

Public assessment report  
EU worksharing project paediatric data

Lamictal  
Lamotrigine

Marketing authorisation holder: GlaxoSmithKline

Rapporteur	Medicines Evaluation Board, The Netherlands
Co-rapporteur	Medicines and Healthcare products Regulatory Agency, UK
Start 1 <sup>st</sup> round	8 January 2007
Clock-off period	18 April 2007 – 1 October 2007
Procedure re-start date	1 October 2007
Finalisation procedure	8 April 2008
Date of this public assessment report	2 February 2009

<p>Currently approved indication(s):</p>	<p><b>Epilepsy</b>  <u>Adults and adolescents aged 13 years and above</u>  Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.  Seizures associated with Lennox-Gastaut syndrome. Lamictal is given as adjunctive therapy but may be the initial antiepileptic drug (AED) to start with in Lennox-Gastaut syndrome.</p> <p><u>Children and adolescents aged 2 to 12 years</u>  Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.  Monotherapy of typical absence seizures.</p> <p><b>Bipolar disorder</b></p> <p><u>Adults aged 18 years and above</u>  Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).</p> <p>Lamictal is not indicated for the acute treatment of manic or depressive episodes.</p>
<p>Pharmaceutical form(s) affected by this project:</p>	<p>Dispersible/chewable tablets  Tablets</p>
<p>Strength(s) affected by this variation:</p>	<p>2, 5, 25, 50, 100 and 200 mg</p>
<p>Marketing authorisation holder</p>	<p>GlaxoSmithKline</p>
<p>Rapporteur</p>	<p>Medicines Evaluation Board, The Netherlands</p>
<p>Co-rapporteur:</p>	<p>Medicines and Healthcare products Regulatory Agency, UK</p>

# I. INTRODUCTION

## I.1 Scope of assessment

Lamictal dispersible/chewable tablets are indicated for the treatment of epileptic seizures and prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes in all EU member states. The active compound of Lamictal is lamotrigine which exhibits its antiepileptic effect primarily by blockade of voltage-gated sodium channels. It is used as monotherapy and adjuvant therapy in partial seizures with or without secondary generalisation, primary generalised seizures and some specific seizure types. Until 2008, the SmPCs in different EU member states differed in precise wording of the indication, restriction of age-categories, seizure types, dose recommendations and interactions. For this reason, the marketing authorisation holder had initiated an Article 30 referral procedure to harmonise the SmPC. In July 2008 a harmonised SmPC for Lamictal was issued by the European Commission.

The use of Lamictal for the treatment of partial seizures as an adjuvant treatment in children above 2 years of age has been approved in all EU member states. The same indication has not been established for children between 1 to 24 months of age. GlaxoSmithKline submitted available data that could support this indication, as a part of the EU Worksharing Procedure for the assessment of paediatric data. The sent data has been assessed, including the supplementary information requested.

# II. SCIENTIFIC DISCUSSION

## II.1 Quality aspects

Not applicable

## II.2 Non-clinical aspects

Not applicable

## II.3 Clinical aspects

### II.3.1 Clinical pharmacology

The data submitted concerns Lamictal dispersible/chewable tablets that were administered as dispersed either into water or pureed, semi-soft food.

The applicant submitted data of two clinical studies, LAM20006 and LAM20007 where pharmacokinetics of lamotrigine were investigated as secondary outcome in paediatric patients aged 1 to 24 months.

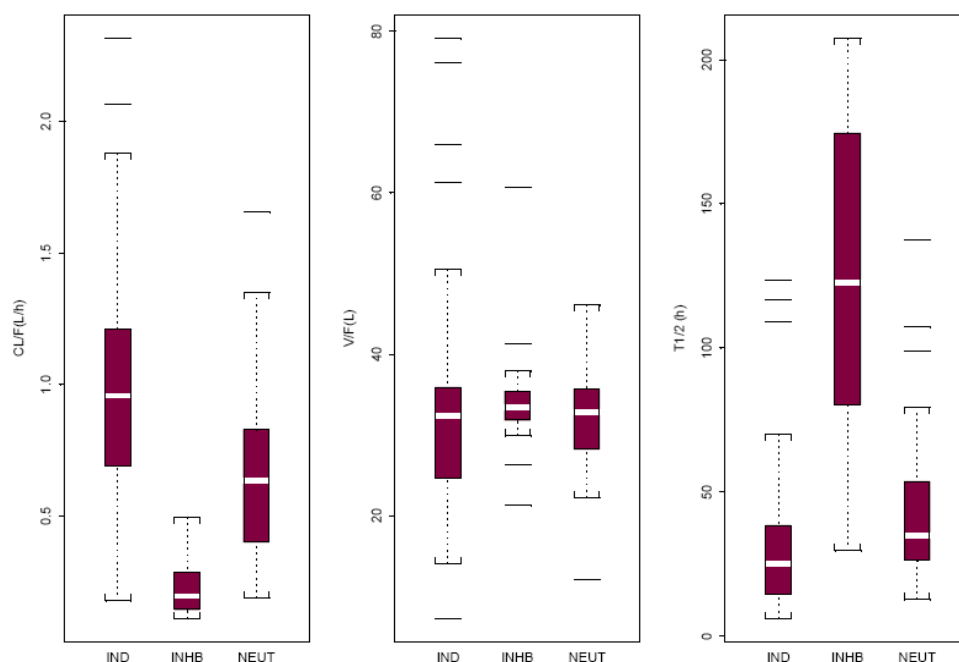
From previous studies in adult population, it is known that lamotrigine displays linear kinetics which means that there is no saturable metabolism. From previous studies in paediatric patients more than 2 years old it is known that clearance capacity is relatively higher in children than in adults, therefore doses must be adjusted. The same, adjusted dosing was applied to children less than 2 years of age in the clinical studies.

