmatic long-term RCT (Marson et al. 2007b,c), judged of *moderate quality*, according to GRADE method, because of the unblinded design. However, there are not major factors suggesting a high risk of bias; moreover the sample of patients included in the RCT are representative of the whole spectrum of disease in the developed countries.

Other 2 short-term RCTs (GSK 2000, Steinhoff et al. 2005) did not find differences of efficacy between LTG and VPA. However these studies are limited by the short length of follow up (24 weeks), the low statistical power and the high risk of bias (*low/very low quality* according to GRADE method).

Table 6: Relevant RCTs testing LTG versus VPA in new onset generalized epilepsy.

RCT/Setting	Study design/ Quality	Interventions (Participants)	Follow up	Outcomes	Results (95% CI)	Absolute risk difference (95% CI)
Marson 2007b,c UK	open pragmatic RCT <i>moderate quality</i>	LTG (239) VPA (238)	median 3.5 years	<ul style="list-style-type: none"> – time to treatment withdrawal – time to treatment withdrawal for inadequate seizure control – time to 12-month remission – time to first seizure – time to treatment withdrawal for unacceptable AEs 	<p>no difference</p> <p>HR 1.95 (1.28 to 2.98) in favour of VPA</p> <p>HR 1.31 (1.06 to 1.62) in favour of VPA</p> <p>HR 1.41 (1.14 to 1.75) in favour of VPA</p> <p>no difference</p>	<p>no difference</p> <p>+13% (4 to 21) of withdrawal for LTG after 3 yrs</p> <p>-7% (-15 to 1) of remission for LTG after 3 yrs</p> <p>+14% (6 to 23) of first seizure for LTG after 3 yrs</p> <p>no difference</p>
Steinhoff 2005 Germany	open RCT <i>very low quality</i>	LTG (33) VPA (33)	24 weeks	<ul style="list-style-type: none"> – time to treatment withdrawal – seizure freedom 	<p>no difference</p> <p>no difference</p>	<p>no difference</p> <p>no difference</p>

GSK 2001 (see Wilby 2005) not reported	RCT <i>low quality</i>	(313)	24 weeks	– seizure freedom	no difference	no difference
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In **children with absence seizure**, LTG was not found to be superior to VPA (the main comparator in this condition) (see **10.2 Section** and **AnnexF_02** for details). The evidence supporting the result is 1 short term RCT of *very low quality* (Posner et al. 2005).

In **new onset partial epilepsy** (see below **table 7**, and also **10.2 Section** and **AnnexF_03** for details) LTG was found to be superior to CBZ (the main comparator in this condition) in the following outcomes:

- time to treatment withdrawal (effectiveness outcome):
 - short-term follow up (range 24-48 weeks): HR 0.62 (95% C.I 0.45-0.86)
 - long-term follow up (median 3.6 years): HR 0.78 (95% C.I 0.63-0.97)
- time to treatment withdrawal for unacceptable AEs (tolerability outcome):
 - long-term follow up (median 3.6 years): HR 0.62 (95% C.I 0.46-0.83)

On the other hand, CBZ was found to be superior to LTG in the following efficacy outcomes:

- seizure freedom in the short-term follow up (24-48 weeks): OR 0.72 (95% C.I 0.54-0.97)
- time to first seizure in the long-term follow up (median 3.6 years): HR 1.23 (95% C.I 1.04-1.45)

The evidence supporting these results is 1 pragmatic long-term RCT of *moderate quality* (Marson et al. 2007a,c), 1 SR of 4 short-term RCTs of *moderate quality*, and further 4 short-term RCTs with quality ranging from *moderate* to *very low*. Overall there are no major factors suggesting a high risk of bias affecting the main results; moreover patients included in the RCTs are representative of the whole spectrum of disease in the developed countries.

Table 7: Relevant RCTs testing LTG versus carabamazepine in new onset partial epilepsy.

RCT	Study design/ Quality	Interventions (Participants)	Follow up	Outcomes	Results (95% CI)	Absolute risk difference (95% CI)
Marson 2007a,c UK	open pragmatic RCT <i>moderate quality</i>	LTG (378) CBZ (378)	median 3.6 years	– time to treatment withdrawal – time to treatment withdrawal for inadequate seizure control – time to 12-month remission – time to first seizure – time to treatment withdrawal for unacceptable AEs	HR 0.78 (0.63 to 0.97) in favour of LTG no difference no difference HR 1.23 (1.04 to 1.45) in favour of CBZ HR 0.62 (0.46 to 0.83) in favour of LTG	-6% (+2% to -13%) of withdrawal for LTG after 3 yrs no difference no difference +7% (0 to +13%) of first seizure for LTG after 3 yrs -10% (-4% to -17%) of withdrawal for LTG after 3 yrs
Gamble 2006 Europe	SR of 4 RCTs <i>moderate quality</i>	LTG (562) CBZ (308)	24-48 weeks	– time to treatment withdrawal – time to first	HR 0.62 (0.45 to 0.86) in favour of LTG no difference	not available no difference

				seizure – seizure freedom	OR 0.72 (0.54 to 0.97) in favour of CBZ	not available
Rowan 2005 USA	double blind RCT <i>moderate quality</i>	LTG (200) CBZ (198)	54 weeks	– time to treatment withdrawal – time to first seizure – seizure freedom	LTG had fewer early terminators than CBZ (p<0.0001) no difference no difference	not available no difference no difference
Steinhoff 2005 Germany	open RCT <i>very low quality</i>	LTG (88) CBZ (88)	24 weeks	– time to treatment withdrawal – seizure freedom	no difference no difference	no difference no difference
Saetre 2007 Europe and USA	double blind RCT <i>low quality</i>	LTG (93) CBZ (91)	40 weeks	– time to treatment withdrawal – time to first seizure – seizure freedom	no difference no difference no difference	no difference no difference no difference
Gilad 2007 Israel	open RCT <i>very low quality</i>	LTG (32) CBZ (32)	54 weeks	– seizure freedom – withdrawal for AEs	no difference LTG had fewer early terminators than CBZ (p<0.05)	no difference not available

In **drug-resistant generalized epilepsy**, LTG was found to be marginally superior to placebo in seizure freedom (RR 1.7, 95% CI 1.0-2.7, and RR 2.8, 95% CI 1.0-7.8) according to 2 short-term RCTs (see **10.2 Section** and **AnnexF_04** for details). In **drug-resistant partial epilepsy**, the results concerning the comparison LTG versus placebo are conflicting (see **10.2 Section** and **AnnexF_05** for details). The evidence supporting the results on drug-resistant epilepsy (both generalized and partial) is overall of *low/very low quality* and thus with high risk of bias.

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Guidelines were searched by consulting the following sources (September 2008):

- database of guidelines
 - National Guideline Clearinghouse
 - National Library of Health
 - CMA Infobase
- government / health agencies
 - Australian Government – National Health and Medical Research Council - Clinical Practice Guidelines
 - National Institute for Health and Clinical Excellence – NICE
 - New Zealand Guidelines Group – NZGG
 - Scottish Intercollegiate Guidelines Network – SIGN
- specialist scientific societies
 - American Academy of Neurology (AAN)
 - International League Against Epilepsy (ILAE)

The strategy adopted was specific to each source. In synthesis, if a “search” function was available the database was checked with the term “lamotrigine”; if a “search” engine was not available the documents were searched through the “browse” function.

The results of the search strategy is summarized in the **Annex E**.

SRs were searched by consulting the following sources (September 2008):

- databases of SRs and technology assessments
 - Cochrane Library (2008, Issue 3): Cochrane Database of Systematic Reviews (CDSR)
 - Cochrane Library (2008, Issue 3): Technology Assessments database
 - Cochrane Library (2008, Issue 3): Economic Evaluations database
 - Database of Abstracts of Reviews of Effects (DARE) - www.crd.york.ac.uk/crdweb/
 - BMJ Clinical Evidence
 - HTA.UK - www.hta.ac.uk
 - AHRQ - www.ahrq.gov/
 - Canadian Agency for Drugs and Technologies in Health (CADTH)
 - National Institute for Health and Clinical Excellence (NICE)
 - Haute Autorité de Santé - <http://www.has-sante.fr/portail/index.jsp>

The strategy adopted was specific to each source. In synthesis, if a “search” function was available the database was checked with the term “lamotrigine”; if a “search” engine was not available the documents were searched through the “browse” function.

- databases of primary publications
 - National Library of Medicine’s MEDLINE database (from 1966 to 2008)

The strategy adopted was the following:

“lamotrigine OR lamotrigine[substance name] AND systematic[sb] AND 2005:2008[dp]”

The results of the search strategy is summarized in the **Annex E**.

RCTs were searched by consulting the following sources (September 2008):

- database of RCTs
 - Cochrane Library (2008, Issue 3): Cochrane Central Register of Controlled Trials (CENTRAL)

The strategy adopted was the following: “lamotrigine AND 2005:2008[dp]”

- database of primary publications
 - National Library of Medicine’s MEDLINE database (from 1966 to 2008)

The strategy adopted was the following:

(lamotrigine OR lamotrigine[substance name]) AND (clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR randomly [tiab] OR trial [tiab] OR groups [tiab])

Limits: Publication Date from 2007 to 2008, Humans, English, French, Italian, Spanish

The results of the search strategy is summarized in the **Annex E**.

10.2 Summary of available estimates of comparative effectiveness (appraisal of quality, outcome measures, summary of results)

Evidence of LTG as AED

Our objective was to evaluate the effectiveness of LTG in the treatment of epilepsy.

