

## ANNEX F\_01

Author(s): Luca Vignatelli

Date: 2008-11-19

Question: Should lamotrigine vs valproic acid be used for new onset generalized epilepsy?

Settings: UK, Germany

Bibliography: Steinhoff et al. 2005 (RCT), GSK 2000 (RCT) reported by Wilby et al. 2005 (SR), Marson et al. 2007 (RCT)

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lamotrigine	valproic acid	Relative (95% CI)	Absolute		
<b>time to treatment withdrawal - Steinhoff RCT (follow-up 24 weeks)</b>												
1	randomised trial	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	33	30	Survival curves <sup>4</sup>		⊕○○○ VERY LOW	
<b>time to treatment withdrawal - Marson RCT (follow-up median 3.5 years)</b>												
1	randomised trial	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	239	238	HR 1.25 (0.94 to 1.68)		⊕⊕⊕○ MODERATE	
<b>time to treatment withdrawal for unacceptable AEs - Marson RCT (follow-up median 3.5 years)</b>												
1	randomised trial	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	239	238	HR 0.72 (0.46 to 1.14)		⊕⊕⊕○ MODERATE	
<b>time to treatment withdrawal for inadequate seizure control - Marson RCT (follow-up median 3.5 years)</b>												
1	randomised trial	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	239	238	HR 1.95 (1.28 to 2.98) <sup>5</sup>		⊕⊕⊕○ MODERATE	
<b>time to 12-month remission - Marson RCT (follow-up median 3.5 years)</b>												
1	randomised trial	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	239	238	HR 1.31 (1.06 to 1.62) <sup>6</sup>		⊕⊕⊕○ MODERATE	
<b>time to first seizure - Marson RCT (follow-up median 3.5 years)</b>												
1	randomised trial	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	239	238	HR 1.41 (1.14 to 1.75) <sup>7</sup>		⊕⊕⊕○ MODERATE	
<b>seizure free - Steinhoff RCT (follow-up 24 weeks)</b>												

1	randomised trial	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	33	30	Survival curves <sup>4</sup>		⊕○○○ VERY LOW
<b>seizure free - GSK 2000 (follow-up 24 weeks)</b>											
1	randomised trial	serious <sup>8</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	313	RR 0.92 (0.78 to 1.10)			⊕⊕○○ LOW

<sup>1</sup> Open study.

<sup>2</sup> Short follow up length (24 weeks).

<sup>3</sup> Low number of patients; study probably underpowered to test the difference between the two groups.

<sup>4</sup> No difference between groups.

<sup>5</sup> HR>1 indicates that failure occurs more rapidly on LTG compared with VPA.

<sup>6</sup> HR>1 indicates that 12-month remission occurs more rapidly on VPA compared with LTG.

<sup>7</sup> HR>1 indicates that first seizure occurs more rapidly on LTG compared with VPA.

<sup>8</sup> Unpublished trial. It is not reported if it was conducted in a blind manner.

## ANNEX F\_02

**Author(s):** Luca Vignatelli

**Date:** 2008-10-29

**Question:** Should lamotrigine vs valproic acid be used for absence seizures in children?

**Settings:** children

**Bibliography:** Posner et al. 2005 (SR)

Quality assessment							Summary of findings				Importance	
							No of patients		Effect			Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lamotrigine	valproic acid	Relative (95% CI)	Absolute		
<b>seizure free - Posner SR (follow-up 12 months)</b>												
1	randomised trial	very serious <sup>1,2</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	19	19	RR 1.30 (0.77 to 2.2)		⊕○○○ VERY LOW	

<sup>1</sup> Open study.

<sup>2</sup> Method of allocation concealment not described.

<sup>3</sup> Low number of patients; study underpowered to detect differences between groups.

## ANNEX F\_03

Author(s): Luca Vignatelli

Date: 2008-10-28

Question: Should lamotrigine vs carbamazepine be used for new onset partial epilepsy?