Clearance (CL/F/kg, where f=bioavailability) and volume of distribution (V/F) were estimated for the study population, including inter-individual variability. Body weight and co-prescribed interactive anti-epileptic agents (AEDs) were taken into account (see table 1 and figure 1). The clearance in younger subjects was estimated to be lower compared to children above 24 months, with the same bodyweight. The data also indicated that the serum exposure was the highest in children with lowest bodyweight in the age group less than 24 months. From 10 kg up the clearance and plasma levels were more similar to children older than 24 months. The population mean estimates for apparent oral clearance (CL/F) and apparent oral volume of distribution (V/F) including associated variability estimates are summarised in table 2.

**Table 1 Summary Table of Population Mean Weight Normalized Apparent Clearance Values versus Body Weight, Separated by AED Therapy**

Weight (kg)	Neutrals	Inhibitors	Inducers
3	0.55	0.16	0.91
6	0.94	0.27	1.54
9	1.06	0.31	1.75
12	1.13	0.33	1.85
15	1.16	0.34	1.92
16	1.18	0.34	1.94

**Figure 1 Box Plot Summary of CL/F(L/h), V/F(L) and T<sub>1/2</sub>(h) versus concomitant AED Therapy (Inducers, Inhibitors or Neutral)**



**Table 2 Summary Table of Final PK model (IIV=inter-individual variation, KA=absorption constant)**

		Effect of Inhibitors	Effect of Weight	Effect of Inducers	IIV
CL/F(L/h)	0.614	-0.708	0.129	0.64	CV% =46.7
(95% CI)	(0.52 – 0.71)*	(-0.78 - -0.64)*	(0.11 -0.15)*	(0.36-0.93)*	(%RSE=22.6)
%RSE	7.62 %	5.23%	6.53 %	22.4 %	
V/F(L)	32.9	not tested.	N.S.	not tested	CV%=64.2
95% CI	(22.3– 43.5)				(%RSE=30.5)
%RSE	16.4 %				
KA	2.25	-	-	-	-
	(0.1-4.41)				
	48.9				

Residual Error: Proportional Error CV% =30.7 (15.1 %), Additive SD = 0.014 ug/mL (LOQ=0.004 ug/mL)

Objective Function: -646.135,

%RSE=SE/Parameter Estimate\*100

\*(95% CI of FIXED Effect, calculated as population mean ± 1.96\*SE)

Although clearance capacity is noticeable lower and maximum concentration is higher consecutively in very young children weighing less than 10 kg, the recommendation for gradual up titration of the dose based on clinical symptoms makes it unnecessary to do dose adjustments for children less than 24

months. Difference in clearance capacity in children with lower bodyweight is probably attributable to developmental factors in terms of hepatic enzyme capacity and renal function.

The mean half life ( $T_{1/2}$ , hrs) of lamotrigine in patients on anti-epileptic drugs inducing therapy was 23 h, those on valproic acid (inhibitor) the mean half-life was 136 h and neutral subjects had a mean half-life of 38 h (see figure 1). This is considerably higher than in patients above 24 months old. Long  $T_{1/2}$  might be induced by relatively large volume of distribution (32.9 L) in this population.

Interindividual variation of pharmacokinetic parameters was high, which is expected in young, fast developing population. This indicates that the doses need to be adjusted regularly.

The clearance, distribution volume and half-life of paediatric patients is reported in detail in SmPC section 5.2.

### II.3.2 Clinical efficacy

The data submitted concerned the indication of Lamictal dispersible/chewable tablets for children aged from 1 to 24 months. The results of the efficacy studies remained inconclusive and therefore a positive benefit/risk assessment in this population could not be supported. It was proposed that this should be reflected in the SmPC, as will be discussed in the final section of this report.

Two studies were submitted to support the application, LAM20006 and LAM20007. The studies will be discussed separately. Both studies complied with the principles of Good Clinical Practice, in accordance with the Declaration of Helsinki and with the approval of Ethics Committees or Institutional Review Boards.

**Study LAM20006** was a randomized, double-blind placebo controlled parallel group withdrawal study in the add-on setting in a responder-enriched population. It was conducted from May 2000 to November 2003. The study incorporated an uncontrolled, open label phase of flexible duration in which lamotrigine was added to an ongoing anti-epileptic drug regimen, a controlled double-blind phase lasting 8 weeks in which lamotrigine was either continued or replaced by placebo and an uncontrolled open label extension phase. In the open label phase lamotrigine was added to the existing antiepileptic regime and titrated to the individually optimized dose. Patients with sustained > 40% reduction in partial seizures compared to the historical baseline (i.e. at least a 7 day period with prospective or retrospective seizure count) could enter the double blind phase. Patients who completed or escaped from the double blind phase could continue on lamotrigine treatment as part of study LAM20007 (see below). Otherwise lamotrigine was tapered in weekly steps of 25%. Intent to treat population was 177 patients. A total of 38 patients were randomised to receive either lamotrigine or placebo in the double blind phase of the study.