The epileptic conditions were classified according to the following categories:

1. New onset generalized epilepsy (including the subgroup of absence seizure in children)
2. New onset partial epilepsy
3. Drug-resistant generalized epilepsy
4. Drug-resistant partial epilepsy

The intervention of interest was LTG (any regimen) versus the main drug comparator for the identified condition:

- VPA for new onset generalized epilepsy;
- CBZ for new onset partial epilepsy;

In case of drug-resistant epilepsy the comparison versus placebo was considered.

Eligible studies were SRs of RCTs and single RCTs published next.

We considered the outcome categories proposed by the International League Against Epilepsy (ILAE Commission on Antiepileptic Drugs 1998), namely the *outcomes of effectiveness*, *outcomes of efficacy*, *outcomes of tolerability*, that are reported in the **table 8**.

Table 8: Definitions of outcomes according to ILAE classification (ILAE Commission on Antiepileptic Drugs 1998).

Effectiveness outcomes (i.e. encompassing both efficacy and tolerability):
<ol style="list-style-type: none"> 1. time to treatment withdrawal after randomization due to inadequate efficacy or poor tolerability 2. retention time
Efficacy outcomes:
<ol style="list-style-type: none"> 1. time to a period of remission from seizures after randomization (this measure evaluates the reduction in seizure frequency and/or severity directly attributable to treatment) 2. time to the first seizure after randomization 3. time to treatment withdrawal after randomization due to inadequate efficacy 4. patients who remain seizure-free at the end of follow up
Tolerability outcomes:
<ol style="list-style-type: none"> 5. time to treatment withdrawal after randomization due to unacceptable AEs 6. withdrawal for AEs

SRs and RCTs have been synthesized in tables of evidence (**Annex F**) using the GRADE profile software (<http://www.gradeworkinggroup.org/toolbox/index.htm>), where studies are tabulated according to the selected outcome (e.g., time to treatment withdrawal, retention rate, time to 12-month remission, time to withdrawal for inadequate seizure control, time to first seizure, time to first seizure, seizure freedom, time to treatment withdrawal for unacceptable AEs).

In this document we did not fully apply the GRADE method (GRADE working group, 2004; Guyatt et al. 2008a; Guyatt et al. 2008b; Guyatt et al. 2008c; Guyatt et al. 2008d; Schünemann et al. 2008), recommending a ranking of the outcomes by relevance, as *critical*, *important*, *not important*, performed by a multidisciplinary panel.

The purposes of this document do not imply involving a multidisciplinary work group, and therefore we have considered all the above listed outcomes as relevant-

Quality assessment of the studies considered for each outcome takes into account study design, limitations, inconsistency, indirectness, and imprecision, as recommended by the GRADE workgroup. Specific motivations for quality ratings are reported in footnotes. In the column 'quality', a qualitative scoring of the study quality for each considered outcome is given: *high*, *moderate*, *low*, or *very low*.

New onset generalized epilepsies

We found 2 published RCTs (Steinhoff et al. 2005, Marson et al. 2007b,c) and 1 unpublished RCT (reported as GlaxoSmithKline 2001 in the Technology Assessment document by Wilby et al. 2005) testing LTG versus VPA; all the studies included patients of all ages with generalized or undetermined epilepsy. Moreover, we found 1 SR (Posner et al. 2005) testing LTG versus VPA for the subgroup of absence seizures in childhood.

LTG versus VPA (Annex F_01)

The first study of this group (GlaxoSmithKline 2001 reported in Wilby et al. 2005) is an randomized 24-week trial; it is not reported if it is a blind trial. A total of 313 participants with newly-diagnosed generalized epilepsy were randomized to LTG or VPA. Recommended maintenance daily dose was 100-500 mg for LTG; the dose for VPA is not reported. The primary end-point was the seizure freedom between at 24 weeks of follow up.

The second study of this group (Steinhoff et al. 2005) is an open-label randomized multicentre 24-week trial. Sixty-three participants with age ≥ 12 years and newly-diagnosed generalized epilepsy were randomized to LTG (33 patients) or VPA (30). Recommended maintenance daily dose was 100-200 mg for LTG, 600-1200 mg in children, 400-1500 mg in adolescents, 1200-2100 mg in adults for VPA. Patients on LTG (13 males, 20 females) had a mean age of 22.3 years (standard deviation (SD) 13.0), patients on VPA (14 males, 14 females) had a mean age of 23.3 years (SD 10.7). The median number of seizures in the previous 6 months was 2 in both groups. The primary end-point was the seizure freedom between the 17 and 24 weeks; other end-point considered in this review is the retention rate from the beginning to the end of follow up (24 weeks).

The third study (Marson et al. 2007b,c) is a pragmatic open-label randomized multicentre long term trial. Seven hundred and sixteen participants with age >4 years and newly-diagnosed generalized epilepsy were randomized to LTG (239 patients), VPA (238), TPM (239). Recommended maintenance daily dose was 3–6 mg/kg in children and 150 mg in adults for LTG, 20–30 mg/kg in children and 1000 mg in adults for VPA, 3–6 mg/kg in children and 150 mg in adults for TPM. Patients on LTG (142 males, 97 females) had a mean age of 22.8 years (SD 14.3), patients on VPA (143 males, 95 females) a mean age of 22.5 years (SD 14.5), patients on TPM (142 males, 97 females) a mean age of 22.3 years (SD 13.3). The mean age at first seizure was 17.8 years (SD 12.5), and the median number of previous seizures was 8, across all groups. The primary end-points were time from randomisation to treatment withdrawal and the time from randomisation to the achievement of a 1 year of remission of seizures. Other end-points considered in this review are the time from randomisation to treatment withdrawal for inadequate seizure control, the time to first seizure, the time from randomisation to treatment withdrawal for unacceptable AEs. The median duration of follow up was 3.5 years across all treatment groups.

All but one RCTs have the methodological limitation to be unblinded; however one of them, with a long term follow up, represents a “real life” population of patients with generalized epilepsy. The main difference between the RCTs is the follow up duration: adequate for a judgment on effectiveness of treatments (median 3.5 years) in the study of Marson et al. 2007b,c, too short (24 weeks) in the case of Steinhoff et al. and GSK 2000. Moreover the latter two studies has too few patients, and they are probably underpowered to detect differences between the two treatments.

Effectiveness outcomes

The study by Steinhoff et al. (2005) did not show a significant difference of retention rates between LTG (88%) and VPA (97%).

The study by Marson et al. (2007b,c) did not show a significant difference of time to treatment failure between LTG and VPA (HR 1.25, 95% C.I 0.94-1.68)

Efficacy outcomes

The study by Marson et al. (2007b,c) showed, in favour of VPA, a significant increase of time to 12-month remission (HR 1.31, 95% C.I 1.06-1.62).

The study by GSK 2001 did not show a statistically significant difference of seizure freedom between LTG and VPA (RR 0.92, 95% CI 0.78-1.10).

The study by Steinhoff et al. (2005) did not show a significant difference of rates in seizure freedom between LTG (60.6%) and VPA (83.3%).

The study by Marson et al. (2007b,c) showed, in favour of VPA, a significant reduction in time to treatment withdrawal for inadequate seizure control (HR 1.95, 95% C.I 1.28-2.98), and a significant reduction in time to first seizure (HR 1.41, 95% C.I 1.14-1.75).

Tolerability outcome

The study by Marson et al. (2007b,c) did not show a statistically significant difference of time to treatment withdrawal for unacceptable AEs between LTG and VPA: HR 0.725 (95% C.I 0.46-1.14).

LTG versus VPA for absence seizures in childhood (Annex F_02)

The SR by Posner et al. (2005) included an open-label randomized 1-year trial. Thirty-eight participants aged 3-13 years with typical absence seizures were recruited and randomized to LTG (19 patients) or VPA (19 patients). Recommended maximum daily dose was 12 mg/kg for LTG, 30 mg/kg for VPA. This study has the limitations to be unblinded and to have included few patients, thus being probably underpowered to detect

differences between the two treatments. In fact, as a result there was not statistically significant difference of rates in seizure freedom (efficacy outcome) between LTG (53%) and VPA (68%) (p not reported).

New onset partial epilepsies

We found 1 SR (Gamble et al. 2006) and further 5 RCTs testing LTG versus CBZ (Steinhoff et al. 2005, Rowan et al. 2005, Marson et al. 2007a,c, Saetre et al. 2007, Gilad et al. 2007). These studies included patients of all ages or only the elderly with partial epilepsy.

LTG versus CBZ (Annex F_03)

The SR by Gamble et al. (2006) included 5 RCT (2 open and 3 double blinded) with a follow up of 24-48 weeks and a total of 903 participants (601 on LTG, 302 on CBZ). Two RCTs included patients with age 13-65 years, 1 RCT patients with age >2 years, 1 RCT patients with age >13 years, 1 RCT patients with age >65 years. In 4 RCTs the maintenance daily doses were fixed in a range of 100-200 mg for LTG and 400-600 mg for CBZ; in another RCT recommended maintenance daily dose was 2 mg/kg in children, 200 mg in adults, 100 mg in elderly for LTG, 5-40 mg/kg in children, 100-1500 mg in patients with age >12 years for CBZ. Two studies have the limitation to be unblinded and all studies have a short follow up (24-48 weeks). In four studies the maximum recommended daily dose for CBZ of 600 mg could be low for some patients. The metanalysis was performed on the basis of individual patient data.