Settings: USA, Germany, UK, Europe, Israel

Bibliography: Gamble et al. 2006 (SR); Rowan et al. 2005 (RCT); Steinhoff et al. 2005 (RCT); Marson et al. 2007 (RCT); Saetre et al. 2007 (RCT); Gilad et al. 2007 (RCT);

Quality assessment							Summary of findings				Quality	Importan
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lamotrigine	carbamazepine	Relative (95% CI)	Absolute		
<b>time to treatment withdrawal - Gamble SR (follow-up 24-48 weeks)</b>												
4	randomised trial	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	562	308	HR 0.62 (0.45 to 0.86)		⊕⊕⊕ LOW	
<b>time to treatment withdrawal - Rowan RCT (follow-up 54 weeks)</b>												
1	randomised trial	no serious limitations	no serious inconsistency	serious <sup>3</sup>	no serious imprecision	none	200	198	Survival curves <sup>4</sup>		⊕⊕⊕ MODERATE	
<b>time to treatment withdrawal - Steinhoff RCT (follow-up 24 weeks)</b>												
1	randomised trial	serious <sup>5</sup>	no serious inconsistency	serious <sup>6</sup>	no serious imprecision	none	88	88	Survival curves <sup>7</sup>		⊕⊕⊕ LOW	
<b>time to treatment withdrawal - Marson RCT (follow-up median 3.6 years)</b>												
1	randomised trial	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	378	378	HR 0.78 (0.63 to 0.97) <sup>8</sup>		⊕⊕⊕ MODERATE	
<b>time to treatment withdrawal - Saetre RCT (follow-up 40 weeks)</b>												
1	randomised trial	no serious limitations	no serious inconsistency	serious <sup>3</sup>	serious <sup>9</sup>	none	93	91	HR 0.77 (0.45 to 1.31)		⊕⊕⊕ LOW	
<b>time to treatment withdrawal for unacceptable AEs - Marson RCT (follow-up median 3.6 years)</b>												
1	randomised trial	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	378	378	HR 0.62 (0.46 to 0.83) <sup>8</sup>		⊕⊕⊕ MODERATE	
<b>time to treatment withdrawal for inadequate seizure control - Marson RCT (follow-up median 3.6 years)</b>												
1	randomised trial	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none			HR 1.17		⊕⊕⊕ MODERATE	

	trial		inconsistency	indirectness	imprecision		378	378	(0.84 to 1.64)		MODERATE	
<b>time to first seizure - Gamble SR (follow-up 24-48 weeks)</b>												
4	randomised trial	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	289	188	HR 1.28 (0.98 to 1.66)		⊕⊕⊕ LOW	
<b>time to first seizure - Rowan RCT (follow-up 54 weeks)</b>												
1	randomised trial	no serious limitations	no serious inconsistency	serious <sup>3</sup>	no serious imprecision	none	200	198	survival curves <sup>10</sup>		⊕⊕⊕ MODERATE	
<b>time to first seizure - Marson RCT (follow-up median 3.6 years)</b>												
1	randomised trial	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	378	378	HR 1.23 (1.04 to 1.45) <sup>11</sup>		⊕⊕⊕ MODERATE	
<b>time to first seizure - Saetre RCT (follow-up 40 weeks)</b>												
1	randomised trial	no serious limitations	no serious inconsistency	serious <sup>3</sup>	serious <sup>9</sup>	none	93	91	HR 1.50 (0.94 to 2.4)		⊕⊕⊕ LOW	
<b>time to 12-month remission - Marson RCT (follow-up median 3.6 years)</b>												
1	randomised trial	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	378	378	HR 0.91 (0.77 to 1.09)		⊕⊕⊕ MODERATE	
<b>seizure free - Gamble SR (follow-up 24-48 weeks)</b>												
5	randomised trial	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	601	302	OR 0.72 (0.54 to 0.97) <sup>11</sup>		⊕⊕⊕ LOW	
<b>seizure free - Rowan RCT (follow-up 54 weeks)</b>												
1	randomised trial	no serious limitations	no serious inconsistency	serious <sup>3</sup>	no serious imprecision	none	200	198	rates <sup>12</sup>		⊕⊕⊕ MODERATE	
<b>seizure free - Steinhoff RCT (follow-up 24 weeks)</b>												
1	randomised trial	serious <sup>5</sup>	no serious inconsistency	serious <sup>6</sup>	serious <sup>13</sup>	none	88	88	rates <sup>12</sup>		⊕⊕⊕ VERY LOW	T
<b>seizure free - Saetre RCT (follow-up 40 weeks<sup>14</sup>)</b>												
1	randomised trial	no serious limitations	no serious inconsistency	serious <sup>3</sup>	serious <sup>9</sup>	none	93	91	rates <sup>12</sup>		⊕⊕⊕ LOW	
<b>seizure free - Gilad RCT (follow-up 12 months)</b>												