The inclusion criteria for the study were a diagnosis of epilepsy with  $\geq 4$  partial seizures per month and received treatment of one or two antiepileptic agents. Subjects on valproic acid should have received the drug for at least 6 months and not use any other antiepileptic agent. Subjects on non-enzyme inducing antiepileptic agents should weigh at least 6.7 kg. Exclusion criteria included maintenance therapy with more than 2 background anti-epileptic drugs, underlying chronic metabolic abnormalities, diagnosis of severe progressive myoclonus, seizures not related to epilepsy or pyridoxine dependency, status epilepticus within 4 weeks of enrolment, progressive or unstable neurologic condition with evidence of deterioration within the last month, clinically significant chronic cardiac, renal, hepatic or gastrointestinal conditions, previous treatment with lamotrigine or concurrent treatment with ketogenic diet, felbamate, ACTH and vagus nerve stimulator.

Lamotrigine was added to the pre-existing drug regimen according to the dose titration schedule outlined in the table 3 below.

**Table 3 Dose titration schedule**

	Week 1 and 2	Week 3 and 4:	Subsequent weekly dose increase	Max. maintenance dose	Max. duration of Dose-Escalation Period
LTG added to VPA or non-EIAEDs	0.15mg/kg/day	0.3mg/kg/day	max. 0.3mg/kg/day rounded to the nearest whole tablet	5.1mg/kg/day or 200mg/day	20 weeks
LTG added to EIAEDs (maximum of two)	0.6mg/kg/day	1.2mg/kg/day	max. 1.2mg/kg/day rounded to the nearest whole tablet	15.6mg/kg/day or 400mg/day	16 weeks

Initial dosing was every other day when necessary. At the end of week 2, lamotrigine serum concentration was measured. If the LTG concentration was higher than 0.41microgram/mL, i.e. the concentration found in adults at Week 2, the subsequent doses for this patient were reduced (see Table 4). Once the subject had reached a large enough total daily dose medication was administered every 8 hours. The dose was increased until optimal clinical benefit was achieved.

**Table 4: Parameters used to calculate dose reduction**

LTG concentration (microgram/mL)	Multiply the subject's weight by this percentage
0.41 - 0.59	83%
0.59 - 0.85	58%
0.85 - 1.22	40%
1.22 - 1.76	28%
1.76 - 2.54	19%
2.54 - 3.66	13%
3.66 - 5.26	9%
5.26 - 7.58	6%

Primary endpoint of the study was the proportion of subjects meeting the escape criteria. Escape criteria was met if one of the following events occurred:

- 50% or greater increase in monthly partial seizure frequency compared to the frequency of seizures during the Optimization Period (period of optimal clinical benefit). Monthly seizure frequency was computed using the last 4 weeks of the Optimization Period and the most recent 4 weeks of the double-blind. If a subject had not reached 4 weeks in the double-blind but had already experienced a total number of seizures  $\geq 150\%$  of the seizures of the Optimization Period, the subject was considered to have met the escape criterion;
- Doubling of the highest consecutive 2-day partial seizure count observed during the Optimization Period;
- Onset of a new and more severe seizure type;
- Clinically significant worsening of non-partial seizures observed during the Historical Baseline Phase or the Optimization Period;
- The need to use any therapeutic intervention to control seizures; or
- Status epilepticus.

### Results

177 patients were enrolled in the open label phase and 38 of those patients continued into the double blind phase (DBP).

The study failed to reach statistical significance on its primary endpoint. 16 out of 19 subjects (84%) in placebo group and 11/19 (58%) in lamotrigine group met the escape criteria. The difference in responders rate between lamotrigine and placebo was 26%. ( $p=0.07$ ).

Secondary endpoint results from study LAM20006 are presented in tables 5 and 6 below

**Table 5 Change in seizure frequency last 28 days in open label phase per dose category**

Lamotrigine dose	n	Seizure free	Reduction		No change	Increase	
mg/kg/day		100%	50-99%	26-49%	+/- 25%	26-49%	>= 50%
+enzyme inducers							
< 4	29	24%	7%	7%	17%	7%	38%
4 - <8	21	43%	33%	5%		10%	10%
8 - < 12	21	14%	48%	5%	14%	5%	14%
12 - < 15	23	17%	39%	13%	17%		13%
> 15	28	4%	29%	32%	11%	4%	21%
non-inducers							
< 2	16	44%	44%	-	6%		9%
2 - < 4	11	45%	18%	-	9%	9%	18%
4 - <6	23	17%	30%	22%	13%	4%	13%

**Table 6. Efficacy**

ITT- analysis	Placebo	Lamotrigine	Diff	CI <sub>95%</sub> by assessor	P <sup>B</sup>	P <sup>C</sup>
Failures (n/N) %	16/19 84%	11/19 58%	26.3%	-2.60% ⇔ 50.2% <sup>A</sup>	0.07	0.15
<b>Secondary analysis /endpoints</b>						
Failures PP- analysis (n/N)	14/17 (82%)	9/17 (53%)	29.4%	-1.9% ⇔ 54.2% <sup>A</sup>	0.07	0.14
Time to escape (median days)	22	42	21	-10 ⇔ 52		0.06 <sup>D</sup>
Failure by age category						
< 6 months	0/1	0/0				
6-12 months	6/6	6/8				
>12 months	10/12	5/11				
Failure by type of cAEDs						
Non-Induced	11/14 (79%)	7/13 (54%)				
Induced	5/5 (100%)	4/6 (67%)				
Failures due to						
Increase > 50%	14 (74%)	5 (26%)				
Doubling 2-day seizure count	9 (47%)	4 (20%)				
New and more severe seizure type	2 (11%)	-				
Therapeutic intervention	1 ( 5.3%)	3 (15.8%)				
<b>Change</b>						
Increase >= 50%	14 (74%)	5 (26.3%)				
26-49%	1 ( 5.3%)	3 (15.8%)				
No change -25% to 25%	3 (15.8 %)	5 (26.3%)				
Decrease 26-49%	1 (5.3%)	2 (10.5%)				
>= 50%	-	4 (21.0%)				
Failures (n/N) in subject >80% improvement at entry	10/11 (91%)	2/7 (29%)	62%	16.7% ⇔ 84.0%		0.013 <sup>B</sup>