Five more RCTs have been found and included in this document.

The first study by Steinhoff et al. (2005) is an open-label randomized multicentre 24-week trial. One hundred and seventy six participants with age ≥ 12 years and newly-diagnosed partial epilepsy were randomized to LTG (88 patients) or VPA (88). Recommended maintenance daily doses was 100-200 mg for LTG, 600-1000 mg in children and 600-1200 mg in adults for CBZ. Patients on LTG (52 males, 36 females) had a mean age of 46.6 years (SD 18.8), patients on CBZ (54 males, 34 females) a mean age of 43.1 years (SD 17.3); the median number of seizures in the previous 6 months was 3 in both groups. The primary end-point was the seizure freedom between the 17 and 24 weeks; other end-point considered in this review is the retention rate from the beginning to the end of follow up (24 weeks).

The second study (Rowan et al. 2005) is a double-blind randomized multicentre 12-month trial. Five hundred and ninety three participants with age ≥ 65 years and newly-diagnosed epilepsy of any type (3/4 of patients with partial epilepsy) were randomized to LTG (200 patients), CBZ (198), GBP (195). Target maintenance daily dose was 150 mg for LTG, 600 mg for CBZ, 1500 mg for GBP. Patients were about 95% males with a mean age of 72 years; 3/4 of patients had a unprovoked remote symptomatic etiology (cerebrovascular in about 1/2 of all patients). The primary end-point was the 12-month retention rate; other end-points considered in this review are the time to first seizure and the seizure freedom.

The third study (Marson et al. 2007a,c) is a pragmatic open-label randomized multicentre long term trial. One thousand seven hundred and twenty one participants with >4 years and newly-diagnosed partial epilepsy were randomized to LTG (378 patients), CBZ (378), TPM (378), GBP (377), OXC (210). Recommended maintenance daily doses was 3-6 mg/kg in children and 150 mg in adults for LTG, 15-20 mg/kg in children and 600 mg in adults for CBZ, 3-6 mg/kg in children and 150 mg in adults for TPM, 30-45 mg/kg in children and 1200 mg in adults for GBP, 15-30 mg/kg in children and 900 mg in adults for OXC. Patients on LTG (208 males, 170 females) had a mean age of 36.8 years (SD 18.3), patients on CBZ (208 males, 170 females) a mean age of 39.2 years (SD 18.3), patients on TPM (208 males, 170 females) a mean age of 38.4 years (SD 18.6), patients on GBP (207 males, 170 females) a mean age of 37.8 years (SD 17.9), patients on OXC (111 males, 99 females) a mean age of 40.1 years (SD 18.0). The median number of previous seizures was 12 across all groups. The primary end-points were the time to treatment failure and the time to the achievement of 1-year remission. Other end-points considered in this review are the time to treatment failure for unacceptable AEs, the time from randomization to treatment failure for inadequate seizure control, and the time to first seizure. The median duration of follow up across all treatment groups was 3.5 years, except for the OXC group 2.7 years.

The fourth trial (Saetre et al. 2007) is a double-blind randomized multicentre 40-week trial. One hundred and eighty six participants with age ≥ 65 years and newly-diagnosed epilepsy of any type (probably more than 3/4 of patients with partial epilepsy) were recruited and randomized to LTG (94 patients) and CBZ (92). Median daily dose was 100 mg (range 25-400 mg) for LTG, 400 mg (range 100-800 mg) for CBZ. Patients were about a half of males with a mean age of 72 years; 2/3 of patients had a unprovoked symptomatic etiology. The primary end-point was the time to withdrawal from any cause; other end-points considered in this review are the time to first seizure and the seizure freedom.

The fifth study (Gilad et al. 2007) is an open randomized 12-month trial. Sixty four participants with a first seizure after an ischemic stroke were randomized to LTG (32 patients) or CBZ (32). Median daily dose was 200 mg (+/- 50 mg) for LTG, 600 mg (+/- 100 mg) for CBZ. Patients were on majority males (65% LTG group, 78% CBZ group) with a mean age of 67 years (range 38-90); about half of patients had a partial seizure with secondary generalization in both groups. End-points considered in this review are seizure freedom and the survival from withdrawal for AEs.

Two out of this 5 RCT have the methodological limitation to be unblinded. However one of the two is a large pragmatic trial mimicking real life management of patients with partial epilepsy. Only one RCT (Marson et al. 2007a,c) have a follow up duration adequate (median 3.5 years) for a judgment on effectiveness of treatments; in the other 4 RCT duration is less than 1 year. Finally, 3 RCT (Steinhoff et al. 2005, Saetre et al. 2007, Gilad et al. 2007) are probably underpowered to detect differences between the treatments.

Effectiveness outcomes

The SR by Gamble et al. (2006) found a statistically significant difference of time to treatment withdrawal in favour of LTG (HR 0.62, 95% CI 0.45-0.86).

The study by Steinhoff et al. (2005) did not show a significant difference in retention rates between LTG (91%) and CBZ (81%).

The study by Rowan et al. (2005) found a statistically significant difference of time to treatment withdrawal in favour of LTG ($p < 0.0001$, log rank statistic).

The study by Marson et al. (2007a,c) found a statistically significant difference of time to treatment withdrawal in favour of LTG (HR 0.78, 95% CI 0.63-0.97).

The study by Saetre et al. (2007) did not show a significant difference in time to treatment withdrawal between LTG and CBZ (HR 0.77, 95% CI 0.45-1.31).

Efficacy outcome

The study by Marson et al. (2007a,c) did not find a significant difference between LTG and CBZ in time to 12-month remission (HR 0.91, 95% CI 0.77-1.09).

The study by Marson et al. (2007a,c) did not find a significant difference between LTG and CBZ in time to withdrawal for inadequate seizure control (HR 1.17, 95% CI 0.84-1.64).

The SR by Gamble et al. (2001) and the studies by Rowan et al. (2005) and Saetre et al. (2007) did not find a statistically significant difference in time to first seizure (respectively HR 1.28, 95% CI 0.98-1.66, log rank statistic not significant, HR 1.50, 95% CI 0.94-2.40). On the other hand, Marson et al. (2007a,c) found a statistically significant difference of time to first seizure in favour of CBZ (HR 1.23, 95% CI 1.04-1.45).

The SR by Gamble et al. (2001) and the studies by Steinhoff et al. (2005), Rowan et al. (2005), Saetre et al. (2007) and Gilad et al. (2007) did not find a statistically significant difference in rates of seizure freedom between LTG and CBZ.

Tolerability outcome - Important

The study by Marson et al. (2007a,c) found a statistically significant difference of time to treatment withdrawal for unacceptable AEs in favour of LTG (HR 0.62, 95% CI 0.46-0.83). The study by Gilad et al. (2007) showed a significant difference in withdrawal rates between LTG (3%) and CBZ (31%), $p = 0.02$.

Drug-resistant generalized epilepsy (Annex F_04)

We found 2 RCTs (Biton et al. 2005, Trevathan et al. 2006) testing LTG versus placebo.

The study by Biton et al. (2005) is a double-blind randomized 20-week trial. One hundred and seventeen participants with age ≥ 2 years and drug-resistant primary generalized epilepsy were randomized to LTG (58 patients) or placebo (59). Recommended maintenance daily doses for LTG was targeted, in patients with age < 12 years, to plasmatic levels ranging between 3.0 and 12.0 mcg depending on the first AED taken, and

in patients with age >12 years to a daily dose ranging 200-400 mg. Patients were about a half males with a mean age of 25 years (range 2-55); the mean age at onset was 12 years and the median number of seizures per month was 2.3 in the LTG group and 3.0 in the placebo group; the most common concurrent AED in both groups was VPA (about 2/5 of patients). End-point considered in this review is seizure freedom.

The study by Trevathan et al. (2006) is a double-blind randomized 24-week trial. Forty five participants with age 2-12 years and drug-resistant primary generalized epilepsy were randomized to LTG (21 patients) or placebo (24). Recommended maintenance daily doses for LTG was targeted to plasmatic levels ranging between 3.0 and 12.0 depending on the first AED taken. Patients had a mean age of 11 years (range 2-13); the mean age at onset was 6 years and the median number of seizures per month was 2.0 in the LTG group and 3.8 in the placebo group; the most common concurrent AED in both groups was VPA (about 2/3 of patients). End-point considered in this review is seizure freedom.

Both RCT are limited by the unbalanced randomization with the presence of more severe patients in the placebo groups, the small number of included patients and the short length of follow up (20-24 weeks).

Efficacy outcomes

The studies by Biton et al. (2005) and Trevathan et al. (2006) found a marginal statistically significant difference of seizure freedom in favour of LTG (respectively RR 1.7, CI 95% 1.0-2.7, RR 2.8, CI 95% 1.0-7.8).

Drug-resistant partial epilepsy (Annex F_5)

We found 1 SR (Ramaratnam et al. 2001) and further 2 RCTs (Naritoku et al. 2007, Pina-Garza et al. 2008) testing LTG versus placebo.

The SR by Ramaratnam et al. (2001, with search updated in 2007) included 11 RCTs (three parallel and 8 cross-over RCT) with a follow up of 8-24 weeks and a total of 1027 participants (619 on LTG, 408 on placebo).

Ten RCTs included patients with age ranging between 16 and 65 years, 1 RCT included children (199 subjects, age 2-16 years). The maintenance daily doses of LTG had a median range of 200-400 mg. All studies have the limitation to have a short follow up (12-24 weeks). Observing the median doses prescribed in the studies, several patients could have undergone to a artificially high dose of LTG.