1	randomised trial	serious <sup>5</sup>	no serious inconsistency	serious <sup>15</sup>	serious <sup>9</sup>	none	32	32	rates <sup>12</sup>		⊕○○○ VERY LOW
<b>withdrawal for adverse events - Gilad RCT (follow-up 12 months)</b>											
1	randomised trial	serious <sup>5</sup>	no serious inconsistency	serious <sup>15</sup>	serious <sup>9</sup>	none	32	32	rates <sup>8</sup>		⊕○○○ VERY LOW

<sup>1</sup> Two studies are open

<sup>2</sup> Short follow up length (range 24-48 weeks). Brodie 1999: elderly patients only.

<sup>3</sup> Only elderly patients with newly diagnosed epilepsy; 1/4 of sample had generalized epilepsy

<sup>4</sup> LTG had fewer early terminators than CBZ (p<0.0001)

<sup>5</sup> Open study

<sup>6</sup> Short follow-up length (24 weeks).

<sup>7</sup> No differences in termination rates.

<sup>8</sup> In favour of LTG.

<sup>9</sup> Study probably underpowered to test the difference between the two groups.

<sup>10</sup> No differences of time to first seizure

<sup>11</sup> In favour of CBZ.

<sup>12</sup> No differences of rates between groups.

<sup>13</sup> Low number of events.

<sup>14</sup> Seizure free after week 20

<sup>15</sup> Patients with poststroke seizure.

## ANNEX F\_04

**Author(s):** Luca Vignatelli

**Date:** 2008-10-29

**Question:** Should lamotrigine be used in drug-resistant generalized epilepsy as add-on therapy?

**Settings:** USA

**Bibliography:** Biton et al. 2005 (RCT); Trevathan et al. 2006 (RCT)

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lamotrigine	control	Relative (95% CI)	Absolute		
<b>seizure free - Biton (RCT) (follow-up 20 weeks)</b>												
1	randomised trial	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	58	59	RR 1.7 (1.0 to 2.7)		⊕○○○ VERY LOW	
<b>seizure free - Trevathan (RCT) (follow-up 24 weeks)</b>												
1	randomised trial	no serious limitations	no serious inconsistency	serious <sup>4</sup>	serious <sup>3</sup>	none	21	24	RR 2.8 (1.0 to 7.8)		⊕⊕○○ LOW	

<sup>1</sup> Method of randomization not described.

<sup>2</sup> Short follow up length (20 weeks).

<sup>3</sup> Low number of patients; the study is probably underpowered to detect differences between groups.

<sup>4</sup> Short follow up length (24 weeks).

## ANNEX F\_05

**Author(s):** Luca Vignatelli

**Date:** 2008-10-29

**Question:** Should lamotrigine be used in drug-resistant partial epilepsy as add-on therapy?

**Settings:** Europe, USA, Australia

**Bibliography:** Ramaratnam et al. 2001 (RS - search updated in 2007); Naritoku et al. 2007 (RCT); Pina-Garza et al. 2008 (RCT)

Quality assessment							Summary of findings				Importance
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lamotrigine	control	Relative (95% CI)	Absolute	
<b>treatment withdrawal - Ramaratnam (RS) (follow-up 8-24 weeks)</b>											
11	randomised trial <sup>1</sup>	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	619	408	OR 0.84 (0.48 to 1.46)		⊕⊕⊕⊕ MODERATE
<b>time to treatment failure - Pina-Garza (RCT) (follow-up 8 weeks)</b>											
1	randomised trial	serious <sup>3</sup>	no serious inconsistency	very serious <sup>2,4</sup>	serious <sup>5</sup>	none	19	19	Survival curve <sup>6</sup>		⊕○○○ VERY LOW
<b>seizure free - Naritoku (RCT) (follow-up 19 weeks)</b>											
1	randomised trial	serious <sup>3</sup>	no serious inconsistency	serious <sup>7</sup>	no serious imprecision	none	118	121	RR 3.8 (1.6 to 8.9)		⊕⊕○○ LOW

<sup>1</sup> Three parallel RCT and 8 cross-over RCT.

<sup>2</sup> Short follow up length (range 8-24 weeks).

<sup>3</sup> Randomization not described.

<sup>4</sup> Short follow up length (8 weeks). Patients were children aged 1 to 24 months.