<sup>A</sup> Newcombe method for small sample size (by assessor)

<sup>B</sup> Chi-square, <sup>C</sup>Fisher exact test

<sup>D</sup> LogRankTest

**Study LAM20007** was an open label uncontrolled long term safety study. Secondary efficacy and pharmacokinetic variables were assessed. An interim analysis with a data cut-off point of January 2006 was submitted. The study had a screening phase, treatment phase and final phase. 206 patients were enrolled at the data cut-off point, 117 patients had completed the study. The inclusion criterion for the study was enrolment in study LAM20006 or being lamotrigine naïve. Exclusion criteria were essentially the same as for study LAM20006.

During the study, patients were monitored at 2 week intervals during titration and 4 week intervals thereafter. Data collected included seizure frequency, physical and neurological examinations, ECGs, adverse events, clinical laboratory tests and PK variables. Treatment with lamotrigine was continued for 48 weeks or up to patients 2<sup>nd</sup> birthday. After the optimal dose for lamotrigine was obtained, concomitant AEDs could be introduced, withdrawn or their dosage changed.

### Results

Table 7 below presents effects of 48 weeks administration of lamotrigine on seizure frequency.

Efficacy results from study LAM20007:

<b>Table 7. Study LAM20007 Change in seizure frequency</b>				
	LTG experienced	LTG naïve	Remarks	
n <sup>A</sup>	119	77		
Seizure frequency (/week)				
Partial seizures				
Historical baseline	21.0	28.5		
During treatment	2.8	7.0		
Reduction in seizure frequency				
Seizure free	21%	3%		
Reduction by 55-99%	42%	57%		
Reduction by 26-49%	9%	5%		
Change between + 25% ; -25%	9%	17%		
Increase by 26-29%	6%	6%		
Increase > 50%	13%	12%		
Median percent reduction	78.9%	66.7%		
Inducers	81.1%	70.3%		
Non-inducers	58.3%	66.7%		
Valproic acid only	96.9%	21.7%		
<b>n=196<sup>A</sup></b>				
<b>Per seizure type</b>	<b>n</b>	<b>Median seizure frequency per week</b>		
		<b>Baseline</b>	<b>Treatment</b>	
All partial seizures	196	21.0	3.9	74.4%
Simple & complex partial seizures	155	4.0	3.7	20.4%
Simple partial seizures	59	2.0	4.0	-100%
Complex partial seizures	121	1.3	2.0	30.3%
Secondary generalised seizures	87	1.5	1.2	18.3%
Primary generalised seizures	54	0.5	6.7	-100.0%

<sup>A</sup> 2 subjects did not receive lamotrigine, 5 subjects had no diary records

The efficacy results of study LAM20007 were interpreted with caution since efficacy parameters were assessed only as secondary objective and because concomitant AEDs could be altered when needed during the study. It was noted that some of the seizure types worsened during treatment.

## Overall assessment of efficacy

The results of clinical efficacy studies of lamotrigine in the treatment of partial seizures as an adjuvant treatment in children between 1-24 months of age were inconclusive. Hence the benefit-risk has not been established.

### II.3.3 Clinical safety

Safety data for lamotrigine as adjunctive therapy in the treatment of infants (1-24 months of age) with partial seizures are available from study LAM20006 and the interim analysis of LAM20007.

A total of 256 subjects were exposed to lamotrigine in LAM20006 and LAM20007 combined. The cumulative exposure by age category is presented in table 8 and exposure by dose in table 9.

	Age		
	< 6 months	6-12 months	>12 months
Cumulative exposure			
0 weeks	40	81	135
< 12 weeks	32	70	126
< 24 weeks	29	59	105
< 36 weeks	25	55	89
< 48 weeks	21	44	72
< 60 weeks	19	30	37
< 72 weeks	15	9	16

Doses (mg/kg/day Induced)	< 5	5-8	> 8-11	> 11-15	> 15
	38	37	39	35	10
Doses (mg/kg/day Non-induced)	< 2.5	2.5-5	> 5-7.5	> 7.5-10	> 10.0
	20	41	7	1	2
Doses (mg/kg/day Valproic acid only)	< 1	1-2.5	> 2.5 -4	> 4-5	>5
	5	4	12	4	1

### Safety results

Adverse events (all adverse events and drug related adverse events) reported on the clinical trials are summarised in table 10.