Two more RCTs have been found and included in our review.

The study by Naritoku et al. (2007) is a double-blind randomized 19-week trial. Two hundred and forty three participants with age > 12 years and drug-resistant partial epilepsy were randomized to LTG extended release (121 patients) or placebo (122). Recommended maintenance daily doses for LTG was targeted to a daily dose ranging 200-500 mg depending on the first AED taken (VPA or enzyme-inducing AED or other AEDs). Patients were half males with a mean age of 35.8 years (SD 12.7) in the LTG group and 37.5 years (SD 14.4) in the placebo group. The mean age at onset was 14.9 years (SD 12.2) in the LTG group and 16.4 years (SD 13.7) in the placebo group; the median number of seizures per week was 2.3 in the LTG group and 2.1 in the placebo group; the most common concurrent AED in both groups was CBZ (about 2/5 of patients). End-point considered in this review is seizure freedom.

The study by Pina-Garza et al. (2008) is a double-blind randomized 8-week trial. Thirty eight infants with age 1-24 months and drug-resistant partial epilepsy were randomized to LTG (19 patients) or placebo (19). Maintenance daily doses for LTG were targeted to a daily dose ranging 5.1-15.6 mg/kg depending on the first AED taken (enzyme-inducing AED or other AEDs). Patients (12 males in LTG group and 9 males in placebo group) had a median age of 14 months. The median duration of epilepsy was 9 months in both groups; there were more complex partial seizures in the placebo groups (84% versus 53%). End-point considered in this review is time to treatment failure.

Both studies have some methodological limitations. The study by Naritoku et al. (2007) had an unbalanced attrition rate in the LTG group of 20% versus 13% in the placebo group; moreover had a short length of follow up. The study by Pina-Garza et al. (2008) has the strong limitation to have excluded from

randomization patients with a response rate <40% to LTG during a baseline phase; moreover patients were unbalanced in the type of seizures (more complex partial seizure in the placebo group), the follow up is very short and the included patients are very few. Finally, the population of interest is very particular (infant of 1-24 months of age).

Effectiveness outcomes

The SR by Ramaratnam et al. (2001) did not find a statistically significant difference of treatment withdrawal between LTG and placebo (OR 0.84, 95% CI 0.48-1.46).

The study by Pina-Garza et al. (2007) did not find a statistically significant difference between LTG and placebo in time to treatment failure ($p=0.059$, log rank test).

Efficacy outcomes

The study by Naritoku et al. (2007) found a statistically significant difference between LTG and placebo in seizure freedom (RR 3.8, 95% CI 1.6-8.9).

11. Summary of comparative evidence on safety

According to data from short-term (24 weeks) RCTs, the commonest AEs of LTG with respect to placebo are ataxia (NNH 8, 95% CI 4-100), diplopia (NNH 8, 95% CI 4-inf), dizziness (NNH 9, 95% CI 6-20), nausea (OR 1.88, 95% CI 1.21-2.91).

Among serious AEs skin rash is not infrequent (up to 4.5%-10% of treated patients).

Among the serious, rare and long-term AEs the following are reported: Stevens-Johnson syndrome/toxic epidermal necrosis, hepatic failure, renal failure, disseminated intravascular coagulation, acute exacerbation of ulcerative colitis.

All AEDs as a class (LTG among them) are associated with a risk of suicidal behavior or ideation (0.43%) which is double than that of patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation has been observed as early as one week after starting AED treatment, and persisted through 24 weeks.

The risk difference of major malformations in offsprings of mothers exposed to LTG monotherapy during pregnancy in relation to the expected risk among women not treated with AEDs is unclear. Recent evidence suggests that orofacial clefts are probably the commonest malformation associated with the use of LTG during pregnancy.

LTG is not superior to VPA (the main comparator in new onset generalized epilepsy) in terms of tolerability in the long term ("time to treatment withdrawal due to unacceptable AEs": HR 0.72, 95% CI 0.46-1.14). Unacceptable AEs cause treatment withdrawal in 19% of patients treated with VPA (weight gain being the most frequent unacceptable AE) and in 28% of patients treated with LTG (skin rash being the most frequent unacceptable AE). Hyperandrogenism, as a component of polycystic ovary syndrome, is reported to occur more frequently with VPA than LTG, especially if medication is started at age younger than 26 years.

Monotherapy with VPA in pregnant women is associated to a risk of major malformations of offsprings (malformation rate 10.73%, 95% CI 8.16-13.29) than the expected risk among women not treated with AEDs (malformation rate 3.27%, 95% CI 1.37-5.17) and than the risk associated to LTG monotherapy (malformation rate 2.91%, 95% CI 2.00-3.82).

Lamotrigine is better tolerated than CBZ in the long term ("time to treatment withdrawal due to unacceptable AEs": HR 0.62, 95% CI 0.46-0.83). The most frequent unacceptable AE associated with CBZ is skin rash (21% withdrawals from treatment), followed by tiredness (13%). Skin rash is also the most frequent unacceptable AE associated with LTG therapy (14% withdrawals).

Offsprings of women treated with CBZ during pregnancy have a higher risk of spina bifida than those born from untreated women (RR 3.84, 95% CI 1.1-10.3).

11.1 Estimate of total patient exposure to date

According to the manufacturer of Lamictal® (GSK – Glaxo Smith Kline) the branded drug is used by at least of 5 millions of people worldwide.

11.2 Description of adverse effects/reactions

Adverse effects of LTG versus placebo in the short-term: data from studies (Annex G)

In this section are reported data about AEs of LTG versus placebo in the short-term treatment, according to data from 2 SRs, (Ramaratnam et al. 2001, Zaccara et al. 2008), and from 1 Technology Assessment document (Wilby et al. 2005).

The following AEs were found to be more frequent in patients treated with LTG than patients treated with placebo:

- ataxia: OR 3.14 (95% CI 1.99-4.95) (Ramaratnam et al. 2001); RD 12% (95% CI 1%-24%) (NNH 8, 95% CI 4-100) (Zaccara et al. 2008)
- diplopia: OR 3.40 (95% CI 2.05-5.62) (Ramaratnam et al. 2001); RD 12% (95% CI 0%-24%) (NNH 8, 95% CI 4-inf) (Zaccara et al. 2008)
- dizziness: OR 2.57 (95% CI 1.80-3.69) (Ramaratnam et al. 2001); RD 11% (95% CI 5%-17%) (NNH 9, 95% CI 6-20) (Zaccara et al. 2008)
- nausea: OR 1.88 (95% CI 1.21-2.91) (Ramaratnam et al. 2001)

Serious, rare and long-term adverse effects of LTG

One Technology Assessment (Wilby et al. 2005), cumulating data from prescription event monitoring, post-marketing surveillance, prospective registry, RCT, uncontrolled trials, cohort studies, case-control studies, reports the following AEs:

- skin rash; it appears within 10 weeks of treatment, with an incidence ranging between 4.5% and 10%; usually it leads to treatment withdrawal
- Stevens-Johnson syndrome/toxic epidermal necrosis: at least 10 reported cases
- other very rare serious AEs (less than 10 reported cases) are hepatic failure, renal failure, disseminated intravascular coagulation, acute exacerbation of ulcerative colitis
- other rare less serious AEs are pruritus, nightmares, hallucinations, macrocytic anemia

Adverse effects of LTG: data from Martindale and FDA

From Martindale

Skin rashes may occur during therapy with LTG; severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, especially in children, and usually occur within 8 weeks of starting LTG. Symptoms such as fever, malaise, flu-like symptoms, drowsiness, lymphadenopathy, facial oedema and, rarely, hepatic dysfunction, leucopenia, and thrombocytopenia have also been reported with rashes as part of a hypersensitivity syndrome.

Other AEs include angioedema and photosensitivity; diplopia, blurred vision, and conjunctivitis; and dizziness, drowsiness, insomnia, headache, ataxia, nystagmus, tremor, tiredness, nausea and vomiting, irritability and aggression, hallucinations, agitation, and confusion. Very rarely, lupus-like reactions have been reported.

Licensed drug information states that there have been rare instances of death after a rapidly progressive illness with status epilepticus, multi-organ dysfunction, and disseminated intravascular coagulation in patients receiving therapy with multiple antiepileptics including LTG, although the role of LTG remains to be established.

It has been suggested¹ that multi-organ failure and disseminated intravascular coagulation, with associated rhabdomyolysis, are complications of severe convulsive seizures rather than of LTG therapy. However, there has been a report² of a patient with no history of generalised seizures who developed a syndrome of disseminated intravascular coagulation, rhabdomyolysis, renal failure, maculopapular rash, and ataxia 14 days after LTG was added to her antiepileptic regimen. Two cases of disseminated intravascular coagulation were found in a cohort of 11 316 patients involved in prescription-event monitoring of LTG therapy in general practice.³

1. Yuen AWC, Bihari DJ. Multiorgan failure and disseminated intravascular coagulation in severe convulsive seizures. *Lancet* 1992; 340: 618.