<sup>5</sup> Low number of patients; the study is probably underpowered to detect differences between groups.

<sup>6</sup> No difference between the two groups.

<sup>7</sup> Short follow up length (19 weeks).

## ANNEX G

Author(s): Luca Vignatelli

Date: 2008-11-06

Question: Should lamotrigine vs placebo be used in patients with epilepsy?

Settings: Europe, USA, Australia

Bibliography: Ramaratnam et al. 2001; Zaccara et al. 2008

Quality assessment							Summary of findings				Importance
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lamotrigine	placebo	Relative (95% CI)	Absolute	
<b>dizziness - Zaccara (SR) (follow-up 8-24 weeks)</b>											
9	randomised trial	no serious limitations <sup>1</sup>	very serious <sup>2</sup>	serious <sup>3</sup>	no serious imprecision	none	503	435	Risk Difference 0.11 (0.05 to 0.17)		⊕○○○ VERY LOW
<b>dizziness - Ramaratnam (SR) (follow-up 8-24 weeks)</b>											
11	randomised trial	no serious limitations <sup>4</sup>	serious <sup>2</sup>	serious <sup>3</sup>	no serious imprecision	none	762	481	OR 2.57 (1.8 to 3.69)		⊕⊕○○ LOW
<b>ataxia - Zaccara (SR) (follow-up 8-24 weeks)</b>											
9	randomised trial	no serious limitations <sup>1</sup>	very serious <sup>2</sup>	serious <sup>3</sup>	no serious imprecision	none	503	435	Risk difference 0.12 (0.01 to 0.24)		⊕○○○ VERY LOW
<b>ataxia - Ramaratnam (SR) (follow-up 8-24 weeks)</b>											
11	randomised trial	no serious limitations <sup>4</sup>	serious <sup>2</sup>	serious <sup>3</sup>	no serious imprecision	none	762	481	OR 3.14 (1.99 to 4.95)		⊕⊕○○ LOW
<b>diplopia - Zaccara (SR) (follow-up 8-24 weeks)</b>											
9	randomised trial	no serious limitations <sup>1</sup>	very serious <sup>2</sup>	serious <sup>3</sup>	no serious imprecision	none	503	435	Risk difference 0.12 (0 to 0.24)		⊕○○○ VERY LOW
<b>diplopia - Ramaratnam (SR) (follow-up 24 weeks)</b>											
2	randomised trial	no serious limitations	no serious inconsistency	serious <sup>3</sup>	no serious imprecision	none	477	185	OR 3.40 (2.05 to		⊕⊕⊕○ MODERATE

									5.62)			
<b>nausea - Ramaratnam (SR) (follow-up 8-24 weeks)</b>												
11	randomised trial	no serious limitations <sup>4</sup>	no serious inconsistency	serious <sup>3</sup>	no serious imprecision	none	762	481	OR 1.88 (1.21 to 2.91)		⊕⊕⊕O MODERATE	
<b>fatigue - Ramaratnam (SR) (follow-up 8-24 weeks)</b>												
10	randomised trial	no serious limitations <sup>5</sup>	no serious inconsistency	serious <sup>3</sup>	no serious imprecision	none	619	408	OR 0.84 (0.48 to 1.46)		⊕⊕⊕O MODERATE	
<b>somnolence - Ramaratnam (SR) (follow-up 8-24 weeks)</b>												
11	randomised trial	no serious limitations <sup>4</sup>	serious <sup>6</sup>	serious <sup>3</sup>	no serious imprecision	none	762	481	OR 1.54 (0.97 to 2.43)		⊕⊕OO LOW	
<b>headache - Ramaratnam (SR) (follow-up 18-24 weeks)</b>												
3	randomised trial	no serious limitations	no serious inconsistency	serious <sup>3</sup>	no serious imprecision	none	575	286	OR 1.18 (0.77 to 1.81)		⊕⊕⊕O MODERATE	

<sup>1</sup> All but one RCT with cross-over design.

<sup>2</sup> Large statistical eterogeneity. Presence of clinical eterogeneity (different doses).

<sup>3</sup> Short length of follow up

<sup>4</sup> Three parallel and eight cross-over RCT.

<sup>5</sup> Two parallel and eight cross-over RCT.

<sup>6</sup> Statistical and clinical eterogeneity between parallel and cross-over RCT.