Descriptor	n=256		Comments
	All	Related	
Any Adverse event	93%	18%	
Deaths	3.4%	none	
Serious adverse events		38%	
Adverse event leading to discontinuation		12%	
Most frequent adverse events			
Pyrexia	53%	<1%	
Upper respiratory tract infection	29%	-	
	27%	4%	No specific pattern observed
All Seizures <sup>1</sup>			
Vomiting	25%	-	
Ear infection	22%	-	
Cough	22%	-	
	20%	2%	No specific pattern observed
All rashes			
Nasopharyngitis	20%	-	

**Table 10 Adverse events profile**

Descriptor	n=256		Comments
Otitis Media	20%	-	
Teething	18%	-	
Constipation	17%	2%	
Irritability	17%	5%	
Diarrhea	12%	-	
Pneumonia	12%	-	
Bronchitis	11%	-	
Pharyngitis	9%	-	
Upper respiratory tract congestion	9%	-	
Nasal congestion	8%	-	
Insomnia	7%	2%	
Respiratory tract infection	7%	-	
Viral infection	7%	-	
Gastroesophageal reflux disease	6%	-	
Somnolence	6%	3%	
Dermatitis diaper	6%	-	
Gastroenteritis	5%	-	
Rhinorrhoea	5%	-	
Lethargy	5%	1%	
Tremor	-	2%	
Ataxia	-	1%	
Vomiting	-	1%	
Decreased appetite	-	<1%	

The incidence of adverse events was 93% (n=239). The most common adverse events were pyrexia (53%), upper respiratory tract infection (29%), seizure-related adverse events (27%), vomiting (25%), ear infection (22%), cough (22%), rash (20%), nasopharyngitis (20%) and otitis media (20%).

Adverse events of special interest were seizure-related and rash. 27% of subjects had a seizure-related adverse event from which 4% was considered drug related. 20% of subjects developed rash from which 2% was considered drug related.

#### *Fatal outcome*

A total of 7 deaths were reported, all occurring in study LAM20007. Causes of death were pneumonia (4 patients), respiratory failure (1), cardiac arrest (1) and intracranial bleeding (1). See for further discussion of these cases pages 14 and 15.

#### *Serious adverse events*

The distribution of the serious adverse events were (percentage of n=256): Complex partial seizures (7%), Pneumonia (7%), Status epilepticus (6%), Convulsion (4%), Pyrexia (4%), Dehydration (4%), Partial seizures with secondary generalization (3%), Gastroenteritis (3%), Bronchiolitis (2%), Upper respiratory tract infection (2%), Bronchitis (2%), Cyanosis (2%), Vomiting (2%), Respiratory distress (2%), Apnoea (2%), Grand mal convulsion (1%), Simple partial seizures (1%), Gastro-oesophageal reflux disease (1%), All rash (1%), Viral infection (1%), Infantile spasms (<1%), Myoclonic epilepsy (<1%), Partial seizures (<1%), Rash (<1%), Angioneurotic oedema (<1%), Urticaria (<1%), Otitis media (<1%), Respiratory syncytial virus infection (<1%), Diarrhoea (<1%), Bronchopneumonia (<1%), Infection (<1%) and Aspiration (<1%).

### Withdrawals

Adverse events leading to withdrawal from the study are presented in table 11. 31 (12%) lamotrigine-patients were withdrawn due to an adverse event.

**Table 11 Adverse events leading to withdrawal**

Adverse event	Number (%) of subjects withdrawn
Any Event	31 (12)
All rash	11 (4)
Rash	6 (2)
Urticaria	2 (<1)
Rash generalized	1 (<1)
Rash maculo-papular	1 (<1)
Rash morbilliform	1 (<1)
All seizure	9 (4)
Complex partial seizures	4 (2)
Status epilepticus	3 (1)
Myoclonic epilepsy	2 (<1)
Infantile spasms	1 (<1)
Pneumonia	4 (2)
Pyrexia	2 (<1)
Increase in ALT and AST	1

### Laboratory data

A small number of subjects ( $\leq 4\%$ ) had haematology clinical chemistry values that were considered abnormalities of clinical significance. There were no clinically meaningful treatment emergent changes in clinical laboratory evaluations attributed to lamotrigine in studies LAM20006 and LAM20007.

### Vital signs

There were no changes in vital signs considered adverse reaction.

Regarding ECGs, there were 36 subjects with treatment-emergent clinically significant ECG abnormalities. The most frequent treatment emergent ECG changes were sinus tachycardia (6%), sinus bradycardia (5%), and right ventricular hypertrophy (3%).

### Assessment safety

Based on the initial data submitted (during the first round of the procedure) it was concluded that the adverse event profile of lamotrigine as adjunctive therapy in paediatric subjects (1-24 months of age) with partial seizures, was similar to that of reported in the current labelling for children 2 years and older of age. However questions were raised regarding some safety issues.

The observed worsening of seizures was regarded as a matter of concern and was asked to be evaluated further (see below). Another safety signal asked to be evaluated further was the occurrence of right (left) ventricular hypertrophy. Also, the number of spontaneous reports of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme (see post marketing experience below) was of concern and was asked to discuss further. An evaluation of causal relation between lamotrigine and 7 reported deaths on study LAM20007 was also requested (see also below).

In response to these requests, the following issues were addressed:

### **Worsening of seizures**

Increase in seizure frequency is considered to be an expected event which is already reflected in the current SmPC of Lamictal. The observed seizure frequencies in studies LAM20006 and LAM20007 were confounded by several factors, such as use of historical baseline data, severe prognosis and developing disease and prolonged titration period of lamotrigine. Furthermore, LAM20007 was a long-term safety study where high doses of concomitant anti-epileptic drugs could be tried and some of the enrolled patients might have suffered from devastating forms of encephalopathy which could explain the increase in frequency of primary generalised seizures.