2. Schaub JEM, et al. Multisystem adverse reaction to lamotrigine. *Lancet* 1994; 344: 481.

3. Mackay FJ, et al. Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; 38: 881-6. (PubMed id:9579888)

Other adverse events

Effects on the blood

Septic shock secondary to leucopenia occurred in a patient when LTG was added to therapy with VPA.¹ There has also been a report of agranulocytosis in a child given high initial doses of monotherapy with LTG.² The fall in the blood count was noted several days after LTG had been discontinued due to skin rash. The UK CSM subsequently reported³ that 7 cases of aplastic anaemia, 12 of bone-marrow depression, and 20 of pancytopenia associated with LTG had been received worldwide. Given the extensive usage of LTG the CSM considered the risk of aplastic anaemia to be small and routine blood monitoring was not recommended. However, prescribers were warned to be alert for symptoms and signs suggestive of bone-marrow depression.

1. Nicholson RJ, et al. Leucopenia associated with lamotrigine. *BMJ* 1995; 310: 504.

2. de Camargo OAK, Bode H. Agranulocytosis associated with lamotrigine. *BMJ* 1999; 318: 1179.

3. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal): rare blood dyscrasias. *Current Problems* 2000; 26: 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 05/05/06)

Effects on bone

For the effects of antiepileptics including LTG on bone and on calcium and vitamin D metabolism, see under Phenytoin, Phenytoin Sodium.

Effects on the liver

Fatal fulminant hepatic failure has been reported¹ in a patient after addition of LTG to antiepileptic therapy with VPA and CBZ.

1. Makin AJ, et al. Fulminant hepatic failure induced by lamotrigine. *BMJ* 1995; 311: 292.

Effects on mental function

For a review of the effects of antiepileptic therapy including LTG on cognition, see Antiepileptics.

Effects on the skin

Rashes account for withdrawal from therapy in about 2% of those given LTG,^{1,2} and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis occur in about 1 in 1000 adult patients.^{3,4} The majority of rashes resolve once LTG has been stopped; however, some patients have developed permanent scarring and there have been rare reports of fatalities. The main risk factors appear to be use with VPA, and exceeding the recommended initial dose of LTG or the recommended rate of dose escalation. The risk appears to be greater in children^{1,4,5} and has been estimated to be between 1 in 300 and 1 in 50. These skin reactions usually occur within 8 weeks of starting therapy with LTG, but onset as early as the first day and as late as 2 years has been noted.⁶ After continuing reports of serious skin reactions in

children, UK recommended dosage regimens for children have been revised to further reduce the risk of such reactions.⁷

1. Mackay FJ, et al. Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; 38: 881-6.
2. Messenheimer J, et al. Safety review of adult clinical trial experience with lamotrigine. *Drug Safety* 1998; 18: 281-96.
3. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal) and serious skin reactions. *Current Problems* 1996; 22: 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015622&RevisionSelectionMethod=LatestReleased (accessed 05/05/06)
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From FDA

The FDA has analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of eleven drugs used to treat epilepsy as well as psychiatric disorders, and other conditions. These drugs are commonly referred to as antiepileptic drugs (...). In the FDA's analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the eleven drugs. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk for suicidality was higher in the patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions.

All patients who are currently taking or starting on any antiepileptic drug should be closely monitored for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression. FDA ALERT [1/31/2008]

11.3 Identification of variation in safety due to health systems and patient factors

Summary of data the use of LTG in women and during pregnancy

Available data are largely consistent with the notion that monotherapy of women during pregnancy with the most commonly used AEDs is associated with an increase in risk of major congenital malformations by two to three times, and that the magnitude of risk increases in offspring exposed to polytherapy (Perucca 2005). The most common major congenital malformations associated with AEDs are heart malformations (e.g., ventricular septal defect), orofacial defects (e.g., cleft lip with or without cleft palate), urologic defects (e.g., hypospadias), skeletal abnormalities (e.g., radial ray defects, phalangeal hypoplasia), and neural tube defects (e.g., spina bifida) (Meador et al. 2008a).

According to data from a recent meta-analysis (Meador et al. 2008b) the pooled risk of total major malformations in offsprings exposed in utero to LTG is not statistically different from the expected rate among women not taking AEDs (2.91%, 95% CI 2.00-3.82 versus 3.27%, 95% CI 1.37-5.17).

However, concern has recently raised about this issue. The North American AED Pregnancy Registry found a markedly increased risk of orofacial clefts identified at birth in infants exposed in utero to LTG monotherapy with respect to a population of unexposed offsprings (0.73% vs. 0.07%, respectively; RR 10.4, 95% CI 4.3–24.9) (Holmes et al. 2008). Controls were newborn infants from the Active Malformations Surveillance Program at Brigham and Women’s Hospital in Boston.

Moreover, a pooled analysis from five pregnancy registries (GSK Interantional Lamotrigine Registry, UK Epilepsy and Pregnancy Register, Swedish Medical Birth Registry, Australian Pregnancy Registry, Danish Multicentre Registry) disclosed 4 infants with orofacial clefts (0.24%) out of 1623 women exposed to LTG monotherapy. This rate, compared to that of the control population of infants from the above cited North American study, gives a RR of 3.5 (95% CI 1.3-9.3) (Holmes et al. 2008). The main limitation of these results is that the control population is not part of the registries, and the possibility of underascertainment of infants with orofacial clefts has raised for the control group, since the prevalence rate of this malformation is low. Another limitation is the possible selection bias due to the non-random enrolment of exposed women in the North American AED Pregnancy Registry.

Another recent case-control study tested the hypothesis of an increase of orofacial clefts relative to other malformations due to LTG exposure. Eeligible subjects were all livebirths, and dead fetuses from 20 weeks and terminations of pregnancy following prenatal diagnosis of the registries, collected in the EUROCAT congenital anomaly registers (Dolk et al. 2008), which covers over one quarter of overall births in Europe. The rate of exposure to LTG was compared between nonchromosomal orofacial clefts (cases) and nonchromosomal major defects without orofacial clefts (controls). No difference of exposure was observed between the two groups (OR 0.80, 95% CI 0.11–2.85).

Also considering the limitations of the above reported studies, we can reasonably assume that an higher risk of orofacial clefts in offsprings of women exposed to LTG during pregnancy is highly probable.

All AEDs are associated with an increased risk of offspring malformations. Orofacial cleft is possibly the most frequent malformation associated with the use of LTG, although available data do not allow conclusions, being obtained from studies with heterogeneous samples.

11.4 Summary of comparative safety against comparators

LTG versus VPA (the main comparator in new onset generalized epilepsy):

According to the RCT from Marson et al. (2007b,c), LTG is not superior to VPA in terms of tolerability in the long term (“time to treatment withdrawal due to unacceptable AEs”: HR 0.72, 95% C.I 0.46-1.14). Weight gain is the most frequent unacceptable AE for VPA (19% of patients withdrew from treatment for unacceptable AEs) as is skin rash for LTG (28% withdrawals).

According to a recent RCT (Morrell et al. 2008), specifically designed to test the incidence of hyperandrogenism and ovulatory dysfunction induced by AEDs, there is evidence that women treated with VPA are at higher risk of ovulatory dysfunction than those treated with LTG (54% vs. 38%, respectively; $p = 0.010$) and of polycystic ovary syndrome (9 vs 2%, respectively; $p = 0.007$). The risk of developing ovulatory dysfunction is higher for women treated with VPA if the treatment is initiated at an age younger than 26 years (44% VPA vs. 23% LTG, respectively; $p = 0.002$) but becomes similar if treatment is started at ages of 26 years or older (24% vs. 22%, respectively).

Among all AEDs, monotherapy with VPA in pregnant women is undoubtedly associated to a higher risk of major malformations in offsprings. Data from a recent metanalysis (Meador et al. 2008b) showed that VPA has the highest pooled risk among all AEDs (10.73%, 95% CI 8.16-13.29 versus 3.27%, 95% CI 1.37-5.17, expected by chance). Anomalies of brain, anomalies of face, coarctation of aorta, and spina bifida are the most frequently reported malformations associated to VPA monotherapy (Arpino et al. 2000).

LTG versus CBZ (the main comparator in new onset partial epilepsy):

According to the above cited RCT from Marson et al. (2007a,c), LTG was superior to CBZ in terms of tolerability in the long term follow up (“time to treatment withdrawal due to unacceptable AEs”: HR 0.62, 95% CI 0.46-0.83). Skin rash is the most frequent unacceptable AE for CBZ (21% of patients retired from CBZ treatment for unacceptable AE), followed by tiredness (13% of patients retired from CBZ treatment for unacceptable AE). For LTG skin rash is the most frequent unacceptable AE too (14% of patients retired from LTG treatment for unacceptable AE).

According to a recent metanalysis (Meador et al. 2008b), the pooled risk of major malformations in offsprings of women exposed to CBZ is 4.62% (95% CI 3.48-5.76), statistically not different to that of LTG (2.91%, 95% CI 2.00-3.82).

However, the risk of spina bifida in offsprings of women exposed to CBZ, even if lower than that reported for VPA (RR 3.84, 95% CI 1.1-10.3 versus RR 7.00, 95% CI 3.4-14.3) is clearly recognized in literature (Arpino et al. 2000, Perucca 2005, Yerby 2003).

12. Summary of available data on comparative costs and cost-effectiveness

Few data are available on the cost-effectiveness of LTG as monotherapy in new onset epilepsy. The most recent studies show conflicting results. In particular, the health economic analysis based on the RCT by Marson et al. (2007c) supported LTG in the monotherapy of new onset partial epilepsy being preferred to CBZ for both cost per seizure avoided and cost per quality-adjusted life-year gained; while VPA remain the drug of first choice for new onset generalized epilepsy. On the other hand, a decision analysis by Knoester et al. (2007) supports the use of old AEDs as first-line options for patients with newly diagnosed epilepsy.