Investigators considered only 10 seizure adverse events out of 132 in studies LAM20006 and LAM20007 to be related to lamotrigine. 29 seizure-related adverse events out of 132 occurred within 35 days of initiating lamotrigine treatment and it is unlikely that lamotrigine contributed to these events since the cases occurred on dose titration phase. The remaining 103 seizure-related adverse events occurred at various time intervals.

In studies investigating older children and adults lamotrigine has not been associated with an increase in seizure frequency greater than that associated with placebo.

49 cases from the medical literature have been identified where lamotrigine was reported as withdrawn due to worsening of seizure activity. A further 2 cases have been reported where lamotrigine has been continued despite transient early morning myoclonus. Although no specific seizure type or syndrome is implicated specifically, myoclonus appears to be a common finding. However, by their very nature, case reports are subject to major reporting bias.

In 2002, the applicant reviewed the association between lamotrigine and seizures aggravated and concluded that there was no clear evidence from spontaneous data to indicate that any particular seizure type was more likely to be worsened by lamotrigine than others.

Reporting an increase in seizure frequency in the adverse event section was considered too weak. Fact is that substantial increases in seizure have been observed in a non-neglectable proportion of subjects. In the open label phase of study LAM20006, 39 out of 172 subjects (22.7%) had an increase in seizure frequency >25% and 39 out of 172 subjects (18.0%) an increase of more than >50%.

Further it was generally agreed that the available evidence was sufficient to conclude that lamotrigine may worsen myoclonic seizures. Hence the following text was added to the SmPC (see section IV of this assessment report):

*A clinically significant worsening of seizure frequency instead of an improvement may be observed. As a consequence the observed benefit of control for one seizure type should be weighted against an observed worsening in another seizure type on a case by case basis.*

and

*Myoclonic seizure may be worsened under lamotrigine.*

### **Right (left) ventricular hypertrophy**

Data from medical literature suggest that the ECG is an insensitive tool used to screen for right ventricular hypertrophy because of its relatively low sensitivity and positive predictive value (Puchalski, 2006). Also for patients under 6 months ECG parameters still evolve during this time.

#### LAM20006 and LAM20007 Clinical Studies

In total there were 6 patients where the ECG revealed right-ventricular hypertrophy and one further patient had left-ventricular hypertrophy confirmed by an echocardiogram.

In the 6 patients where an ECG revealed right-ventricular hypertrophy:

- The time to event from initiation of lamotrigine to the ECG reading ranged from 56 to 628 days
- One patient, with multiple non-cardiac congenital anomalies continued lamotrigine during the study and the ECG reading by the end of the study was normal.
- One patient had a history of a heart murmur and chronic lung disease.

- In 3 cases, the patients discontinued lamotrigine and ECGs were normal within 2 weeks at the follow up visit, suggesting other reasons for the ECG changes rather than hypertrophy.
- One patient had an ECG at follow up, but there was no baseline ECG to demonstrate that the abnormal ECG was treatment emergent.

In the patient that had left ventricular hypertrophy confirmed by an echocardiogram, the ECG was interpreted as normal suggesting that ECG is not sensitive. In this patient a neonatal echocardiogram had demonstrated a small atrial level shunt and mild mitral insufficiency. An echocardiogram performed for evaluation during the study demonstrated concentric left ventricular hypertrophy with mild left ventricular outflow tract obstruction. The atrial level shunt was again noted on this echocardiogram. An external paediatric cardiologist reviewed this subject's data and determined that, while the exact aetiology of the left ventricular hypertrophy is not known, the possibility that it was related to study drug, though unlikely, cannot be ruled out. The applicant believed that more plausible causes of the hypertrophy were persistent hypertension, as blood pressure assessment showed systolic blood pressure greater than the 95th percentile for age, or outflow tract obstruction.

#### Post-marketing Experience

The GSK clinical safety database was searched on 26 March 2007 and four reports of ventricular hypertrophy with lamotrigine were retrieved.

- One concerned a patient in whom an echocardiogram demonstrated left ventricular hypertrophy. However, this patient also had coarctation of the aorta.
- The second patient was a neonate born with ventricular hypertrophy following in utero exposure to lamotrigine.
- The remaining two reports concerned adult patients.

Although ECG's were taken during the study, ECG is an insensitive tool for evaluating ventricular hypertrophy in paediatric patients. As such it can only be considered to be a hypothesis generating tool and does not provide robust evidence of a causal association. The two patients who had hypertrophy confirmed by echocardiogram have more likely explanations as to the cause.

Additionally, with over 15 years of market experience and an estimated 7.4 million patient-years exposure with lamotrigine, the applicant have only received four spontaneous reports of ventricular hypertrophy, all of which have plausible alternative explanations.

It was agreed that there is no evidence to confirm a reasonable possibility of a causal association between treatment with lamotrigine and the development of ventricular hypertrophy.

#### ***Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme***

There is already significant information relating to the risk of severe skin reactions in the product information, including specific warnings concerning the risk of rash in children and the particular care required in dealing with rash in this population. The cases described in children under 2 years are consistent with that advice.

The nature of spontaneous reports means that it is impossible to determine the denominator to calculate a meaningful reporting rate for the population aged less than 2 years of age. Therefore, these data do not allow us to compare the incidence of severe skin reactions in this population with that of older children. In addition, due to the well documented association between lamotrigine and skin reactions it is highly likely that there is significant reporting bias that further complicates the analysis. Furthermore, many of the spontaneous cases are lacking in detail and consequently, the applicant is unable to determine whether alternative causes may have been apparent or whether appropriate dose regimens were used.

In the current lamotrigine SmPC, serious rash is defined as a rash associated with hospitalization and the discontinuation of lamotrigine or rash reported to be SJS or TEN. The applicant considers that it is worthy of note that there were no such cases of serious skin reactions reported from studies, LAM20006 and LAM 20007, that exposed 256 infant patients to lamotrigine. Whilst 3 (1%) subjects experienced a case of rash reported as a serious adverse event in the open label phase of these studies, these did not meet the SmPC definition of serious rash.

Furthermore, the incidence of SJS and TEN was much higher in the initial years of marketing than in subsequent and current years, as shown in the table 12 below. Subjects in recent studies received

initial starting doses and dose escalations of lamotrigine in line with current dose recommendations while subjects who contributed to the rate of rash in the SmPC were dosed with more aggressive initial doses used in earlier studies. This is further supported by data from Wong *et al.* who examined cases of serious and non-serious rash with lamotrigine in a retrospective case record survey at five tertiary referral epilepsy centres in the UK, before and after the dose change for adults in 1994. While not focused on SJS and TEN, the results indicate a similar reduction in the rate of serious rash in adult patients (1% of 804 patients with the original dosing versus 0/245 with the current dosing) with lower starting doses and slower titration.

**Table 12 Lamotrigine, incidence of serious rash from the German Registry**

Adults	1993 (First Launch)	Subsequent Years
	0.8 / 1000	0.2 / 1000
Paediatrics	1998 and 1999 (First Launch)	Subsequent Years
	1 / 1000 to 0.9 / 1000	3 / 10000

It was agreed that there are no indications of an extra risk in the toddlers population. It is agreed that the information in the SmPC relating to the risk of severe skin reactions is sufficient.

**Reported cases of deaths in study LAM20007**

Following the review of the events (Table 13), the applicant does not believe that these 7 reports provide evidence of a “reasonable suspicion” of causality and therefore warrants a SmPC labelling.

**Table 13 Analysis of the 7 deaths which occurred in study LAM20007**

Case	Time to onset	Pre-existing condition	Cause of death	Investigator attribution
1	~ 6 weeks	Hypotonic quadriplegia	Sepsis-unknown origin	Unrelated
2	~ 4 months	Gastroesophageal reflux, meningitis	Bronchopneumia	Unrelated
3	~ 7 months	Not stated	Aspiration pneumonia	Unrelated
4	~ 2½ months	Not stated	Recurrent pneumonia-4 episodes	Unrelated
5	~ 7 months	Meningitis encephalopathy	Pneumonia	Unrelated
6	~ 9 months	Hydrocephalus	Intra-cranial bleed	Unrelated
7	12 days	Cerebral palsy, static encephalopathy	Cardiac arrest	Unrelated

Following a best evidence assessment of the events in question, the applicant concluded that the data available do not confirm a reasonable possibility of causal association, for the following reasons:

- There is a high risk of respiratory illness and mortality in these patients who had significant pre-existing neurological conditions e.g. post meningitis encephalopathy, gastro-oesophageal reflux and hypotonic quadriplegia.
- Furthermore, apart from the 5 cases relating to aspiration, pneumonia or sepsis that have been discussed in the question, there is no consistent pattern to the events described with one case of cardiac arrest/ sudden unexplained death in a patient with a prior history of respiratory arrest and one case of intracranial bleed in a patient with underlying hydrocephalus.
- Of the 7 cases in question, there is no consistent time to onset of event from initiation of lamotrigine therapy; with times extending from approximately 6 weeks to approximately 9 months.
- None of the events were considered by the investigator to be related to study medication

The argumentation is accepted as the cause of deaths indicates complication of the underlying condition rather than a causal relationship with lamotrigine. Apparently lamotrigine was not sufficient to

achieve complete seizure control, which is not unexpected in this highly treatment refractory population.

### **Other safety issues**

Moreover a warning statement regarding the lack of data in children on cognition and growth was included:

*There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural developments in young children.*

### **Post marketing experience**

The applicant's database identified 87 post-marketing reports up to 27 July 2006 in children less than 24 months of age in which lamotrigine was reported as a suspect drug.

3 deaths were reported:

- A child developed Stevens-Johnson Syndrome and died 3 weeks after starting lamotrigine.
- A child developed disseminated intravascular coagulation (DIC) with facial swelling and increased liver enzymes. Lamotrigine was withdrawn. The child died after 76 days. The events were considered possibly related to lamotrigine. The cause of death was considered to be severe encephalopathy.
- A child was found dead 21 days after starting lamotrigine, autopsy results were 'apparently inconclusive' (sic).

There were 6 reports of Stevens-Johnson Syndrome (including the fatal one described above), 1 case of toxic epidermal necrolysis and 1 case of erythema multiforme which necessitated treatment in intensive care. 2 of the reports of Stevens-Johnson Syndrome were receiving concomitant valproate and one concomitant vigabatrin and clonazepam. The case of toxic epidermal necrolysis was reported in a child who was also receiving concurrent valproate.