In any case, since the above reported data are referred to developed countries, whether LTG may be cost-effective in developing countries need to be established.

As reported in the paragraph n. 8 (page 11) of this document, a recent cost-effectiveness analysis by Chrisholm on behalf of WHO-CHOICE (2005) found that in developing countries older first-line AEDs phenobarbital or phenytoin are even more cost-effective than CBZ (the main comparator for new onset partial epilepsy) and than VPA (the main comparator for new onset generalized epilepsy), because of their roughly similar efficacy and their lower cost in comparison with other AEDs.

12.1 Range of cost of the proposed medicine

LTG is not included in the *International Drug Price Indicator Guide*, published by Management Sciences for Health (MSH).

Below, the prices of lamotrigine (brended and non proprietary) are reported for United Kingdom (price in £) and Italy (price in €).

The DDD of LTG is 300 mg (oral administration route).

Drug	DDD	United Kingdom (price in £)		Italy (price in €)	
		Non proprietary Price DDD	GSK Price DDD	Non proprietary Price DDD	GSK Price DDD
Lamotrigine tablets 25 mg	0,3 g	0.63	4.37	-	-
Lamotrigine tablets 50 mg	0,3 g	0.44	3.71	-	-
Lamotrigine tablets 100 mg	0,3 g	0.30	3.21	-	-
Lamotrigine tablets 200 mg	0,3 g	0.35-1.38	2.73	-	-
Lamictal dispersible tablets, chewable 2 mg	0,3 g	-	43.55	-	-
Lamotrigine dispersible tablets 5 mg	0,3 g	8.83	17.32	-	18.25
Lamotrigine 25 mg dispersible tablets (if GSK chewable)	0,3 g	1.32	4.37	3.84	4.24-6.36
Lamotrigine 50 mg dispersible tablets (if GSK chewable)	0,3 g	-	-	3.44	3.55-5.52
Lamotrigine 100 mg dispersible tablets (if GSK chewable)	0,3 g	0.95	3.21	3.10	3.16
Lamotrigine 200 mg dispersible tablets (if GSK chewable)	0,3 g	-	-	2.72	2.74

12.2 Comparative cost-effectiveness presented as range of cost per routine outcome

We used the *International Drug Price Indicator Guide* (erc.msh.org; 2007), published by Management Sciences for Health (MSH), to obtain present prices (US\$) of comparators (VPA and CBZ):

Drug	DDD	High/Low Ratio	Price (US\$)	Price DDD (US\$)
CARBAMAZEPINE 100 mg tab-cap (PO)	1g			
Supplier Number of Prices=1			0.0707/tab-cap	0.707
Buyer Number of Prices=1			0.1390/tab-cap	1.39
CARBAMAZEPINE 100 mg/5 ml suspen (PO)	1g			
Buyer Number of Prices=4		3.57	0.0360/ml (median)	1.8
CARBAMAZEPINE 200 mg tab-cap (PO)	1g			
Supplier Number of Prices=11		2.82	0.0195/tab-cap (median)	0.0975
Buyer Number of Prices=9		7.71	0.0170/tab-cap (median)	0.085
CARBAMAZEPINE (sustained-release) 200 mg tab-cap (PO)	1g			
Buyer Number of Prices=2		1.95	0.1183/tab-cap (median)	0.5915
CARBAMAZEPINE (sustained-release) 400 mg tab-cap (PO)	1g			
Buyer Number of Prices=1			0.3597/tab-cap	0.89925
SODIUM VALPROATE 200 mg tab-cap (PO)	1.5 g			
Supplier Number of Prices=5		4.79	0.0804/tab-cap (median)	
Buyer Number of Prices=1			0.0978/tab-cap	
VALPROIC ACID 150 mg tab-cap (PO)	1.5 g			
Supplier Number of Prices=1			0.0787/tab-cap	0.787
VALPROIC ACID 200 mg tab-cap (PO)	1.5 g			
Supplier Number of Prices=1			0.0424/tab-cap	0.318
Buyer Number of Prices=1			0.1580/tab-cap	1.185
VALPROIC ACID 500 mg tab-cap (PO)	1.5 g			
Buyer Number of Prices=2		1.05	0.1229/tab-cap	0.3687
VALPROIC ACID (sodium valproate) 200 mg/5 ml syrup (PO)	1.5 g			
Buyer Number of Prices=1			0.0518/ml	1.9425

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

LTG has been approved for use in US since 1994.

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

LTG:

- British Pharmacopoeia (BP): Lamotrigine monograph is not published in BP 2009 but it has been published in the European Pharmacopoeia Supplement 6.3 which was published in June 2008. This monograph will be reproduced in BP 2010.
- US Pharmacopoeia: Lamotrigine monograph will be included in USP32 Supplement 1 with an effective date of August 1, 2009. The Expert Committee has balloted the and approved it for official adoption. Please look in USP32 Supplement 1 for the official text.
- European Pharmacopoeia: Yes.
- JP Pharmacopoeia: No

15. Proposed (new/adapted) text for the WHO Model Formulary

Lamotrigine

Tablets: 25 mg; 50 mg; 100 mg; 200 mg

Tablets (chewable dispersible): 2 mg, 5 mg; 25 mg; 50 mg; 100 mg; 200 mg

Uses:

Monotherapy of new onset partial epilepsy in patients not tolerating carbamazepine.

Monotherapy of new onset generalized epilepsy in women who are contemplating pregnancy and for which the severity of the disease (e.g. number and/or type of seizures threatening the patient's safety and/or seriously limiting her quality of life and/or threatening the fetus' safety) makes therapy with antiepileptic drugs strongly recommended.

Contraindications: lamotrigine is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

Precautions:

Hepatic impairment

<i>Medicine</i>	<i>Degree of impairment</i>	<i>Comment</i>
Lamotrigine	moderate to severe without ascites	Reduce doses by 25%
Lamotrigine	severe with ascites	Reduce doses by 50%

Renal impairment

<i>Medicine</i>	<i>Degree of impairment</i>	<i>Comment</i>
Lamotrigine	severe	Use with caution

Pregnancy

<i>Medicine</i>	<i>Comment</i>
Lamotrigine	Available data do not allow to draw conclusions on possible risk differences in terms of offspring malformations between women exposed to lamotrigine therapy during pregnancy and women not exposed to the drug, although recent epidemiological studies suggest that the risk of orofacial cleft may be higher among offsprings of women treated with lamotrigine during pregnancy.

These assumptions need further confirmation.
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Breastfeeding

<i>Medicine</i>	<i>Comment</i>
Lamotrigine	Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking lamotrigine is not recommended.

Cardiac disease; Skin reactions (see Adverse effects and Warning box); increased risk of suicidal thinking and behaviour in children and adolescents; eye disorders; avoid sudden withdrawal.

Warning box

Serious rashes requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of lamotrigine with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine. Nearly all cases of life-threatening rashes associated with lamotrigine have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash. Accordingly, lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring.

Interactions:

In the following table the symbol * indicates a **potentially hazardous interaction** and the combined administration of the drugs involved should be **avoided**, or only taken with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences.

Acetaminophen	Reduction of lamotrigine plasma concentration, decreasing the therapeutic effect
Carbamazepine	Higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine Lamotrigine steady-state concentrations lowered by approximately 40%.
Folate inhibitors	Lamotrigine is a weak inhibitor of dihydrofolate reductase
Oral contraceptives	Reduction of lamotrigine plasma concentration, decreasing the therapeutic effect
Other hormonal contraceptives or hormone replacement therapy	Reduction of lamotrigine plasma concentration, decreasing the therapeutic effect
Oxcarbazepine	Reduction of lamotrigine plasma concentration, decreasing the therapeutic effect
Phenobarbital, primidone:	Reduction of lamotrigine plasma concentration, decreasing the therapeutic effect
Phenytoin	Reduction of lamotrigine plasma concentration, decreasing the therapeutic effect

Rifamycins	Reduction of lamotrigine plasma concentration, decreasing the therapeutic effect
Succinimides (eg, ethosuximide)	Reduction of lamotrigine plasma concentration, decreasing the therapeutic effect
Topiramate	Increase of topiramate concentrations
Valproic acid	Increase of lamotrigine plasma levels and decrease of valproic acid steady-state concentration

BLOOD, HEPATIC OR SKIN DISORDERS. Patients or their carers should be told how to recognize signs a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) and that the patient should report any such occurrence to a physician immediately. Patients or their carers should be advised of the possibility of blood dyscrasias and/or acute multiorgan failure and to contact their physician immediately if they experience any signs or symptoms of these conditions. Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breast-feed or are breastfeeding an infant.

SKILLED TASKS: Patients should be advised that lamotrigine may cause dizziness, somnolence, and other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on lamotrigine to gauge whether or not it adversely affects their mental and/or motor performance.

Dose:

Monotherapy: ADULT 25 mg once daily *by mouth* for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 50 to 100 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily, given as a single dose or in 2 divided doses. Some patients have required up to 500 mg daily. The use of lamotrigine as monotherapy is not recommended for children under 12 years of age.

Adjunctive therapy with enzyme-inducing antiepileptics (but not with valproate): ADULT 50 mg once daily for 2 weeks followed by 50 mg twice daily for 2 weeks; thereafter the dose is increased by a maximum of 100 mg every 1 to 2 weeks to usual maintenance doses of 200 to 400 mg daily given in 2 divided doses. Some patients have required up to 700 mg daily.

For children aged 2 to 12 years the initial dose of lamotrigine is 600 micrograms/kg daily *by mouth* in 2 divided doses for 2 weeks followed by 1.2 mg/kg daily in 2 divided doses for 2 weeks; thereafter the dose is increased by a maximum of 1.2 mg/kg every 1 to 2 weeks to usual maintenance doses of 5 to 15 mg/kg daily given in 2 divided doses. If the calculated daily dose for children lies between 1 and 2 mg then 2 mg may be given on alternate days for the first 2 weeks of therapy. Lamotrigine should not be administered if the calculated dose is less than 1 mg daily. If the potential for interaction with adjunctive antiepileptics is unknown, treatment with lamotrigine should be started with lower doses such as those used with valproate.

Adjunctive therapy with valproate: 25 mg every other day for 2 weeks followed by 25 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 25 to 50 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily given as a single dose or in 2 divided doses. The doses above are also permitted in children over 12 years of age.

In children taking valproate, the initial dose of lamotrigine is 150 micrograms/kg once daily for 2 weeks followed by 300 micrograms/kg once daily for 2 weeks; thereafter the dose is increased by a maximum of 300 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 5 mg/kg, which may be given once daily or in 2 divided doses. If the calculated daily dose for children lies between 1 and 2 mg then 2 mg may be given on alternate days for the first 2 weeks of therapy.

Lamotrigine should not be administered if the calculated dose is less than 1 mg daily. If the potential for interaction with adjunctive antiepileptics is unknown, treatment with lamotrigine should be started with lower doses such as those used with valproate.

NOTE. A therapeutic plasma concentration range has not been established for lamotrigine.

Adverse effects:

Adjunctive therapy in adults: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate

Monotherapy in adults: vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed ($\geq 5\%$) adverse experiences associated with the use of lamotrigine during the conversion to monotherapy (add-on) period were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

Adjunctive Therapy in Pediatric Patients: The most commonly observed ($\geq 5\%$) adverse experiences seen in association with the use of lamotrigine as adjunctive treatment in pediatric patients were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.

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Annex A

3Q2008 ALLEXCEL

DMF #	SUBMIT DATE	HOLDER	SUBJECT
19892	5-Oct-2006	LUPIN LIMITED INDIA	LAMOTRIGINE (MICRONISED) AS MANUFACTURED IN MAHARASHTRA INDIA
19908	26-Oct-2006	AUROBINDO PHARMA LTD	LAMOTRIGINE (NON-STERILE DRUG SUBSTANCE) AS MANUFACTURED IN ANDHRA PRADESH INDIA
21390	3/20/2008	ALKEM LABORATORIES LTD	LAMOTRIGINE AS MANUFACTURED BY AMI LIFESCIENCES PVT LIMITED IN GUJARAT STATE, INDIA
20129	11-Jan-2007	APOTEX PHARMACHEM INC	LAMOTRIGINE AS MANUFACTURED IN ANDHRA PRADESH INDIA
16480	24-Mar-2003	DR REDDYS LABORATORIES LTD	LAMOTRIGINE AS MANUFACTURED IN ANDHRA PRADESH, INDIA.
17740	8-Oct-2004	MATRIX LABORATORIES LTD	LAMOTRIGINE AS MANUFACTURED IN ANDHRA PRADESH, INDIA.
18439	20-Jun-2005	UNION QUIMICO FARMACEUTICA SA	LAMOTRIGINE AS MANUFACTURED IN BARCELONA, SPAIN.
15924	4-Apr-2002	TEVA GROUP	LAMOTRIGINE AS MANUFACTURED IN BE'ER SHEVA AND PETAH TIQVA, ISRAEL
16259	20-Nov-2002	CHEMAGIS LTD	LAMOTRIGINE AS MANUFACTURED IN BEER SHEVA, ISRAEL.
18353	17-May-2005	GEDEON RICHTER LTD	LAMOTRIGINE AS MANUFACTURED IN BUDAPEST AND DOROG, HUNGARY.
18137	3-Mar-2005	CF PHARMA LTD	LAMOTRIGINE AS MANUFACTURED IN BUDAPEST, HUNGARY.
17231	12-Mar-2004	MEDICHEM SA	LAMOTRIGINE AS MANUFACTURED IN CELRA (GIRONA), SPAIN.
20289	22-Feb-2007	TORRENT PHARMACEUTICALS LIMITED	LAMOTRIGINE AS MANUFACTURED IN GUJARAT INDIA
18090	17-Feb-2005	CADILA HEALTHCARE LTD	LAMOTRIGINE AS MANUFACTURED IN GUJARAT, INDIA.
18732	9-Sep-2005	ALEMBIC LTD	LAMOTRIGINE AS MANUFACTURED IN GUJARAT, INDIA.
18960	17-Nov-2005	TARO PHARMACEUTICAL INDUSTRIES LTD	LAMOTRIGINE AS MANUFACTURED IN HAIFA BAY, ISRAEL.
16142	24-Sep-2002	JUBILANT ORGANOSYS LIMITED	LAMOTRIGINE AS MANUFACTURED IN KARNATAKA STATE, INDIA.
20835	10-Sep-2007	UNICHEM LABORATORIES LTD	LAMOTRIGINE AS MANUFACTURED IN MADHYA PRADESH, INDIA
18356	18-May-2005	SUN PHARMACEUTICAL INDUSTRIES LTD	LAMOTRIGINE AS MANUFACTURED IN MAHARASHTRA, INDIA.
21105	28/11/2007	CAMBREX PROFARMACO MILANO SRL	LAMOTRIGINE AS MANUFACTURED IN MILAN, ITALY
20548	23-May-2007	PHARMACEUTICAL WORKS POLPHARMA SA	LAMOTRIGINE AS MANUFACTURED IN STAROGARD GDANSKI POLAND
19541	20-Jun-2006	ZHEJIANG SUPOR PHAMRACEUTICALS CO LTD	LAMOTRIGINE, NON-STERILE DRUG SUBSTANCE AS MANUFACTURED IN ZHEJIANG PROVINCE, CHINA.
18421	9-Jun-2005	CIPLA LTD	LAMOTRIGINEAS MANUFACTURED IN BANGALORE, INDIA.

Source: Drug master File (DMF), Food and Drug Administration (as of 3Q2008).

Annex B

Epileptic seizure: “a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena which may include alterations of consciousness, motor, sensory, autonomic, or psychic events, perceived by the patient or an observer” (**Commission 1993**)

Epileptic seizure classification (Commission 1993)

Etiologic classification

Group	Explanation/subgroups
Provoked (acute) symptomatic seizure	occurring in close temporal association with systemic or central nervous system insult (head injury, cerebrovascular accident, infection, tumor, postintracranial surgery, toxic, withdrawal, metabolic, multiple causes, undefined). These events are presumed to be an acute manifestation of the insult and may not recur when the underlying cause has been removed or the acute phase has elapsed.
Unprovoked remote symptomatic seizure	owing to conditions resulting in a static encephalopathy (head injury, cerebrovascular disease, infection or infestation, pre- and perinatal risk factors, alcohol related, postencephalopathic states)
Unprovoked progressive symptomatic seizure	owing to progressive central nervous system disorders (tumor, infection, autoimmune, metabolic, degenerative)
Idiopathic seizure	no clear etiology (reserved for certain partial or generalized epileptic syndromes with particular clinical and EEG characteristics)
Cryptogenic seizure	no clear etiology (when no factor associated with increased risk of seizures was identified)

Semeiologic classification

Group	Explanation/subgroups
Generalized seizure	no indication of an anatomic localization and no clinical evidence of focal onset. The subgroups are convulsive (tonic, clonic, or tonic-clonic), nonconvulsive (absence), myoclonic
Partial seizure	evidence of a clinical partial onset. The subgroups are simple (no consciousness impairment), complex (consciousness impairment, amnesia or confusion during or after the seizure), secondarily generalized
Unclassified seizure	

Annex C

Global Burden of Disease (source WHO 2006)

To assess the burden of disease, the Global Burden of Disease Study used a time-based metric that measures both premature mortality (years of life lost because of premature mortality or YLL) and disability (years of healthy life lost as a result of disability or YLD, weighted by the severity of the disability). The sum of these two components, disability-adjusted life years (DALYs), provides a measure of the future stream of healthy life (years expected to be lived in full health) lost as a result of the incidence of specific diseases and injuries. One DALY can be thought of as one lost year of healthy life and the burden of disease as a measure of the gap between current health status and an ideal situation where everyone lives into old age free from disease and disability.

In summary, one DALY is 1 lost year of healthy life:

DALYs = YLLs + YLDs (Burden = Mortality + Disability).

Income categories (source WHO 2006)

the income categories are based on World Bank estimates of gross national income (GNI) per capita in 2001. Each country is classified as *low income* (GNI US\$ 745 or less), *lower middle income* (GNI US\$ 746–2975), *upper middle income* (GNI US\$ 2976–9205), and *high income* (GNI \$ 9206 or more).

Treatment gap (source Meinardi et al. 2001)

The definition for the **seizure treatment gap** recommended is:

The difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given time, expressed as a percentage. This definition includes diagnostic and therapeutic deficits.

Subdefinitions:

Active epilepsy: Two or more unprovoked epileptic seizures on different days in the prior year that are disabling to the individual.