The incidence of serious skin reactions associated with lamotrigine use in children is known, i.e. 1/300 – 1/100. Taken into account the widespread use of lamotrigine in paediatric patients these figures (6 cases of SJS) probably lie within this known incidence. Moreover it is known that concurrent use with valproate increases the risk of developing a serious skin reaction.

Regarding reported cases of death see also discussion on deaths on page 14.

There have been 36 reported serious adverse events (including 3 deaths). The most common primary adverse events were (by MedDRA system organ class): skin and subcutaneous tissue disorders (10), nervous system disorders (5) and metabolism and nutrition disorders (4).

Rash is an adverse event of special interest in the infant population as, during the early development of lamotrigine, a higher incidence of both rash and serious rash was noted in pediatric subjects compared with adults. Among the 10 skin and subcutaneous tissue disorders considered serious adverse events there were 6 reports of Stevens-Johnson Syndrome (including the report with a fatal outcome), one of toxic epidermal necrolysis, one of erythema multiforme and 2 of rash. Two of the reports of Stevens-Johnson Syndrome were receiving concomitant valproate and one concomitant vigabatrin and clonazepam. The case of toxic epidermal necrolysis was reported in a child who was also receiving concurrent valproate.

### **Overall assessment of safety**

It is concluded that the adverse event profile of lamotrigine as adjunctive therapy in paediatric subjects (1-24 months of age) with partial seizures, is similar to that stated in the current labelling for children 2 years of age and older.

It was decided that the following warnings should be added to section 4.4 of the SmPC for lamotrigine (see also section IV of this assessment report):

#### Development in children

*There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural developments in children.*

#### Precautions relating to epilepsy

*A clinically significant worsening of seizure frequency instead of an improvement may be observed. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.*

*Myoclonic seizures may be worsened by lamotrigine.*

*There is a suggestion in the data that responses in combination with enzyme inducers is less than in combination with non- enzyme inducing antiepileptic agents. The reason is unclear.*

### **III. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

The benefit-risk of Lamictal (lamotrigine) dispersible/chewable tablet for the treatment of partial seizures with or without secondary generalisation in the add-on setting between 1 month and 24 months of age has not been sufficiently established. The results in clinical efficacy studies were inconclusive. Therefore an indication could not be warranted.

Lamictal® has been used off-label in children between 1 and 24 months and the currently approved age limit of 2 years was considered to be rather artificial.

Therefore it was agreed:

- to add the following wording in section 4.2 of the SmPC:

#### “Children below 2 years

*There are limited data on the efficacy and safety of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see section 4.4). There are no data in children below 1 month of age. Thus Lamictal is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections 4.4; 5.1 and 5.2.”*

- and that the (sections 4.2; 4.4; 5.1 and 5.2 of the) SmPC should contain information concerning the safe use of Lamictal® in age group of 1 month to 24 months based on the data in children between 1 month and 24 months as provided for Lamictal (lamotrigine). See section IV of this assessment report below.

## IV. FINAL AGREED CHANGES IN THE SmPC

### Section 4.2 Posology and method of administration

#### Children below 2 years

*There are limited data on the efficacy and safety of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see section 4.4). There are no data in children below 1 month of age. Thus Lamictal is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections 4.4; 5.1 and 5.2.*

### Section 4.4 Special warnings and special precautions for use

#### Development in children

*There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural developments in children.*

#### Precautions relating to epilepsy

*A clinically significant worsening of seizure frequency instead of an improvement may be observed. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.*

*Myoclonic seizures may be worsened by lamotrigine.*

*There is a suggestion in the data that responses in combination with enzyme inducers is less than in combination with non-enzyme inducing antiepileptic agents. The reason is unclear.*

### Section 5.1 Pharmacodynamic properties

#### Clinical efficacy and safety in children aged 1 to 24 months

*The efficacy and safety of adjunctive therapy in partial seizures in patients aged 1 to 24 months has been evaluated in a small double-blind placebo-controlled withdrawal study. Treatment was initiated in 177 subjects, with a dose titration schedule similar to that of children aged 2 to 12 years. Lamotrigine 2 mg tablets are the lowest strength available, therefore the standard dosing schedule was adapted in some cases during the titration phase (for example, by administering a 2 mg tablet on alternate days when the calculated dose was less than 2 mg). Serum levels were measured at the end of week 2 of titration and the subsequent dose either reduced or not increased if the concentration exceeded 0.41 µg/mL, the expected concentration in adults at this time point. Dose reductions of up to 90% were required in some patients at the end of week 2. Thirty-eight responders (> 40% decrease in seizure frequency) were randomised to placebo or continuation of lamotrigine. The proportion of subjects with treatment failure was 84% (16/19 subjects) in the placebo arm and 58% (11/19 subjects) in the lamotrigine arm. The difference was not statistically significant: 26.3%, CI95% -2.6% <> 50.2%, p=0.07.*

*A total of 256 subjects between 1 to 24 months of age have been exposed to lamotrigine in the dose range 1 to 15 mg/kg/day) for up to 72 weeks. The safety profile of lamotrigine in children aged 1 month to 2 years was similar to that in older children except that clinically significant worsening of seizures (>=50%) was reported more often in children under 2 years of age (26%) as compared to older children (14%).*

## Section 5.2 Pharmacokinetic properties

### Infants aged 2 to 26 months

*In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg bodyweight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher C<sub>max</sub> levels are likely to be observed in some children with a body weight below 10 kg.*