Appropriate treatment: Diagnosis and treatment of underlying causes; treatment of recurrent seizures according to international standards.

To estimate the percentage of people with epileptic seizures who are not treated [i.e., the seizure treatment gap (STG)], it is recommended that the following formula be used: [(0.005 multiplied by the population size) minus people treated for epilepsy] divided by 1% of people treated for epilepsy.

To estimate the number of people treated for epilepsy, it is recommended that the total amount of each AED dispensed be divided by its DDD, with the results being added together. [The denominator (the DDD) may have to be adjusted according to the average body weight of the population and/or the use of AEDs for other indications than epilepsy].

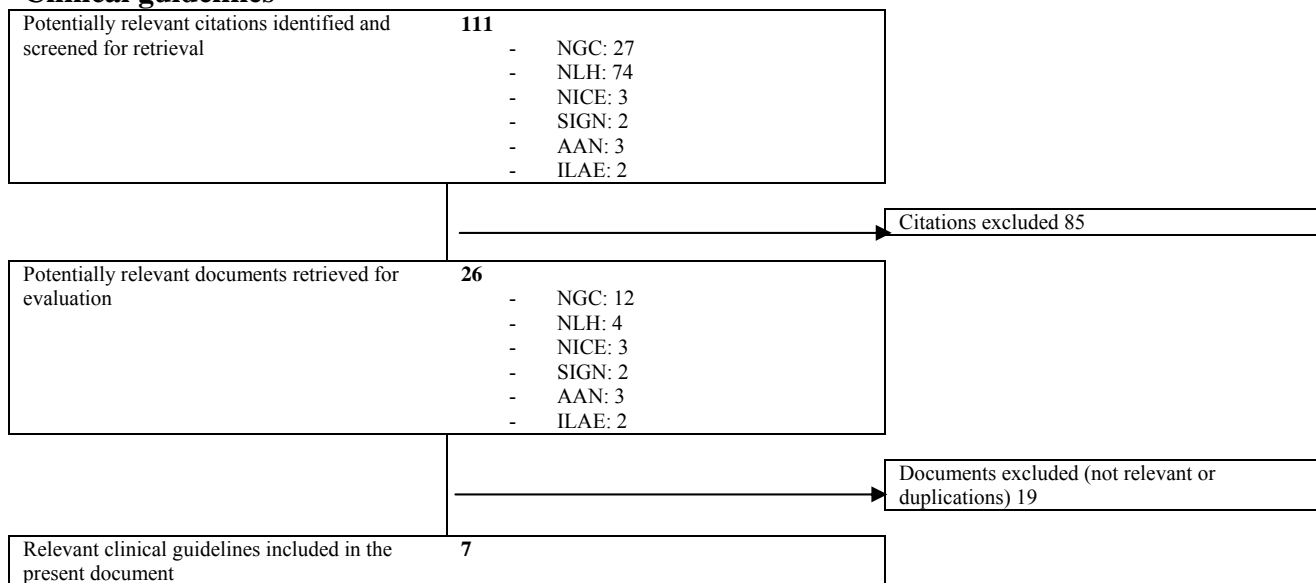
Annex D**Table:** Synopsis of the recommendations from guidelines dealing with treatment of epilepsy.

Question	AAN 2004*		ILAE 2006**		NICE 2004***		SIGN 2005/2005****	
	Adults	Children	Adults	Children	Adults	Children	Adults	Children
<i>first choice drug/s for treatment of new onset generalized epilepsy</i>	CBZ phenytoin VPA phenobarbital LTG not for absence seizures: gabapentin, oxcarbazepine, topiramate	the same as for adults	for generalized tonic-clonic seizures: CBZ LTG oxcarbazepine phenobarbital phenytoin topiramate VPA	for generalized tonic-clonic seizures: CBZ phenobarbital phenytoin topiramate VPA for absence seizures: ethosuximide LTG VPA	VPA LTG only for generalized tonic-clonic seizures: topiramate, CBZ only for absence seizures: ethosuximide	the same as for adults	VPA LTG	the choice should be determined by the syndromic diagnosis and potential AEs. The following AEDs may worsen specific syndromes: CBZ, vigabatrin, tiagabine, phenytoin (absence, juvenile myoclonic epilepsy) clonazepam (Lennox-Gastaut Syndrome) LTG (Dravet's syndrome, juvenile myoclonic epilepsy)
<i>first choice drug/s to add for treatment of drug-resistant generalized epilepsy</i>	only for generalized tonic-clonic seizures: topiramate	the same as for adults	not considered		levetiracetam clobazam clonazepam only for generalized tonic-clonic seizures: oxcarbazepine	the same as for adults	levetiracetam topiramate clonazepam clobazam	the same as for adults
<i>first choice drug/s for treatment of new onset partial epilepsy</i>	CBZ phenytoin VPA phenobarbital gabapentin LTG oxcarbazepine topiramate	the same as for adults	CBZ phenytoin sodium VPA	oxcarbazepine only for benign epilepsy with centrotemporal spikes: CBZ, VPA:	CBZ LTG oxcarbazepine VPA topiramate	the same as for adults	CBZ VPA LTG oxcarbazepine	phenytoin VPA CBZ clobazam LTG topiramate oxcarbazepine vigabatrin
<i>first choice drug/s to add for treatment of drug-resistant partial epilepsy</i>	gabapentin LTG levetiracetam oxcarbazepine tiagabine topiramate zonisamide	gabapentin LTG oxcarbazepine topiramate	not considered		clobazam gabapentin levetiracetam phenytoin tiagabine	the same as for adults	gabapentin levetiracetam tiagabine topiramate vigabatrin	gabapentin LTG topiramate oxcarbazepine

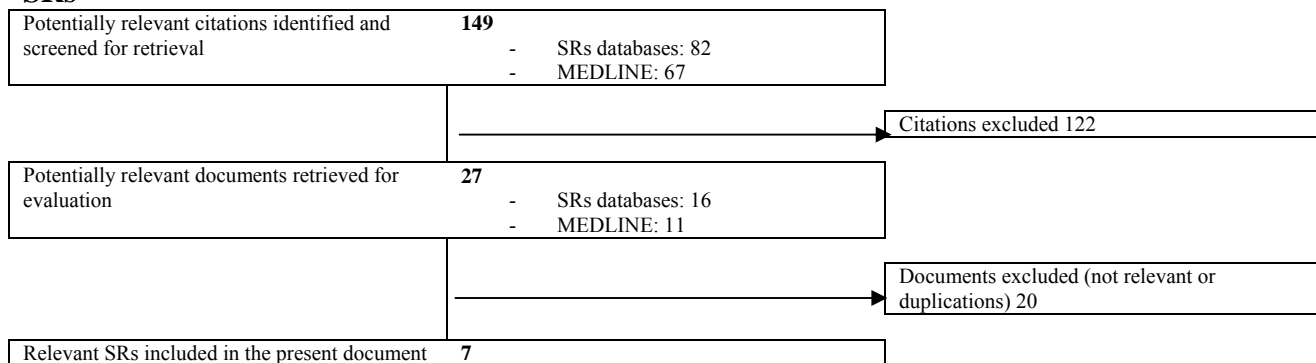
*from French et al. 2004a and French et al. 2004b; **from Glauser et al. 2006; ***from National Collaborating Centre for Primary Care 2004, ****from SIGN 2003 and SIGN 2005

Annex E
Results of the search strategy and process of inclusion

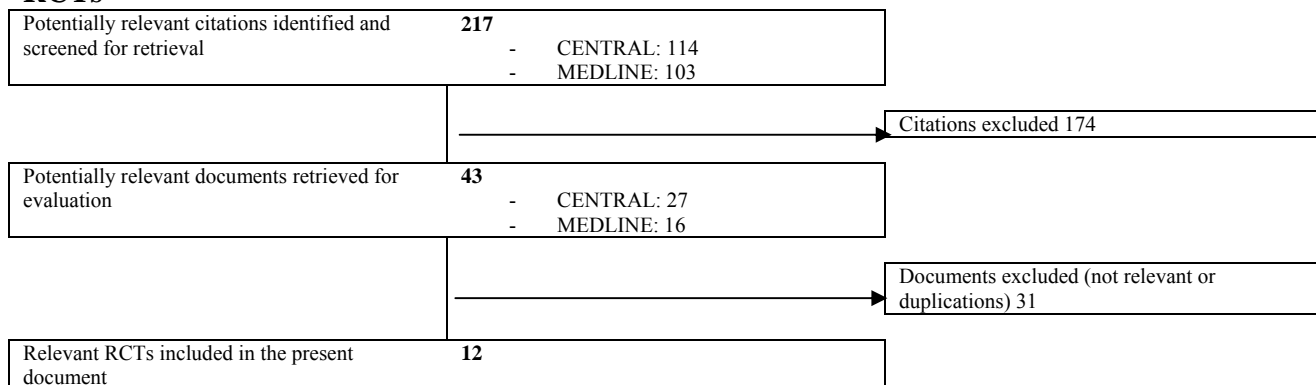
Clinical guidelines



SRs



RCTs



Annex F and G

Tables of evidence according to GRADE method

Annex H

Glossary

AE = adverse event

AED = antiepileptic drug

CBZ = carbamazepine

CI = confidence interval

DDD = Defined Daily Dose

HR = hazard ratio

LTG = lamotrigine

NNH = number needed to harm

OR = odds ratio

RCT = randomized controlled trial

RR = relative risk

SR = systematic review

VPA = valproic acid